National Center for Complementary and Integrative Health

Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP)

IRBNet #1753168

Grant Award # 1UG3NR020929-01

National Clinical Trial (NCT) Identified Number: UG3 Pilot: NCT06568250; UH3: TBD

Center for Veterans Research and Education (CVRE) #F10058

Funding Mechanism: UG3/UH3

Funding Agency: National Institutes of Health National Institute of Nursing Research (NIH NINR)

Helping to End Addiction Long-term (HEAL) Initiative

Minneapolis VA Multiple Principal Investigator (MPI): Diana J. Burgess

University of Minnesota MPI: Roni Evans

University of Iowa MPI: Katherine Hadlandsmyth

Version 7 – 8/22/2025

Confidentiality Statement: This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

Contents

Revision History

Protocol Version #	Revision Date	Summary of Changes	Rationale for change	Protocol Section(s)
2	February 2024	Integrated IRBNet project "Stakeholder Engagement 1754182" with IRBNet project "Feasibility and RCT 1753168"	To best meet NIH funder protocol requirements, the lower risk, IRB- exempted protocol with "Advisors" as participants (IRBNet 1754182), has been integrated with the protocol with "Study Participants" (IRBNet 1753168). Upon approval of new IRBNet 1753168, the previous IRBNet 1754182 will be closed.	Throughout document
2	February 2024	Revised study acronym from RAMP-WH to RAMP	Project team and external feedback decided RAMP is preferable acronym.	Throughout document
2	February 2024	Added using Docusign for HIPAA authorization signatures.	Electronic HIPAA signing necessary as little to no in-person contact with participants and advisors	5.3 Informed Consent Procedures and 7.0 Privacy and Confidentiality
2	February 2024	Added using VA REDCap for data collection.	Project team determined VA REDCap favorable tool for some data collection.	5.5 Study Evaluations and 7.0 Privacy and Confidentiality
2	February 2024	Added using Webex	Previously stated using "approved VA videoconferencing program" but now specifying example of Webex.	pp. 29, 35
2	February 2024	Added using ClinCard pre-paid debit cards from Greenphire for participant payment purposes; physical checks remain alternative/backup payment method	When contract with Greenphire fully executed, the faster and more secure pre-paid debit cards will provide payment to participants. Slower-to-arrive physical checks will be used when ClinCard through Greenphire is not available.	pp. 40, 41
2	February 2024	Changed use of word "stakeholder" to "advisor"	Revised wording to best current practice.	Throughout document
2	February 2024	Revise follow-up timepoints from 13 and 26 weeks to 16 and 32 weeks	Revised follow-up timepoints to account for feasibility/logistics.	Throughout document
2	February 2024	Added 1 one-on-one intervention session at end of intervention period	Based on Veteran feedback added post-group one-on-one session with facilitator.	Throughout document

2	February 2024	Revised inclusion and exclusion criteria	Revisions made to ensure target population who can most benefit from study is reached while maintaining safety.	5.4 Inclusion/Exclusion criteria
2	February 2024	Revised screener, baseline, and follow-up measures	Revisions made based on updated best practices and funder requirements	2.3 Schedule of Activities
2	February 2024	Add Rose Degerstrom to study.	Additional staff person needed.	1.0 Study Personnel Project Staff - Minneapolis VAHCS, CCDOR
3	April 2024	Added Milestones.	Not included in original protocol.	2.4 Milestones
3	April 2024	Responded to informal feedback questions/comments from NINR.	NINR is study sponsor.	Throughout document
3	April 2024	Added possible RAMP VEP recruitment source is former LAMP study (IRBNet 1613709) participants	Participants in a prior similar study have a relevant perspective on RAMP.	5.2.1 Advisor Engagement
3	April 2024	Additional contacts with advisors and participants to share study results and/or other research opportunities.	Based on previous studies, advisors and participants appreciate hearing about results and other research.	5.1.1 Advisor Engagement and 5.1.2 Feasibility/Pilot and RCT
3	April 2024	Added saving data from feasibility and RCT participants in a secure repository/bank for other research studies in the future.	We are required by our funder (NIH HEAL Initiative) to share data with an approved repository. 2)	9.0 Repository/Data Banking
3	April 2024	Added option to re-contact RAMP participants in the future (while the study is still open) if they say “yes” to the follow-up survey question, “We’d sometimes like to gather more information and opinions, or let you know about other opportunities. Are you willing to be contacted again in the future?”	It can be advantageous to reach out to interested participants again (e.g., with more information, to ask follow-up questions, etc.).	5.2.2 Feasibility/Pilot and RCT
4	November 2024	Revised Appendix A- Data and Safety Monitoring Plan (DSMP)	Revisions and additional details based on requests and recommendations from Data and Safety Monitoring Board (DSMB).	Appendix A - DSMP
4	November 2024	Revised Lee Cross’s title role from Project Manager to Project Director	“Project Director” was determined to be a better description of the role Lee has.	Throughout document

4	November 2024	Terminology revisions (e.g., procedure and protocol, project staff vs. study staff, health coach vs. Whole Health Coach)	Revisions for consistency across project documents. For example, the current document is the *protocol*, and the project team also uses supplementary project *procedure* documents and a manual of operations that include additional detailed instructions and information.	Throughout document
4	November 2024	Remove one-on-one intervention session at end of intervention period, which changes intervention to 12 sessions rather than 13 for the pilot.	Based on Veteran feedback and changes with VA Whole Health, the one-on-one sessions are not adding enough value. Removing them allows group sessions to work more cohesively together.	Throughout document
4	November 2024	Revision of Mallory Mahaffey's role.	Mallory Mahaffey's study role changed somewhat with her reduction of hours.	1.0 Study Personnel
4	November 2024	Add Kimberly Behrens and Gloria Yang to protocol.	Kimberly Behrens and Gloria Yang joined the study team and were added with Administrative Change documentation in September 2024.	1.0 Study Personnel
4	November 2024	Add Sarah Schroeder.	Sarah Schroeder joined the study team.	1.0 Study Personnel
4	November 2024	Remove Rose Marie Degerstrom	Ms. Degerstrom is leaving the study team due to retiring.	1.0 Study Personnel
4	November 2024	Repository for data sharing named.	As the study sponsor, NIH HEAL requires data sharing through a HEAL approved repository. The RAMP project will use the NIMH Data Archive (NDA).	9.0 Repository/Data Banking
4	November 2024	Add clinicaltrials.gov NCT.	Pilot/feasibility study now registered with clinicaltrials.gov	Title page
4	November 2024	Increase maximum IRB allowed number of participants enrolled in full RCT.	The phase 2 RCT enrollment goal remains n=500.Asking for administrative approval to allow enrollment up to n=550. Our recruitment goal based on our power calculations remains set at 500, but we ask for approval to exceed this goal, since the way the study randomizes participants in large waves makes it difficult to perfectly hit recruitment numbers.	5.8 Data Analysis

4	November 2024	In addition to utilizing Docusign to email HIPAA forms to participants, we'd like to send physical letters along with HIPAA forms and return envelopes to non-signers.	As our protocol states, we've used Docusign to email HIPAA forms to participants, and while many have signed, about 20 have not (about 12% of our total baseline survey completers). As a result, we're unable to pay these people for completing the baseline survey. We believe the Docusign process may be creating undue burden on these participants. We believe that alternative approaches, such as sending physical letters along with the HIPAA forms would place less of a burden on participants and make it easier to pay them for their time.	5.3 Informed Consent Procedures
5	January 2025	Revise duties and data access description for Co-Investigator Stephanie Taylor and Marianne Matthias.	Drs. Taylor and Matthias may be conducting interviews/data collection with VA employee partners.	1.0 Study Personnel
6	February 2025	Add Raina Rooney to protocol.	Raina Rooney joined the study team and were added with Administrative Change documentation in January 2025.	1.0 Study Personnel
6	February 2025	Revisions to intervention: remove initial individual session and decrease number of group sessions to 9.	Improvements to intervention based on pilot feedback and findings.	Throughout document
6	February 2025	Revise description of follow-up time points to be in terms of months rather than weeks.	More accurate to say follow-up timepoints will occur at 3 and 6 months rather than particular weeks.	Throughout document
6	February 2025	Remove framing RAMP in terms of how VA Whole Health works.	RAMP can potentially be implemented in other areas of the VA beyond VA Whole Health.	Throughout document
6	February 2025	Administrative updates	Including revised phrasing of recruitment goal, adding missing abbreviations, revising "RAMP-WH" to "RAMP" where not previously corrected, and fixing typos.	List of Abbreviations, throughout document
7	August 2025	Terminology and clarification revisions.	Revisions based on recommendations from DSMB and NINR.	Throughout document
7	August 2025	Remove Mallory Mahaffey, Robin Austin, Gloria Yang.	Updates due to regular staff turnover.	1.0 Study Personnel

7	August 2025	Increase incentive payment for each completed survey to $40.	The surveys take more time to complete than originally estimated, so we've increased the incentive payment accordingly.	5.2.2 Feasibility/Pilot and RCT
7	August 2025	Add additional quality of life measures to surveys (EQ5D5L).	Additional questions will aid in the budget impact analysis.	2.3 Schedule of Activities (SOA)

Statement of Compliance

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent procedure(s), recruitment materials, and all participant materials will be submitted to the Minneapolis VA Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent procedure(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the Minneapolis VA IRB before the changes are implemented to the study. In addition, all changes to the consent procedure will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent procedure.

Abstract

Our long-term objective is to improve pain management and reduce opioid use among rural patients in the VA. To accomplish this, we will conduct a randomized clinical trial (RCT) to test the effectiveness of an innovative multi-component complementary and integrative intervention, Reaching **R**ural Veterans: **A**pplying **M**ind-Body Skills for **P**ain Using a **W**hole **H**ealth Telehealth Intervention (RAMP) delivered via group telehealth, at improving rural Veterans' pain management, function, and wellbeing, within the VA healthcare system. This project addresses the significant challenge of implementing effective, non-opioid interventions for chronic pain management among rural Veterans, who experience a disproportionate share of the national pain burden, with more chronicity, opioid harms, comorbid mental health conditions and substance abuse, and are prescribed more opioids and have less access to evidence-based, chronic pain care that addresses their "whole-person" or biopsychosocial needs. The RAMP program strategically coalesces multiple evidence based CIH self-management strategies to address rural Veterans' biopsychosocial needs and overcome existing barriers to implementation. Comprised of pain education, mindfulness, pain specific exercises, and cognitive behavioral strategies, the program is cohesive and scalable. Designed to meet the needs of VA interest holders, it uses health coaches as program facilitators. RAMP is a 9-week program comprised of group sessions with pre-recorded expert-led education videos, mind-body skill training and practice, and facilitated discussions. Participants will be rural dwelling VA patients with chronic pain, recruited through the electronic health record, and then screened through an online survey. For the preparatory phase (UG3/Phase 1) we will conduct 1) ***advisor engagement activities*** including identifying and developing new community partnerships and using mixed methods data collection from multiple levels of advisors (n=35-50 patients, community partners, VA healthcare system leaders and staff), guided by the established RE-AIM/PRISM framework, to learn about key factors that can affect long-term adoption; and 2) conduct a ***feasibility study*** of 40 rural VA patients with chronic pain to assess the feasibility of delivering RAMP (pilot) in terms of recruitment and engagement, intervention fidelity and adherence, data collection, and other key metrics. For UH3/Phase 2, we will conduct a randomized pragmatic clinical trial of RAMP compared to Usual Care, among rural patients (n=500) in the VA healthcare system. Participants randomized to the Usual Care (UC) condition will not be asked to do anything besides complete the follow-up surveys. In keeping with our pragmatic approach, patients will not be asked to limit any other treatment. After completing the final follow-up survey, they will be mailed information about how to access the intervention materials online. UH3/Phase 2 Aim 1 will assess the relative effectiveness of RAMP in rural VA patients in terms of pain interference at 3 and 6 months (**primary outcome**) and **secondary outcomes** of opioid use and other HEAL recommended outcomes (e.g., pain intensity, pain impact, physical function, sleep disturbance, fatigue, anxiety, depression, post-traumatic stress disorder, participation in social roles and activities, global impression of change). We will ask intervention participants about their experience with the RAMP program. We will also perform additional exploratory analyses of women and minoritized Veterans' primary and secondary outcomes. In UH3/Phase 2 Aim 2 we will work iteratively with multiple levels of advisors (from UG3/Phase 1) to evaluate intervention implementation strategies used in the trial and adapt

these strategies to scale up RAMP within the national VA healthcare system. This will include a) conducting mixed-methods assessments of advisor and randomized trial participant views of implementation-related barriers and facilitators, resource needs, and other RE-AIM/PRISM domains; b) working with advisors to co-create additional plausible strategies for overcoming barriers to implementation of RAMP; and c) conducting budget impact analyses using models informed by advisor views to inform future decision making.

List of Abbreviations

AEs– Adverse Events

ATLAS– Accessing Telehealth through Local Area Stations program

BPS– Biophysical, Psychological, Social (factors of chronic pain)

CAP – Community Advisory Panel

CBOCs– The VA's Community-Based Outpatient Clinics

CCDOR – Center for Care Delivery and Outcomes Research

CDW– Corporate Data Warehouse

CIH– Complimentary and Integrative Health

COIN – Center of Innovation

CONSORT – Consolidated Standards of Reporting Trials framework

CVRE – Center for Veterans Research and Education

DART – Data Access Request Tracker

DSMB – Data and Safety Monitoring Board

DSMP – Data and Safety Monitoring Plan

DUA– Data Use Agreement

EHRs– VA Electronic Health Records

HEAL – Helping End Addiction Long-term

HRSA – Health Resources & Services Administration

HSR&D – Health Science Research & Dissemination

IMC – Independent Monitoring Committee

JLV – Joint Legacy Viewer

LATIS – Liberal Arts Technologies & Innovation Services

MBIs– Mindfulness Based Interventions

MOUs– Memoranda of Understandings

MPI – Multiple Principal Investigator

NDA – NIMH Data Archive

NDS – National Data Services

NIH – National Institute of Health

NIMH – National Institute of Mental Health

NINR – National Institute of Nursing Research

NPC – Non-Profit Research Corporation

OCC– The VA's Office of Connected Care

OHRP – Office of Human Research Protections

OPCC&CT– The VA's Office of Patient Centered Care and Cultural Transformation

ORH– The VA's Office of Rural Health

PHI– Protected Health Information

PRISM– The Practical Implementation Sustainability Model

PTSD– Post-Traumatic Stress Disorder

RAMP – **R**ural Veterans: **A**pplying **M**ind-Body Skills for **P**ain Using a **W**hole **H**ealth Telehealth Intervention

RCT– Randomized Clinical Trial

RE-AIM– Reach, Effectiveness, Adoption, Implementation, and Maintenance.

RUCA – Rural-Urban Commuting Areas

SAEs–Severe Adverse Events

SMS – short message service (i.e., text messages)

UAPs–Unanticipated Problems

UC– Usual Care

UCLA – University of California Los Angeles

UMN – University of Minnesota

UPIRTSO – Unanticipated Problems Involving Risk to Subjects or Others

U-SAEs – Unanticipated Serious Adverse Events

VA– Veterans Healthcare Administration

VAHCS – VA Healthcare System

VINCI – VA Informatics and Computing Infrastructure

VISN– VA Veteran Integrated Service Network

1.0 Study Personnel

Multiple Principal Investigators (MPIs)

NIH Contact Multiple Principal Investigator, Minneapolis VA Healthcare System (VAHCS), Center for Care Delivery and Outcomes Research (CCDOR)
Diana J. Burgess, PhD
Minneapolis VA Healthcare System
One Veterans Drive (mail code 152)
Minneapolis, MN 55417-2309
612-467-1591
Diana.burgess@va.gov
Duties: Dr. Burgess will provide oversight to the entire project, jointly with the other MPIs, including development and implementation of all policies, procedures, and processes related to the project and implementation of the scientific agenda, leadership plan, and all activities necessary to achieve the project aims. Jointly with the other MPIs she will ensure procedural mechanisms are in place to guarantee institutional compliance with US law and NIH policies including biosafety, human subject protection, data security, and facilities compliance. Dr. Burgess will serve as contact PI and will assume primary fiscal and administrative management including maintaining communication with NIH and among MPIs and key personnel. At the study level, Dr. Burgess will chair the Investigator Steering Committee and the Implementation Science Teams. She will be part of the Regulatory, Data & Technology, Data &Safety Monitoring and Intervention Effectiveness project teams. The MPIs will work closely together and with the Data & Technology and Regulatory Teams to prepare annual reports. Drs. Burgess, Evans, and Hadlandsmyth will work together with the Coordinating Center leadership regarding any changes in the direction of the research project and any reallocation of funds, in accordance with NIH policy and permissions. The MPIs will be responsible for ensuring that the research is conducted in compliance with all appropriate federal rules and regulations. They will jointly lead weekly videoconferences with the project teams, reach out and participate in collaborations with the Coordinating Center and investigators from the other study centers, attend annual research meetings with the Steering Committee (virtually or in person), and will share responsibility for interpreting and presenting research findings.
Data access: Dr. Burgess will have access to protected health information (PHI). She will be involved in recruitment and obtaining informed consent. She will be involved in data analysis of coded and raw data.

University of Minnesota School of Nursing Center for Spirituality and Healing
Roni Evans, PhD, MS, DC
612-301-9006
Evans972@umn.edu
Duties: Dr. Evans will provide oversight to the entire project, jointly with the other MPIs, including development and implementation of all policies, procedures, and processes related to

the project and implementation of the scientific agenda, leadership plan, and all activities necessary to achieve the project aims. Jointly with the other MPIs she will ensure procedural mechanisms are in place to guarantee institutional compliance with US law and NIH policies including biosafety, human subject protection, data security, and facilities compliance. Dr. Evans will Chair the Intervention Effectiveness Team. The MPIs will work closely together and with the Data & Technology and Regulatory Teams to prepare annual reports. Drs. Burgess, Evans, and Hadlandsmyth will work together with the Coordinating Center leadership regarding any changes in the direction of the research project and any reallocation of funds, in accordance with NIH policy and permissions. The MPIs will be responsible for ensuring that the research is conducted in compliance with all appropriate federal rules and regulations. They will jointly lead weekly videoconferences with the project teams, reach out and participate in collaborations with the Coordinating Center and investigators from the other study centers, attend annual research meetings with the Steering Committee (virtually or in person), and will share responsibility for interpreting and presenting research findings.
Data access: Dr. Evans will have access to protected health information (PHI). She will be involved in conducting fidelity checks of health coaches. She will be involved in data analysis of coded and raw data.

University of Iowa Carver College of Medicine and Iowa City VA Healthcare System (VAHCS)
The current project has been approved for an exception to the single IRB rule. A separate IRB application will be submitted to the University of Iowa. The University of Iowa and the Iowa City VA Healthcare System are included in the HIPAA authorization form so identifiable data can be shared with both entities. Approved data sharing will be conducted via VA Box or another approved method.

Katherine (Katie) Hadlandsmyth, PhD
Katherine.hadlandsmyth@va.gov
katherine-hadlandsmyth@uiowa.edu
Duties: Dr. Hadlandsmyth will provide oversight to the entire project, jointly with the other MPIs, including development and implementation of all policies, procedures, and processes related to the project and implementation of the scientific agenda, leadership plan, and all activities necessary to achieve the project aims. Jointly with the other MPIs she will ensure procedural mechanisms are in place to guarantee institutional compliance with US law and NIH policies including biosafety, human subject protection, data security, and facilities compliance. Dr. Hadlandsmyth will chair the Advisor Engagement Team. The MPIs will work closely together and with the Data & Technology and Regulatory Teams to prepare annual reports. Drs. Burgess, Evans, and Hadlandsmyth will work together with the Coordinating Center leadership regarding any changes in the direction of the research project and any reallocation of funds, in accordance with NIH policy and permissions. The MPIs will be responsible for ensuring that the research is conducted in compliance with all appropriate federal rules and regulations. They will jointly lead weekly videoconferences with the project teams, reach out and participate in collaborations with the Coordinating Center and investigators from the other study centers,

attend annual research meetings with the Steering Committee (virtually or in person), and will share responsibility for interpreting and presenting research findings.
Data access: Dr. Hadlandsmyth will have access to protected health information (PHI) for both advisors and pilot and trial participants. She will be involved in recruitment of advisors. She will be involved in data analysis of coded and raw data.

Co-Investigators

University of Minnesota (UMN)
The University of Minnesota is included in the HIPAA authorization form so identifiable data can be shared with UMN project team members, including MPI Dr. Evans. Approved data sharing will be conducted via VA Box or another permitted method.

School of Medicine and Minneapolis VAHCS, CCDOR
Brent Taylor, PhD, MPH
612-467-4941
Brent.taylor2@va.gov
Duties: Dr. Taylor will be the senior statistician and methods expert, overseeing both the Data and Statistics Teams (responsibilities described below). He will serve as the Chair of the Regulatory Team and the Data and Technology Team and will serve as a member of the Investigator Steering Committee. He will also serve on the Biostatistics and Study Design PRISM/Collaboratory Work Group. Dr. Taylor will also participate in the interpretation of quantitative and qualitative data, manuscript preparation and other dissemination activities.
Data access: Dr. Taylor will be involved in data analysis of coded data. He will have access to protected health information only if necessary to maintain rigorous study methodology and/or for the safety of participants. He will not be recruiting, obtaining informed consent, or conducting surveys.

School of Medicine Department of Rehabilitation Medicine
John Ferguson, PhD
612-625-2661
Fergu170@umn.edu
Duties: Dr. Ferguson will serve on the Regulatory and Data and Technology Teams. He will provide guidance on Qualtrics and website related technologies and will support the ongoing processes of adaptation, optimization, troubleshooting, and implementation of the intervention assets in an online environment. He will also offer expertise in interpretation of quantitative and qualitative data, contribute to manuscript writing, and participate in other dissemination activities. He will serve on the on the Regulatory and Ethics PRISM/Collaboratory Work Group.
Data access: Dr. Ferguson will have access to protected health information (PHI). He will be involved in data analysis of coded and raw data. He will not be recruiting, obtaining informed consent, or conducting surveys.

Liberal Arts Technologies & Innovation Services (LATIS)
David Olsen, Research System Engineer
Duties: Mr. Olsen will develop code (e.g., API) to enhance communication between databases (e.g., Qualtrics FedRAMP and the internal VA participant tracking database) and with participants. Improving these lines of communication will assist in increasing participant retention, engagement, and maximizing data collection.
Data access: Mr. Olsen will not have access to protected health information. He will not be involved in recruiting subjects, obtaining informed consent, administering surveys procedures, or performing data analysis.

Sasha Zarins, Survey Methodologist and Project Designer
Duties: Ms. Zarins will provide expertise in developing online surveys, online communication with study participants, and Qualtrics programming.
Data access: Ms. Zarins will not have access to protected health information. She will not be involved in recruiting subjects, obtaining informed consent, administering surveys procedures, or performing data analysis.

School of Nursing Center for Spirituality and Healing

Alexander (Alex) Haley, JD, MBA, MS
612-301-9006
Haley045@umn.edu
Duties: Mr. Haley will work with Dr. Evans and other investigators to further develop and adapt RAMP to include individual coaching sessions, and additional materials to bolster Veterans' biopsychosocial health. He will also work closely with the investigators and staff to seamlessly integrate technology with intervention delivery to provide a user-friendly support resource for Veterans with pain. Mr. Haley will provide training and ongoing support to health coach Facilitators delivering the program; participate in the Intervention Effectiveness team; and conduct fidelity assessments of RAMP sessions. He will also work with investigators to make necessary adaptations of RAMP in preparation for the UH3/Phase 2 phase, and after its completion for implementation. Mr. Haley will also take part in the interpretation of study results and the preparation of scientific manuscripts and presentations.
Data Access: Mr. Haley will have access to protected health information (PHI). He will conduct fidelity checks of health coaches. He will be involved in data analysis of coded and raw data.

Brent Leininger, PhD, DC, MS
612-301-9006
Lein0122@umn.edu
Duties: Dr. Leininger will share patient support resources (e.g., exercise videos, workbooks) from his on-going NIH funded trial (R34AT011209) and associated protocols which can be modified for Veteran use in the RAMP program. Dr. Leininger will assist with training of health coaches in pain-related competencies and in the development of fidelity forms. He will also work closely with the investigators to develop the effectiveness and implementation data collection

instruments, monitor, analyze, and interpret the UG3/Phase 1 related milestones and intervention experience data. He will work with Dr. B. Taylor and his team to further develop the methods and to conduct the budget impact analysis as part of the UH3/Phase 2 and contribute to the qualitative analyses. Dr. Leininger will serve on the Investigator Steering Committee, Implementation Science Team, Data & Technology Team, and Regulatory Team. He will also serve on the PRISM/Collaboratory Electronic Health Record Work Group. He will participate in the preparation of manuscripts describing the design and results of the study.
Data access: Dr. Leininger will have access to protected health information (PHI). He will conduct fidelity checks of health coaches. He will be involved in data analysis of coded and raw data.

Indiana University

School of Medicine and Roudebush VAHCS
Marianne Matthias, PhD
317-278-2516
mmatthia@iupui.edu
Duties: Dr. Matthias will actively work with the team throughout each phase of the project. She will serve on the Implementation Science Team, and participate in advisor/partner data collection, interpretation of data, dissemination activities, and planning of next steps.
Data access: Dr. Matthias will be involved in interviewing/data collection of advisors/partners, performing data analysis, and interpretation of data. She will be interacting with advisors. She will not have access to protected health information or have direct contact with pilot/RCT participants (e.g., she will not be recruiting, obtaining informed consent, or conducting surveys).

University of California Los Angeles (UCLA)

Schools of Medicine and Public Health and West Los Angeles VAHCS
Stephanie Taylor, PhD
310-941-0291
Stephanie.taylor8@va.gov
Duties: Dr. Taylor will provide her nationally recognized expertise to assist in examining the effectiveness and implementation of CIH for pain. She will be an active participant on the PRISM/Collaboratory Implementation Science Work Group and the project-level Implementation Science Team. She will be integral to analysis, manuscript writing, and dissemination efforts.
Data access: Dr. Taylor will be involved in interviewing/data collection of advisors/partners, performing data analysis, and interpretation of data. She will be interacting with advisors. She will not have access to protected health information or have direct contact with pilot/RCT participants (e.g., she will not be recruiting, obtaining informed consent, or conducting surveys).

Consultant

John G. Serpa Consulting and West Los Angeles VAHCS
John (Greg) Serpa, PhD
310-343-3459
gregserpa@yahoo.com
john.serpa@va.gov
Duties: Dr. Serpa's primary role will be to serve on the Intervention Effectiveness and Implementation Science Teams, helping to develop strategies for implementing the RAMP intervention successfully within VA Whole Health. He will provide guidance on refining the RAMP program and on developing a successful model for training health coaches.
Data access: Dr. Serpa will be involved in performing data analysis and interpretation of coded data. He will not have access to protected health information or have direct contact with participants (e.g., he will not be recruiting, obtaining informed consent, or conducting surveys).

Project Staff

Minneapolis VAHCS, CCDOR

Role: Project Director
Lee Cross, MPH
612-629-7568
Lee.cross@va.gov
Duties: Ms. Cross will work closely with Drs. Burgess, Evans, and Hadlandsmyth and the entire rest of the team. She will plan and organize meetings, including the project team meetings, and document decisions and action items. Ms. Cross will lead the efforts to ensure all logistical and human subjects protection matters are taken care of for success during all phases of data collection. This will include planning videoconferences, IRB approvals, informed consent, incentive payment, and budgeting. She will take the lead in documenting all study procedures (e.g., mailing protocols, recruitment staff training, recruitment instructions, randomization procedures, telephone support line procedures, mental health crisis management, and communication with participants). She will provide training and guidance to staff in these procedures as well as in the conduct of human subjects research, good clinical research practices, and data privacy and security. Ms. Cross will serve as the manager between all sites and will be in regular contact with health coaches. She will also cross-train on Intervention Coordinator and Study Coordinator duties. She will be an active member of the Regulatory, Intervention Effectiveness, Implementation Science, Data & Safety Monitoring and Data & Technology teams. She will participate in data analysis, manuscript preparation, and other dissemination activities.

Data access: Ms. Cross will have access to protected health information. She will be involved in recruiting subjects, obtaining informed consent, administering survey procedures, and will be involved in data analysis of coded and raw data.

Role: Lead Intervention and Engagement Coordinator/Study Coordinator
Kimberly Behrens, MPH
612-467-1983
kimberly.behrens@va.gov
Duties: Ms. Behrens will be integral in the development of RAMP materials. In conjunction with Ms. Mahaffey, she will lead Health Coach training and day-to-day supervision, perform medical chart reviews as a step in determining participant eligibility, facilitate Patient Engagement Panel meetings, and be cross-trained on Project Director duties. She will coordinate and communicate with the Project Director, and provide regular progress reports, which will include required human subjects' research documentation and ensuring all human subjects' ethics regulations are followed. Ms. Behrens has extensive expertise in safety monitoring and crisis management and will be integral in developing and maintaining related protocols and procedures. She will be a member of the Intervention Effectiveness Team and actively participate in data analysis, manuscript preparation, and dissemination activities within traditional academic routes and without.
Data access: Ms. Behrens will have access to protected health information. She will be involved in recruiting subjects, obtaining informed consent, administering survey procedures, and will be involved in data analysis of coded and raw data.

Role: Intervention Coordinator/Study Coordinator

Role: Health Coach & Support Assistants

Raina Rooney, BS
612-467-4391
Raina.Rooney@va.gov

Duties: The Health Coach and Support Assistants will be trained and then facilitate RAMP intervention sessions. They will coordinate and communicate regularly with the Project Director and Intervention/Study Coordinator. They will provide regular progress reports and receive feedback, which will include required human subjects' research documentation and ensuring all human subjects' ethics regulations are followed.
Data access: They will have access to protected health information. They will be involved in recruiting subjects and obtaining informed consent. They may be involved in data analysis of coded and raw data.

Role: Research Assistant
Sarah Schroeder, MPH

Sarah.schroeder@va.gov
Duties: The Research Assistant will to assist the Project Director and Intervention/Study Coordinator, including with generating and sending recruitment materials, conducting randomization over the phone, retention and engagement efforts, answering participant questions, and miscellaneous tasks related to qualitative data collection and organization. They will assist as needed with study close-out and coordinating manuscript submissions.
Data access: The Research Assistant will have access to protected health information. They will be involved in recruiting and randomizing subjects, obtaining consent, and administering survey procedures. They may be involved in data analysis of coded and raw data.

Role: Data Management Team
Ann Bangerter, BS
612-467-1384
Ann.bangerter@va.gov
Duties: The data team offers support in the following areas: study design; database design and development; administrative data extraction; survey design, development and support; scannable technology; design, development and implementation of custom applications and web sites; project management; and technical writing. The team maintains a balanced portfolio of permissions allowing them as a group to access the full scope of data that are necessary for project support. For this project, the CCDOR Data Management Team will: 1) create the secure SQL database; 2) extract patient data from CDW for identified facilities; 3) extract primary care provider data from the Primary Care Management Module for identified patients; 4) support the study staff in designing and using the Qualtrics FedRAMP and VA REDCap software, supervise the data quality assurance process, and ensure secure data transmission between FedRAMP and VA VINCI servers; 5) support the study staff in designing and maintaining the study website; 6) request special permission from National Data Systems to access patient name and address information in order to create a patient mailing list for project staff; 7) extract and clean administrative data, and create data files for analysis; and 8) assist with preparation of reports and dissemination of results. Dr. Brent Taylor leads the Data team and provides overall coordination and planning for team activities. The Data team, along with Dr. Taylor will take an active role in coordination and planning of data sharing efforts (including HEAL data sharing).
Data access: Ms. Bangerter will have access to protected health information but will not have direct contact with participants (e.g., she will not be recruiting or obtaining informed consent). She will be creating coded data files for analysis.

Role: Statistics Team
Emily Hagel Campbell, MS
612-467-7451
Emily.hagelcampbell@va.gov
Duties: Ms. Hagel Campbell will handle day-to-day data analyses under Dr. Brent Taylor's supervision. Budgeted effort increases over the course of the 5-year project as data is collected and analysis needs increase. This includes time for clinical and data coordination to comply with

data sharing activities (including HEAL data sharing). Ms. Hagel Campbell will be involved in analyses for manuscripts and other dissemination products.
Data access: Ms. Hagel Campbell will be involved in performing data analysis of coded data. They will have access to protected health information. They will have no direct contact with participants (e.g., she will not be recruiting, obtaining informed consent, or conducting surveys).

Memoranda of Understandings (MOUs) and Subawards

Center for Veterans Research and Education (CVRE)
VA Non-profit Research Corporation (NPC)
Grant award funds go through CVRE.

- An MOU between CVRE and CCDOR will be created on an annual basis.
- Subawards between non-Minneapolis VA sites will be created at the beginning of the study and amendments will be created in subsequent study years.
- Authorization will be obtained before CCDOR study staff share any participant PII with CVRE staff. The reason for needing to share PII is to pay participants study incentives.

Role: Executive Director
Nadine Rogers
Nadine.rogers@cvre.org

Role: Grants Administration Manager
Pamela Sharpe
Pamela.sharpe@cvre.org

2.0 Protocol Summary

2.1 Synopsis

This research is part of a two-phase project (UG3/UH3) supported through the National Institutes of Health's Helping to End Addiction Long-term (HEAL) Initiative. The project is summarized below in Tables 1 and 2, and in Figure 1.

The following provides a synopsis for the **UG3 (Phase I)** of the project:

Table 1. UG3 (Phase 1) Synopsis	
Title:	UG3 (Phase I) Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP)

Study Description:	The UG3/Phase 1 will prepare for the future UH3/Phase 2 trial. It focuses on advisor engagement activities (Aim 1) and a single arm pilot study (Aim 2) to assess feasibility.
Objectives/Aims:	**UG3/Phase 1 Aim 1:** We will conduct advisor engagement activities including identifying and developing new community partnerships and using mixed methods data collection from multiple levels of advisors (n=35-50 patients, community partners, VA healthcare system leaders and staff), guided by the established REAIM/PRISM framework, to learn about key factors that can affect long-term adoption. **UG3/Phase 1 Aim 2:** We will conduct a *feasibility study* of 40 rural VA patients with chronic pain to assess the feasibility of delivering RAMP (pilot) in terms of recruitment and engagement, intervention fidelity and adherence, data collection, and other key metrics.
Endpoints:	**UG3/Phase 1 Aim 1:** advisors named, panels established, assessments collected and analyzed (implementation-related barriers and facilitators, resource needs, etc.) **UG3/Phase 1 Aim 2:** rates of recruitment, engagement, intervention fidelity adherence and data collection, and other key metrics
Study Population:	**UG3/Phase 1 Aim 1:** 35-50 patients, community partners, VA healthcare system leaders and staff. **UG3/Phase 1 Aim 2:** 40 rural VA patients from the VA healthcare system.
Phase or Stage:	First phase (UG3) of two-phase project (UG3/UH3).
Description of Sites/Facilities Enrolling Participants:	**UG3/Phase 1 Aim 1:** Advisors found nationally within VA and advisors found locally including those in VISNs (Veterans Integrated Service Networks) 7 and 23 (representing the Southeast and Midwest regions of the US) **UG3/Phase 1 Aim 2:** rural VA patients including those in VISN 7, which is the VA Southeast Network including Georgia, Alabama, and South Carolina.
Description of Study Intervention:	RAMP (pilot) is a 12-week program; it includes an individual session with the Health Coach, plus 11 group sessions including pre-recorded expert-led education videos, mind-body skills training and practice, and facilitated discussions.
Study Duration:	9 months from when study opens to enrollment until completion of data analysis
Participant Duration:	Each individual participant will take 8 months to complete all study-related tasks (enrollment to final follow-up data collection)

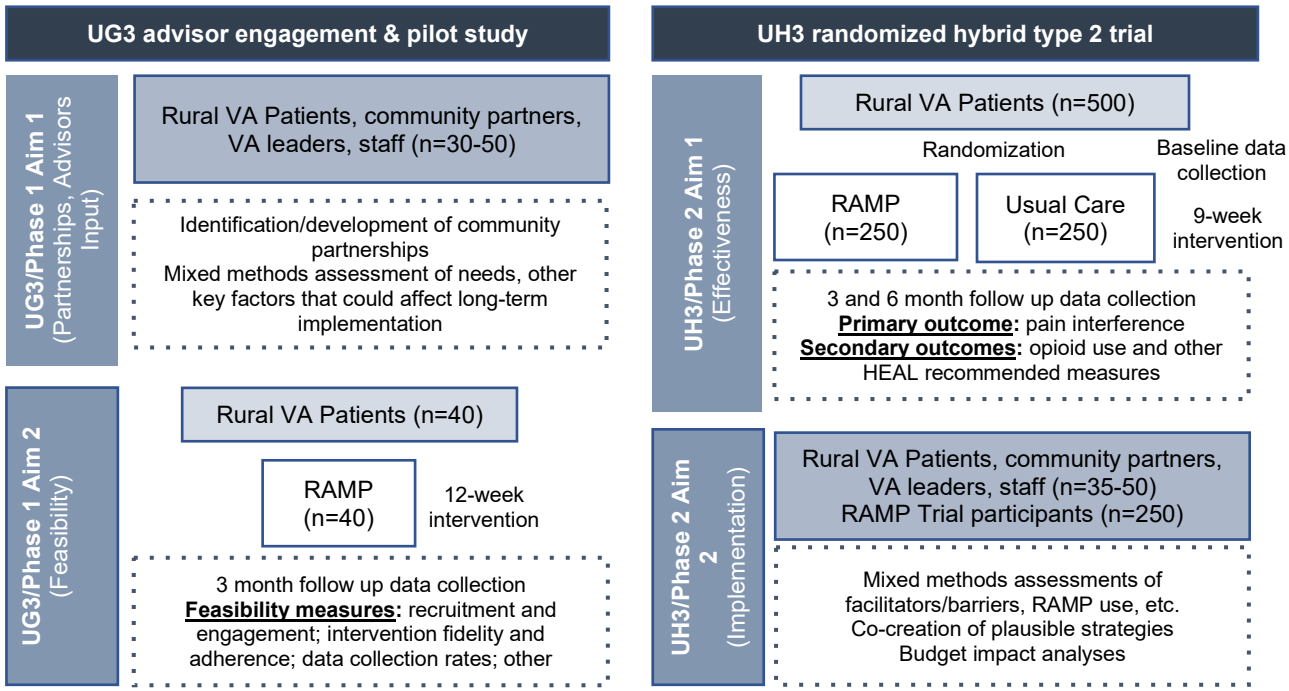
The following provides a synopsis for the **UH3 (Phase II)** of the project:

Table 2. UH3 (Phase II) Synopsis

Title:	UH3 (Phase II) Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP)
Study Description:	During the UH3/Phase 2 we will conduct a randomized hybrid type 2 effectiveness-implementation pragmatic clinical trial of RAMP compared to Usual Care, enrolling 500 rural VA patients from the VA healthcare system, oversampling female and racial/ethnic minority patients.
Objectives/Aims:	**UH3/Phase 2 Aim 1 (Effectiveness):** To assess the relative effectiveness of RAMP in rural patients in terms of pain interference (primary outcome) at 3 and 6 months and secondary outcomes of opioid use and other HEAL recommended outcomes. We will also perform additional exploratory analyses of women and minority Veterans' primary and secondary outcomes. **UH3/Phase 2 Aim 2 (Implementation):** To work iteratively with multiple levels of advisors (n=35-50 patients, community advisors, VA healthcare system leaders and staff) to evaluate intervention implementation strategies used in the trial and adapt these strategies to scale up RAMP within the national VA healthcare system. This will include: a. Conducting mixed-methods assessments of advisor and randomized trial participant views of implementation-related barriers and facilitators, resource needs, and other RE-AIM/PRISM domains. b. Working with advisors to co-create additional plausible strategies for overcoming barriers to implementation of RAMP in the national VA healthcare system. c. Conducting budget impact analyses using models informed by advisor views to inform future decision making.
Endpoints:	**UH3/Phase 2 Aim 1:** analysis of primary and secondary outcomes, rates of recruitment, engagement, intervention fidelity, adherence, and satisfaction, rates of follow-up data collection, and other key metrics **UH3/Phase 2 Aim 2:** assessments completed and analyzed, implementation strategies created, and budget impact analysis completed.
Study Population:	**UH3/Phase 2 Aim 1:** 500 rural VA patients from the VA healthcare system. **UH3/Phase 2 Aim 2:** 35-50 patients, community partners, VA healthcare system leaders and staff.
Phase or Stage:	Second phase (UH3) of two-phase project (UG3/UH3).
Description of Sites/Facilities Enrolling Participants:	**UH3/Phase 2 Aim 1:** rural VA patients including those in VISN 7, which is the VA Southeast Network and includes Georgia, Alabama, and South Carolina, and VISN 23, which is the VA Midwest Network and includes North Dakota, South Dakota, Nebraska, Minnesota, Iowa, and part of Illinois. **UH3/Phase 2 Aim 2:** Advisors found nationally within VA and advisors found locally including those in VISNs (Veterans Integrated Service Networks) 7 and 23 (representing the Southeast and Midwest regions of the US)
Description of Study Intervention:	RAMP is a 9-week program comprised of weekly group sessions including pre-recorded expert-led education videos, mind-body skills training and practice, and facilitated discussions.
Study Duration:	30 months from when study opens to enrollment until completion of data analysis
Participant Duration:	Each individual participant will take 12 months to complete all study-related tasks (enrollment to final follow-up data collection)

2.2 Project Overview

Figure 1. UG3/Phase 1 and UH3/Phase 2 Design Overview



We have applied complementary models and frameworks to facilitate the project's long-term objective (see **C.2 Guiding Theoretical Models and Frameworks**).

RE-AIM/PRISM: provides overall guidance for improving and measuring Reach, Effectiveness, Adoption, Implementation and Maintenance of the RAMP intervention.

COM-B Model: provides guidance for assessing needs, facilitators and barriers and identifying intervention solutions aligned with desired outcomes.

Dynamic Biopsychosocial (BPS) Model: provides insight into whole person needs and BPS risk and protective factors, including social determinants of health (SDH)

2.3 Schedule of Activities (SOA)

Table 3. Schedule of Activities for UG3/Phase 1 Pilot/Feasibility (Aim 1) and UH3/Phase 2 RCT (Aim 2)	**Screener**	**BL**	**Enrollment call**	**Intervention Sessions**	**3m to up to the start of 6m assessment**	**6m + 3m (UH3/Phase 2 only)**
Feasibility of recruitment, enrollment, intervention, and data collection rates (see 2.4 Milestones for more detail)	x	x	x	x	x	
Inclusion/Exclusion criteria	x		x			
Demographic (including core SDH measures)		x				
Consent			x			
Enrollment/randomization			x			
Primary Outcome						
Pain interference (BPI)	x	x			x	x
Secondary Outcomes						
Pain intensity (BPI)		x			x	x
Pain impact (GCPS-R)		x			x	x
Quality of life (WHO QOL 2 item & EQ5D5L)		x			x	x
Use of opioids (self-report, EHR)		x			x	x
Physical function (PROMIS)		x			x	x
Sleep (PROMIS)		x			x	x
Fatigue (PROMIS)		x			x	x
Anxiety (GAD2)		x			x	x
Depression (PHQ2)		x			x	x
PTSD (PC-PTSD-5)		x			x	x
Participation in social roles and activities (PROMIS)		x			x	x
Global improvement and satisfaction (PGIC)					x	x
Use of CIH and non-pharmacological pain management		x			x	x
Adverse events				x	x	x
Mediation Measures						
Pain catastrophizing (PCS)		x			x	x
Pain management self-efficacy (PROMIS)		x			x	x
Perceived stress (PSS)		x			x	x
Body Awareness (MAIA)		x			x	x
Other Measures						
Substance Use Screener (TAPS)		x			x	x
Intervention-related measures*					x	x

BL=baseline; 3m=3 months; 6m=6 months; SDH=social determinants of health; BPI=brief pain inventory; GCPS-R=graded chronic pain scale-revised; WHO QOL=World Health Organization Quality of Life; EQ5D5L=5-level Euro Quality of Life-5D; PROMIS=patient-reported outcomes measurement information system; GAD2=generalized anxiety disorder; PHQ2=patient health questionnaire depression scale; PC-PTSD-5=PTSD checklist for DSM-5; EHR=electronic health record; PCS=pain catastrophizing scale; PSS=perceived stress scale; MAIA=multidimensional assessment of interoceptive awareness; TAPS=Tobacco Alcohol Prescription medications and other Substance; *Intervention related measures are also considered patient-level RE-AIM/PRISM measures.

2.4 Milestones

2.4.1 UG3/Phase 1 Milestones

UG3/Phase 1 Milestone Timeline (Years 1-2 of Project)	Year 1												Year 2											
Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Quarter	1	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6	7	7	7	8	8	8
Agreements and Regulatory Approvals																								
All necessary approvals received (IRB, NIH, DSMB) for all required protocols and plans (e.g., clinical protocol; accrual/retention plan, data and safety monitoring plans)																								X
Advisor Engagement																								
Community-based partners named																								X
Multi-level (patient, community, and VA) advisor/partner panels established																								X
Multi-level advisor assessments (of implementation-related barriers and facilitators, resource needs, and other RE-AIM/PRISM domains) collected and analyzed (n = 35-50)																								X
Pilot Study																								
Recruitment and Enrollment																								
40 rural-dwelling VA patients recruited																		X						
At least 35% female and 35% racial/ethnic minority patients recruited																		X						
Experimental Intervention																								
75% satisfied with RAMP program																								X
75% of intervention participants attend/engage with recommended # of sessions (≥ 7/12)																								X
Health Coach Facilitators deliver 90% of session activities 90% of the time																								X
Data Collection																								
>80% complete post-treatment data collection (at 3 months)																							X	
Key: DSMB=Data and Safety Monitoring Board; IRB=Institutional Review Board; NIH=National Institutes of Health; VA=Veterans Healthcare Administration.																								

Successful completion of these milestones will establish the feasibility of our processes and ensure that we are prepared for the proposed UH3/Phase 2 randomized hybrid type 2 effectiveness-implementation pragmatic clinical trial of RAMP.

2.4. UH3/Phase 2 Milestones

UH3/Phase 2 Timeline (Years 3-5 of Project).	Quarter
Administrative	
All staff hired and trained	10
Manual of Procedures (MOP) finalized	12
100% compliance with PRISM Program policies and practices, including workgroup participation (Annual)	12, 16, 20

100% compliance with Protocol (Annual)	12, 16, 20
100% compliance with Data and Safety Monitoring Plan (Annual)	12, 16, 20
Investigator Steering Committee meets monthly & project teams meet 1-4X/monthly (Annual)	12, 16, 20
All staff maintain "trained" status each year including required human subjects training (Annual)	12, 16, 20
Results submitted to clinicaltrials.gov	20
Final report submitted	20
UH3 Aim 1: Randomized Trial	
Recruitment and Enrollment	
Study Open to Enrollment	10
50% total sample enrolled (w/ completed baseline) per year (35% female; 35% racial/ethnic minority)	13, 17
Intervention delivery	
50% total sample participate in intervention per year (Annual)	15, 19
75% satisfied with RAMP program	19
75% of intervention participants attend/engage with recommended # of sessions (≥ 6/9)	19
15% of intervention sessions fidelity checked and Health Coach Facilitators achieve high fidelity rates (> 90%)	18
Data assessment and retention (Assess all participants at 3- and 6-month timeframes)	
Data collected at 3 and 6 months for 50% of participants per year	15, 19
> 80% of participants each year retained for primary outcome at 6 months	15, 19
Data analysis	
Final dataset transferred to statisticians for data analysis	20
Aim 1 data analysis completed	20
UH3 Aim 2: Implementation Aim	
Meet with patients and community advisors at least 3X/year	12, 16, 20
Meet with VA advisors at least 1X/year.	12, 16, 20
Aim 2a. Conduct mixed-methods assessments of advisor and randomized trial participant views of implementation-related barriers and facilitators, resource needs, and other RE-AIM/PRISM domains	
Aim 2a data collection and data analysis completed	20
Aim 2b. Work with advisors to co-create additional plausible strategies for overcoming barriers to implementation of RAMP in the national VA healthcare system	
Aim 2b process plans and implementation strategies completed	20
Aim 2c: Conduct budget impact analyses using models informed by advisor views to inform future decision making	
Aim 2c budget impact analysis completed	20
Implementation and Dissemination	
Experimental intervention Adaptations	
Necessary intervention adaptations based on results completed	20
Dissemination and manuscript writing	
Design manuscript submitted	11
Main trial results manuscript submitted	20
Main implementation results manuscript submitted	20
Ongoing learnings disseminated via channels identified by multi-level advisors	12, 16, 20

3.0 Introduction

3.1 Study Rationale

This project addresses the significant challenge of implementing effective, non-opioid interventions for chronic pain management in rural and remote dwelling Veteran populations. Pain is a complex biophysical, psychological, and social (BPS) condition and there is a growing evidence base to support several complementary and integrative health (CIH) approaches, which can address pain in a more holistic way. While the VA has become a leader in advancing CIH through its Whole Health Initiative, there remain many barriers, especially for rural patients. Our team has co-developed, with multiple-levels of VA advisors (including rural patients), an innovative telehealth evidence-based intervention that builds upon our team's previous research. The Reaching **R**ural Veterans: **A**pplying **M**ind-Body Skills for **P**ain Using a **W**hole **H**ealth Telehealth Intervention (**RAMP**) project strategically coalesces multiple evidence-based CIH self-management strategies to address Veterans' BPS needs and overcome existing barriers. Comprised of pain education, mindfulness, pain specific exercises, and cognitive behavioral strategies, the program is cohesive and scalable, and designed to meet the needs of VA interest holders. RAMP is a 9-week program comprised of group sessions including pre-recorded expert-led education videos, mind-body skill training and practice, and facilitated discussions. For the preparatory phase (UG3/Phase 1) we will conduct 1) ***advisor engagement activities*** including identifying and developing new community partnerships and using mixed methods data collection from multiple levels of advisors (n=35-50 patients, community partners, VA healthcare system leaders and staff), guided by the established RE-AIM/PRISM framework, to learn about key factors that can affect long-term adoption; and 2) conduct a ***pilot study*** of 40 rural VA patients with chronic pain to assess the feasibility of delivering RAMP (pilot) in terms of recruitment and engagement, intervention fidelity and adherence, data collection, and other key metrics. For the UH3/Phase 2, we will conduct a randomized hybrid type 2 effectiveness-implementation multi-site pragmatic clinical trial of RAMP compared to Usual Care, among rural patients (n=500) in the VA healthcare system. UH3/Phase 2 Aim 1 will assess the relative effectiveness of RAMP in terms of the **primary effectiveness outcome** of pain interference at 3 and 6 months and **secondary outcomes** including opioid use and other HEAL recommended outcomes. In UH3/Phase 2 Aim 2 we will work iteratively with multiple levels of advisors (from UG3/Phase 1) to evaluate intervention implementation strategies used in the trial and adapt these strategies to scale up RAMP within the national VA healthcare system. This will include: a) conducting mixed-methods assessments of advisor and randomized trial participant views of implementation-related barriers and facilitators, resource needs, and other RE-AIM/PRISM domains; b) working with advisors to co-create additional plausible strategies for overcoming barriers to implementation of RAMP; and c) conducting budget impact analyses using models informed by advisor views to inform future decision making.

3.2 Background

Chronic pain is a pervasive problem in the United States that disproportionately affects Veterans.[4] The Veterans Healthcare Administration (VA) is the nation's largest integrated care system, serving over 9 million Veterans, including 2.7 million rural-dwelling Veterans.[3,34] Two-thirds of all Veterans report chronic pain, resulting in significant functional limitations and high healthcare utilization.[4,35]The most common chronic pain conditions among VA patients are

musculoskeletal disorders, with joint pain, back pain and osteoarthritis having the highest prevalence.[36] Despite reductions in overall opioid prescribing across the VA in recent years, there remains a significant subset who continue to receive long-term opioid medications for chronic pain.[37,38] VA patients are more likely than the general population to be treated with opioids,[39] and rural VA patients are disproportionately prescribed these medications.[8] Further, VA patients have nearly twice the rate of accidental fatal poisoning as US adults overall, and opioid analgesics are the drug class most commonly involved in these deaths.[5]

Pain in Rural America. Rural-dwelling individuals in the United States have increased prevalence of pain, less access to comprehensive chronic pain care, are more likely to be prescribed opioid medications, and experience greater harms from opioids compared to urban residents.[1,2,7,40-43] Rural VA patients receive over 30% more opioids than urban VA patients,[8] are less likely to receive comprehensive and specialty pain care,[6,7] and are less likely to use self-management interventions for pain.[9] Compared to men, female VA patients have greater rates of pain, are more likely to experience multiple comorbid chronic pain conditions,[10,44] and rural-dwelling female VA patients receive more pharmacologic and less specialty pain care, relative to their urban counterparts.[6]

The Need for Whole Health Approaches to Pain Management. Pain, like most health conditions, has become widely recognized as more than a physical phenomenon. It is a complex condition influenced by interrelated biophysical, psychological, and social (BPS) factors.[18,19] Pain is frequently associated with psychological risk factors including poor cognitive and emotional coping strategies, depression, catastrophizing, and fear avoidance behaviors.[45,46] There is also growing evidence that social determinants of health are associated with greater likelihood of chronic pain and poorer outcomes.[47-49] Lack of social support,[50-52] and occupation and related factors such as physical workload, education, injury compensation, and dissatisfaction can also have a negative effect on pain.[43,46] Poor quality relationships, social stressors (e.g., due to racism, ostracism, injustice, invalidation, isolation), and low income and education status also have been shown to contribute to poor outcomes.[43,53,54] Further, there is growing recognition of the important intersections among trauma, violence, substance use, and pain.[55] Veterans in the VA healthcare system are especially impacted by these factors; they have lower levels of income and education and higher levels of trauma exposure compared to non-Veterans and Veterans not enrolled in VA care.[56,57] Compared to men, female VA patients are more likely to report history of interpersonal trauma, military sexual trauma, mood disorders, and anxiety disorders,[10,44] all of which can adversely affect treatment outcomes. Rural-dwelling female VA patients are even more impacted, with a high probability (50%) of interpersonal and/or sexual traumas,[58] high rates of emotional distress, and low levels of social support.[10,11,58]

To reduce the burden of pain, patients require greater access to evidence-based care that addresses their "whole-person" or biopsychosocial needs.[59-61] There has been a growing recognition that pain, like other chronic health conditions, requires ongoing attention to lifestyle factors and engagement in effective self-management.[62,63] While patients recognize the need

for self-management strategies, they often need support and validation to initiate and maintain optimal self-care. [64,65]

The VA and Whole Health: In response to the opioid crisis which has disproportionately affected Veterans, [4] the VA has adopted policies and devoted resources to replace opioid-centric models of pain management with multi-modal approaches that prioritize evidence-based non-pharmacological pain treatments, including evidence-based complementary and integrative health (CIH) approaches. [66-73] The VA's Office of Patient Centered Care and Cultural Transformation (OPCC&CT) has significantly expanded the provision of CIH services over the last decade, supported by the passage of the Comprehensive Addiction and Recovery Act in 2016. [33,74] Central to this has been the implementation of a Whole Health model of care which aligns with established BPS models of pain. In the U.S., the VA is recognized as a national leader in Whole Health and nearly one third of VA patients with pain engage in some Whole Health services. [33] Noteworthy is the threefold reduction in opioid use that has been observed among VA patients with chronic pain who engaged Whole Health services compared to those who have not. [33]

CIH and Non-Pharmacologic Self-Management Interventions: There are a range of evidence-based ***CIH and non-pharmacologic self-management modalities*** for improving pain outcomes, [20,76-81] including psychological strategies (e.g., behavioral or cognitive), mind-body approaches (e.g., mindfulness practices, meditation, relaxation, guided imagery), physical activity (e.g., general and rehabilitative exercise, yoga, tai chi), lifestyle advice (e.g., for sleep, daily activities, social support), and pain education (e.g., pain neuroscience, and pain management tips). [82,83]

Mindfulness-Based Interventions (MBIs) are an especially popular CIH approach and central to the VA's Whole Health model for promoting health. [75] MBIs have been shown to improve chronic pain through multiple pathways[84-86] and have demonstrated effectiveness for improving conditions commonly co-occurring with chronic pain in VA patients, such as PTSD, sleep disorders, depression, and substance abuse. [87-89] MBIs have also demonstrated promise for improving opioid-related outcomes. [90] Results by our team have found a group telehealth MBI for pain can be safely delivered, is acceptable, engaging, and improved pain and other biopsychosocial outcomes among Veterans with chronic pain and high levels of psychiatric comorbidity. We have also found a similar group MBI to be significantly more satisfactory and effective in increasing mindfulness and social connectedness than an active control in older adults in a community-based setting. However, because of the complex biopsychosocial nature of chronic pain, as well as heterogeneous treatment responses and varied preferences and needs, MBIs alone (or any other single approach) are unlikely to meet the chronic pain needs of the majority of VA patients. [22,54] Indeed, this was the case in our prior group telehealth MBI for pain, in which 34% experienced a meaningful improvement (30% or greater) at 10 weeks, compared to those in Usual Care (16%). Importantly, VA patients have expressed a desire for more integration of multiple modalities (e.g., mindfulness with more physical movement). [91] Indeed, interventions integrating multiple evidence-based approaches are increasingly advocated to optimize pain management. [22] Multimodal approaches that support patients in

better self-managing their emotional reactions, unhelpful coping and thinking patterns, and maladaptive behaviors (e.g., activity avoidance, inactivity, substance over use) are especially promising, particularly for pain sufferers experiencing intersecting biopsychosocial challenges. [61]

Whole Person CIH Self-Management. There has been a growing number of multi-modal CIH self-management programs that address pain from a whole-person perspective (i.e., taking into account BPS factors), [92-94] including in our own research. [25] Evidence shows that such programs can lead to improved pain and health behaviors, self-efficacy, and overall health. [92,95-97] In much of the research, however, effect sizes are modest, and the research is limited by inattention to underlying theoretical frameworks that align individuals' specific pain-related needs with appropriate program elements. [63,92,95,98] A major limitation of the existing research of multi-modal CIH self-management programs is that most of the study populations have been mainly White, highly educated, with relatively high levels of self-reported health. [92,95 96,97] This leads to questionable generalizability to Veterans and rural-dwelling populations, including those from racially diverse backgrounds, who are more likely to experience negative social determinants of health and poorer health outcomes. [56,57]

Barriers to CIH and Whole Health Care: Although the VA has made great strides in providing CIH approaches to pain, as part of its Whole Health model of care, these approaches remain underutilized, [99] particularly among rural VA patients. [6,7,9] Studies with VA patients, leadership, and frontline staff managers, including those conducted by our team, have identified key barriers and facilitators to widespread implementation of CIH in the VA, [64,72,73,100-107] including for rural populations. [6,24] Examples include difficulty traveling to the main VA medical centers where CIH services are offered, [24,108] need for a provider referral, [109,110] as well as lack of awareness and knowledge about CIH options for pain. [21-23] Additionally, some female VA patients are reluctant to go to the VA in person due in part to experiences of sexual harassment[111] and history of military sexual trauma. [112]

Telehealth in the VA: Telehealth is an evidence-based approach for delivering healthcare, which can reduce some of the barriers to care and improve appointment attendance and patient satisfaction. [113-116] The VA is the largest federal provider of telehealth services, [117] which rapidly expanded with the onset of the COVID-19 pandemic. [118] In 2022, more than 2.3 million Veterans used VA telehealth services. [119] Recent studies have demonstrated the effectiveness of telehealth programs for rural Veterans, [113,120,121] including those with chronic pain. [24,108,122] The VA's Office of Connected Care (OCC), which oversees the VA's Telehealth Program, has developed multiple programs to facilitate remote access to telehealth care, in conjunction with the Office of Rural Health (ORH). These efforts include the OCC's work to enhance telehealth options and provide mobile applications to support clinical services and overall patient health, with particular attention to the needs of rural Veterans, who experience greater barriers to accessing telehealth than urban Veterans. [118,123] The OCC has also developed innovative programs to increase access to telehealth such as the Accessing Telehealth through Local Area Stations (ATLAS) program, which offers convenient locations in communities to access the internet for telehealth services, [124] as well as programs that distribute tablets to VA patients. [125]

This project is innovative in its comprehensive and rigorous assessment of a multi-component CIH telehealth intervention in the nation's largest health system, the VA. Optimized to meet Veterans' BPS needs, we will address critical barriers that currently exist to supporting rural Veterans' pain care. Our approach will not only support larger scale implementation across the VA but will serve as a model for non-VA organizations to integrate novel solutions that promote equitable access to evidence-based non-opioid pain care across rural America.

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

The risks across study phases and aims are summarized in Table 4.

Table 4. Risks According to Study Phase and Aims

Study Phase (Aims)	Approach (Population)	Risks	Risk Level
Phase I (UG3 Aim 1)	Advisor engagement (patients, community partners, VA healthcare system leaders and staff)	Breach of confidentiality/privacy	Minimal
Phase I (UG3 Aim 2)	Feasibility/Pilot Study (Study Participants with Pain)	Breach of confidentiality Completing health surveys Group education programs Natural history of pain	Minimal
Phase II (UH3 Aim 1)	Randomized Hybrid Effectiveness-Implementation Trial (Study Participants with Pain)	Breach of confidentiality Completing health surveys Group education programs Natural history of pain	Minimal
Phase II (UG3 Aim 2)	Advisor engagement (patients, community partners, VA healthcare system leaders and staff)	Breach of confidentiality/privacy	Minimal

Advisors: New information will be gathered from advisors and is not anticipated to place them at risk of criminal or civil liability or be damaging to their financial standing, employability, educational advancement, or reputation.

Research Participants: The potential risks to study participants of the UG3/Phase 1 Pilot Study and UH3/Phase 2 Randomized Trial are considered minimal. They include:

Breach of Confidentiality and Privacy. New information will be gathered from participants and is not anticipated to place individuals at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

Completing Health Surveys. Participants will be asked to complete health surveys as part of the screening and follow up data collection; they may feel uncomfortable answering questions they feel are too personal.

Taking Part in Group Based Behavioral Interventions. Participants will be asked to take part in group behavioral interventions (via a VA-approved videoconferencing program, for example, Webex); the interventions are not physically invasive, embarrassing, or offensive, and not expected to have adverse lasting impact. Some participants may experience some anxiety or nervousness when participating in group activities.

RAMP Program (Experimental Intervention). Risks associated with the experimental educational intervention may occur in program sessions and practicing on one's own. Expected risks are mild short-lasting physical discomfort (e.g., muscle and joint soreness) as a result of performing short periods of exercises (~5-10 minutes); participants might also feel emotional when doing the brief mind-body practices (~5-10 minutes) which include mindfulness and behavioral coping strategies (e.g., relaxed breathing, guided imagery, progressive muscle relaxation).

See Appendix A – DSMP for additional detail about the known potential risks.

3.3.2 Known Potential Benefits

Advisors: We anticipate few direct benefits to advisors taking part in UG3/Phase 1 Aim 1 and UH3/Phase 2 Aim 2, although in similar studies we have found that participants find it valuable to be able to share their perspectives with researchers and with each other (for members of the Veteran Engagement Panel and Community Engagement Panel).

Research Participants: The research participants taking part in the UG3/Phase 1 Feasibility/Pilot Study and UH3/Phase 2 Randomized Trial (potentially both intervention and UC conditions) may benefit from learning new information about pain. They may experience health benefits, particularly improvements in their ability to self-manage their pain condition and improve related outcomes (decreased pain intensity and interference, impact, medication use; increased quality of life, function). Consequently, the benefits of participation are likely to exceed the risks.

It is possible that participants will experience no direct benefit from taking part in this research study (in particular, we believe this more likely to be the case for the UC condition). Still, the information participants provide from this study might help us treat future patients with chronic pain. This research will help guide the development of strategies to improve health care within the VA Healthcare system, particularly for patients with chronic pain and underserved subgroups (e.g., women, rural-dwelling, racial/ethnic minorities).

3.3.3 Assessment of Potential Risks and Benefits

This project addresses the significant challenge of delivering nonpharmacological treatment for chronic pain to a large number of rural-dwelling patients, many of whom have co-morbid conditions that contribute to and are exacerbated by their chronic pain. The proposed research poses “minimal risk” to subjects. There are no experimental procedures involved in this study. The potential risks to study participants include a negative reaction to all or parts of the intervention program, and loss of privacy and confidentiality. There are minimal economic and social risks with participating.

Protections Against Risk

Privacy, confidentiality, and data security. There is a very small risk of breach of confidentiality and privacy. Protections are in place to ensure a breach does not occur.

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

Research Participants: Pilot/Feasibility and RCT participant confidentiality will be safeguarded by the use of password protected databases and locked file cabinets. Research databases will be stripped of all identifying information, with keys identifying individual subjects available only to the MPIs or selected designees.

All Participants: All participants will have the option of skipping any interview or questionnaire questions they do not wish to answer. Further, access to identifiable private information from study participants will only be accessible to study related personnel who have met the training requirements for the responsible conduct of research, HIPAA and data security and have completed all initial and annual study specific training. See section 5.5 Study Evaluations – Data Collection and 7.0 Privacy and Confidentiality for more security details.

Study Personnel Training. Prior to initiation of participant enrollment (and annually thereafter), all project personnel will undergo project specific human subjects training that addresses risks to subjects; protection against risks; potential benefits of research to subjects and others; and the importance of knowledge to be gained. Additionally, all study personnel will be required to

complete training in the Responsible Conduct of Research every three years. This includes online CITI training in responsible conduct of research, good clinical practice, and human research protections.

Participant Screening. Potential research participants will undergo a baseline evaluation to ensure they meet eligibility criteria, and it is safe for them to participate. Adverse events will be minimized by identifying and excluding patients at high risk during the screening process (described in section 5.4 Inclusion/Exclusion criteria).

Intervention. Participants will be monitored for side effects and adverse events during all study intervention sessions. The RAMP intervention is considered an introductory program and has been designed to minimize risks and meet the needs and skill level of participants. RAMP integrates mindfulness practices, pain education, pain-specific exercises, and cognitive and behavioral strategies. Based on our previous studies and the existing literature, we believe RAMP to be minimal risk. It is expected that some participants may experience limited and short-lasting physical and/or mental agitation. All participants will be provided health contact information as part of the study materials (e.g., workbook, website). Contact information will include the national Veterans Crisis Line (dial 988 and press 1) and local VA Healthcare System contacts.

Intervention facilitators (health coaches) will be trained by investigators and monitored for fidelity to ensure they are implementing the interventions in a manner that optimizes patient safety. This will include how to monitor for potential emotional or physical discomfort during session activities and how to implement safety procedures if needed.

Project Personnel Support. All participants will have access to the telephone support line and email address, staffed by trained team members, who will provide technical assistance and be able to answer basic questions related to intervention. We will continually update our procedures and manual of operations to reflect commonly asked questions.

Our team has developed safety procedures to address any physical or mental issues in real-time. Our aim is always to keep participants safe, give them resources they might need, and adhere to timely adverse event classification and reporting (e.g., severe adverse events (SAEs), unanticipated problems (UAPs), and adverse events (AEs)). If the participant endorses self-harm ideation or is in emotional distress (e.g., in session, on the phone with a member of the study staff, via email), staff will follow a mental health protection for human subjects procedures, on which all study staff will be trained. This procedure has been used successfully in a similar study conducted by MPI Burgess (NH170001).

All participants will be encouraged to contact the project staff (e.g., project director, an investigator) and their primary care physician regarding any side effects or adverse events that occur. Adverse events impacting participant safety may result in withdrawal from the study intervention.

Participants will be asked about potential adverse events in all self-report surveys. Participants will be asked to report side effects/adverse events related to the interventions by choosing from a list generated from the literature and the investigators' experience (see below). In addition, we will query any new or worsening issues.

Question: <u>Since you started your participation in the study</u> have you experienced any of the following? Check all that apply.

- Worsening pain
- Increased muscle soreness
- Feeling more upset than usual when something reminded you of the past
- Increased feelings of sadness
- Increased feelings of anxiousness
- Feeling more tired or fatigued than usual
- Feeling more isolated or lonely
- Other physical or mental symptoms (please describe)

Please let us know if you think these symptoms were possibly related to the study

- [Show selected items with yes/no for related to study]
- [If yes] Please explain what happened: _____

Question: <u>Since your survey</u>, have you experienced a NEW or WORSENING medical issue or event which resulted in any of the following?

a. Required you to stay overnight in a hospital?

No
Yes

- When did this occur?_____
- What happened?_____
- Are you still being treated for this?
  - No
  - Yes
- Anything else you want to share about this?_____

b. Experienced a problem that resulted in a severe or permanent disability?

No
Yes

- When did this occur?_____
- What happened?_____
- Are you still being treated for this?
  - No
  - Yes

- Anything else you want to share about this?_____

c. Experienced a life threatening injury or event?

No
Yes

- When did this occur?_____
- What happened?_____
- Are you still being treated for this?
  - No
  - Yes

  Anything else you want to share about this?_____

4.0 Objectives and Endpoints

This project addresses the significant challenge of implementing effective, non-opioid interventions for chronic pain management in rural and remote dwelling Veteran patients. [1,2] The Veterans Healthcare Administration (VA) is the nation's largest integrated healthcare system and serves an estimated 2.7 million rural Veterans. [3] Rural Veterans experience a disproportionate share of the national pain burden, with more chronicity, opioid harms, comorbid mental health conditions and substance abuse, compared to non-rural Veterans and non-Veterans. [4,5] Rural Veterans are also less likely to receive comprehensive and specialty pain care, [6,7] are prescribed over 30% more opioids, [8] and are less likely to use self-management interventions for pain than non-rural Veterans. [7,9] Importantly, rural women and minority Veterans living in rural areas experience additional challenges that prevent equitable pain care. [6,10-17]

Pain is a complex biophysical, psychological and social (BPS) condition[10,11] and there is a growing evidence base to support several complementary and integrative health (CIH) approaches to manage chronic pain in a more holistic way. [18-20] While the VA has become a leader in advancing CIH through its Whole Health Initiative, there remain many barriers, especially for rural patients. This includes lack of awareness/knowledge about CIH, shortage of availability and accessibility of CIH/Whole Health pain care services, and absence of the necessary support to successfully engage in CIH self-management. [3,21-24]

Our long-term objective is to improve pain management and reduce opioid use among rural patients in the VA. Our multidisciplinary team has co-designed, with multiple levels of advisors, an innovative telehealth/virtual intervention that builds upon our team's previous research. [6,25-32] The Reaching **R**ural Veterans: **A**pplying **M**ind-Body Skills for **P**ain Using a Whole Health Telehealth Intervention (**RAMP**) project strategically coalesces multiple evidence based CIH self-management strategies to address Veterans' BPS needs and overcome existing barriers. Comprised of mindfulness training, pain education, pain specific exercises, and cognitive behavioral strategies, the program is cohesive and scalable. RAMP is a 9-week program comprised of weekly group sessions with pre-recorded expert-led education videos, mind-body

skill training and practice, and facilitated discussions. To ensure long-term sustainability, we will collaborate with advisors including Veteran patients and an established network of VA health system partners including the Office of Rural Health; the Office of Pain Management, Opioid Safety, & Prescription Drug Monitoring (which has been investing in telehealth for pain); and the Office of Patient Centered Care and Cultural Transformation. We will also cultivate new community partnerships with the VA's Community-Based Outpatient Clinics (CBOCs) and local and national Veteran organizations. There are two phases to the project, a UG3 and UH3.

The specific aims for the UG3/Phase 1 and UH3/Phase 2 of the project are:

UG3/Phase 1 Aim 1: We will conduct ***advisor engagement activities*** including identifying and developing new community partnerships and using mixed methods data collection from multiple levels of advisors (n=35-50 patients, community partners, VA healthcare system leaders and staff), guided by the established REAIM/PRISM framework, to learn about key factors that can affect long-term adoption.

UG3/Phase 1 Aim 2: We will conduct a ***feasibility study*** of 40 rural VA patients with chronic pain to assess the feasibility of delivering RAMP (pilot) in terms of recruitment and engagement, intervention fidelity and adherence, data collection, and other key metrics.

UH3/Phase 2 Aim 1: We will conduct a ***randomized hybrid type 2 effectiveness-implementation pragmatic clinical trial (RCT)*** of RAMP compared to Usual Care, randomizing 500 rural VA patients from the VA healthcare system, oversampling female and racial/ethnic minority patients. The aim is to assess the relative effectiveness of RAMP in rural VA patients in terms of pain interference (**primary outcome**) at 3 and 6 months and **secondary outcomes** of opioid use and other HEAL recommended outcomes. We will ask intervention participants about their experience with the RAMP program. We will also perform additional exploratory analyses of women and minority Veterans' primary and secondary outcomes.

UH3/Phase 2 Aim 2: We will work iteratively with multiple levels of advisors (n=35-50 patients, community partners, VA healthcare system leaders and staff) to evaluate intervention implementation strategies used in the trial and adapt these strategies to scale up RAMP within the national VA healthcare system. This will include:

a. Conducting mixed-methods assessments of advisor and randomized trial participant views of implementation related barriers and facilitators, resource needs, and other RE-AIM/PRISM domains.

b. Working with advisors to co-create additional plausible strategies for overcoming barriers to implementation of RAMP in the national VA healthcare system.

c. Conducting budget impact analyses using models informed by advisor views to inform future decision making.

5.0 Study Procedures

5.1 Overall Design

This is a two-phase study with a UG3 phase in years 1-2 and a UH3 phase in years 3-5 (see Figure 1).

5.1.1 Advisor Engagement

We will ask the stakeholders to complete iterative qualitative assessments and use participatory research methods to collaborate and problem solve for implementing RAMP given the internal and external contexts that may be affecting the VA and Whole Health System initiatives at the time. Data collection will include a combination of primary data collection via surveys, qualitative interviews, and focus groups. Meeting times will be agreed upon ahead of time between facilitators and stakeholders. All reasonable efforts will be made to work with each stakeholders' schedule and preference for meeting. Additional contact reasons, particularly towards the end of the study, may include alerting advisors to study results and other research participation opportunities.

Advisor Population Characteristics
This study will include Veteran, Community and VA stakeholders/partners who will help evaluate intervention implementation strategies within the trial and adapt these strategies to scale out Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP) to rural-dwelling patients in the national VA healthcare system. All advisors will be 18 years or older. We plan to specifically include advisors from diverse backgrounds (e.g., in terms of race/ethnicity, sex).

Advisors involved in our study may require additional protection, either because they are from under-supported populations, minority populations, are women, and/or are employees of the VA. All study subjects are expected to be 18 years of age or older (no children will be included). We will follow all required protocols when working with VA employees as study participants, including communication with employee unions. Because our long-term goal is to provide evidence-based pain management to the many rural-dwelling patients in the VA healthcare system with chronic pain and under-supported populations are disproportionally affected by chronic pain, it is critical we include advisors from such populations in our study. In addition, because the program delivery and success are dependent on VA employees, they are also crucial to our study.

5.1.2 Feasibility/Pilot and RCT

Interventions
RAMP (UG3/Phase 1 Aim 2 and UH3/Phase 2 Aim 1)
Eligible participants will be enrolled in the RAMP intervention group and mailed (by

postal mail) tailored informational materials, including an introductory letter, copy of the information sheet, schedule with meeting dates/times, a workbook, and directions for accessing the intervention materials online. In keeping with our pragmatic approach, participants will not be asked to limit any other treatment. RAMP will take place over a 3-month period, delivered virtually via a VA-approved program (e.g., Microsoft Teams, Webex). For the UG3/Phase 1, the first session was a one-to-one session (60 minutes) with a health coach to complete a Personal Health Plan. This was followed by 11 weekly group sessions (90 minutes each) facilitated by the health coach. For the UH3/Phase 2, revisions were made, and all 9 weekly sessions will be held as a group (90 minutes each) facilitated by the health coach. Videos will be interspersed with workbook reflections and group discussions facilitated by the health coach. In session, group viewing of expert narrated videos will provide consistent education and training in content (e.g., pain education, mind-body skill training like mindfulness, physical movement, wellbeing). A range of customizable options and resources will be provided to meet Veterans' preferences, needs, and abilities. Email, SMS (using Qualtrics FedRAMP), and/or phone communication will provide reminders of sessions ahead of time. Participants will be asked to remain in close contact with health coaches and let them know of any need to miss a session. Study staff will follow-up with participants who do not attend session(s). Additional contact reasons, particularly towards the end of the study, may include alerting participants to study results and other research participation opportunities.

Usual Care (UH3/Phase 2 Aim 1 only)
Participants randomized to the Usual Care (UC) condition will not be asked to do anything besides complete the follow-up surveys. In keeping with our pragmatic approach, patients will not be asked to limit any other treatment. They will be mailed (by postal mail) an introductory letter, copy of the information sheet, and schedule of when they will be contacted to complete the follow-up surveys. After completing the final follow-up survey, they will be mailed information about how to access the intervention materials online.

Follow-up
Participants will be asked to complete follow-up surveys online at 3 months (UG3/Phase 1 and UH3/Phase 2) and 6 months (UH3/Phase 2 only) after the intervention period began. Survey invitations will be sent via email and SMS (using Qualtrics FedRAMP). Reminders will be sent to non-responders, including phone and mail follow-up if necessary.

All recruitment and follow-up activities will be performed by project staff at the Minneapolis VA.

Participant Population Characteristics
In order to qualify for the US Military, and eventually become a Veteran, individuals must be at least 18 years old. Since children (less than 18 years of age) do not exist in the population of interest, they will not be included in the study. This is also consistent with NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

People from under-supported populations requiring additional protection will be included in our study sample. This includes females, rural and varied heritage groups. These populations of Veterans are disproportionally affected by chronic pain. For our centrally managed recruitment strategy we will be using the VA (Veterans Affairs) Electronic Health Records (EHRs) to find VA Veteran Integrated Service Network (VISN) 7 and 23 patients who meet our selection criteria, including living in an area classified as rural. The U.S. is divided into 18 Veterans Integrated Service Networks or VISNs—regional systems of care. VISN 7 is the VA Southeast Network, which includes Georgia, Alabama, and South Carolina. It consists of 8 VA hospitals and affiliated community-based outpatient clinics or CBOCs. VISN 23 is the VA Midwest Healthcare Network, which includes North Dakota, South Dakota, Nebraska, Minnesota, Iowa, and part of Illinois. It consists of 9 VA hospitals and affiliated community-based outpatient clinics or CBOCs. We have chosen these two VISNs to obtain geographic diversity and because VISN 7 has a large percentage of rural racial and ethnic minorities, and a relatively large percentage of women compared to other VISNs. We will oversample Hispanic/Latino Veterans from VISNs 7 and 23 who meet our study criteria (N = 3763), using the EHR, with the goal of having at least 7.5% of our sample be Hispanic/Latino. This target is well above the current level of Hispanic/Latino Veteran representation in rural areas and will help provide more information for this important and growing demographic group.

5.2 Recruitment Methods, Randomization Procedures and Blinding (for Feasibility/Pilot and RCT), Participant Enrollment, and Retention

5.2.1 Advisor Engagement

Patient Partners (n=15-20).
RAMP Veteran Engagement Panel (VEP). We will establish a RAMP VEP comprised of rural VA patients with chronic pain from diverse backgrounds (e.g., geography, race/ethnicity, sex, age). Patients will be recruited to the VEP in collaboration with the Growing Rural Outreach through Veteran Engagement (GROVE) Center that has extensive experience recruiting rural VA patients for Veteran engagement activities. We will also reach out to prior LAMP participants (award W81XWH-18-2-0003, CIRB 18-21, IRBNet 1613709; led by Dr. Burgess) who expressed interested in being contacted again and who are rural-dwelling.

Other Ongoing Veteran Engagement Panels and Expert Consultants. We will draw on other established Veteran Engagement Panels throughout the project to provide broader perspectives. These include the *Center for Access & Delivery Research and Evaluation (CADRE) Veteran Engagement Panel* comprised of rural VA patients; the *Growing Rural Outreach through Veteran Engagement (GROVE) Midwest Veteran Engagement Panel*, and the *Pain/Opioid Care Veteran Engagement Panel,* a diverse panel of patients with chronic pain, who meet regularly to provide feedback to VA research investigators involved in pain and opioid

research. We will also be in regular contact with our Expert Veteran Consultants, Vanessa Meade, Sean Green, and Adam Anicich.

Community Partners (n=10-15).
RAMP Community Advisory Panel (CAP). As part of the UG3 preparatory activities, we will identify and develop new community partnerships, and establish a RAMP CAP. The RAMP telehealth intervention is intended to reach rural Veterans, who are dispersed throughout different rural communities and receive care at different CBOCs. Because RAMP participants will be dispersed among rural communities in the Southeast (VISN 7) and the Midwest (VISN 23), we will identify organizations serving Veterans in local communities in these regions, such as local branches of the American Legion and the Veterans of Foreign Wars (VFW). We will also identify organizations serving diverse Veteran communities such as women and racial, ethnic and sexual minority Veterans, which may be local or national, since those communities may not be represented by local organizations such as the VFW. Recruiting and successfully partnering with such community organizations that specifically serve rural-dwelling patients, will be facilitated via the GROVE center and other experts in partnering with organizations serving diverse Veteran communities. We will also ensure that our CAP includes individuals from diverse backgrounds (e.g., race/ethnicity, sex). We will accomplish this during the UG3 period, through our collaboration with the national Growing Rural Outreach through Veteran Engagement (GROVE) Center and our Veteran partners. We will also actively develop relationships with Veteran Service Organizations that serve under-supported communities.

VA Healthcare System Partners (n=10-15).
We will partner with *leaders from national VA Program Offices* who oversee VA policy and programs that will be key to implementing the proposed trial and to integrating RAMP into the VA healthcare system nationwide (Office of Patient Centered Care and Cultural Transformation; Pain Management, Opioid Safety, Prescription Drug Monitoring Program; the Office of Rural Health and the Office of Connected Care). We will also work with the *VA Community Based Outpatient Clinics* (CBOCs) leaders & staff in the Southeast (VISN 7) and the Midwest (VISN 23) and *VA Medical Center leaders and staff* from “parent” facilities in those regions that provide in-person and virtual clinical care to affiliated, rural CBOCs (e.g., leaders: Pain Committee Lead, Telehealth hub lead, staff: Whole Health coach, Whole Health manager, Whole Health Flagship Site staff, primary care providers, integrative health providers). We will also ensure that our VA Healthcare System Partners include individuals from diverse backgrounds (e.g., race/ethnicity, sex). These employees will be recruited during the UG3 phase.

To facilitate successful collaborations between the stakeholders/partners and researchers and optimize retention, we will develop a formative evaluation strategy for our engagement plan, to understand, refine, and continually improve our engagement activities. We also will be guided by the ConNECT Framework for advancing health equity in behavioral health. This framework provides actionable principles that can be infused throughout the entire research process. Use of ConNECT helps ensure greater and sustained consideration to how the researchers work with communities who experience health disparities, including giving greater attention to social

contexts (e.g., socioecological determinants, biological/physical and psychological influences). It also emphasizes processes that foster a norm of inclusion, ensure equitable diffusion of innovations, harness communication technology, and prioritize specialized training for project team members.

Communication with Partners

Study personnel will recruit and have continuous communication with partners via their preferred method of communication. We expect communication methods to primarily be email (see Table 5 below for allowed methods depending on partner type), secure messenger with VA healthcare system partners (e.g., Microsoft Teams chat), virtual meetings (e.g., Webex), phone, and in-person. We may also use postal mail.

Table 5. Approved Communication Methods by Type of Stakeholder Partner Panel

Advisor Partner Panel	**Approved Communication Methods**
Veteran patient partners (RAMP Veteran Engagement Panel and other ongoing Veteran Engagement Panels)	• Shared VA email account (e.g., vhaminRAMP@va.gov) • Institutional study personnel email (e.g., diana.burgess@va.gov, evans972@umn.edu, katherine-hadlandsmyth@uiowa.edu, mallory.mahaffey@va.gov, mahaf016@umn.edu) • Qualtrics FedRAMP (email and text message/SMS) • Virtual meetings (e.g., Webex) • Phone • Postal mail
Community partners, CAP, consultants	• Institutional study personnel email (e.g., diana.burgess@va.gov, evans972@umn.edu, , katherine-hadlandsmyth@uiowa.edu, mallory.mahaffey@va.gov, mahaf016@umn.edu) • Shared VA email account (e.g., vhaminRAMP@va.gov) • Qualtrics FedRAMP (email and text message/SMS) • Virtual meetings (e.g., Webex) • Phone • Postal mail
VA healthcare system partners (i.e., VA employees)	• Institutional study personnel email (e.g., diana.burgess@va.gov, evans972@umn.edu, katherine-hadlandsmyth@uiowa.edu, mallory.mahaffey@va.gov, mahaf016@umn.edu) • Secure messenger (e.g., Microsoft Teams chat) • Shared VA email account (e.g., vhaminRAMP@va.gov) • Qualtrics FedRAMP (email and text message*) • Virtual meetings (e.g., Webex) • Phone • Postal mail

*We will send text messages to VA employees if they have a VA cell phone

5.2.2 Feasibility/Pilot and RCT

RECRUITMENT METHODS

Veteran patients will be recruited and randomized to participate in the UG3/Phase 1 Aim 1 Feasibility Study (n=40) and UH3/Phase 2 Aim 1 RCT (n=500). A proactive recruitment strategy will be used to contact potential participants. Rural-dwelling patients with chronic pain from the VA healthcare system (Veterans Integrated Service Networks (VISNs) 7 and 23, representing the U.S. Southeast and Midwest) will be recruited to participate. Trained project staff will identify patients by searching the VA Electronic Health Record (EHR) using an algorithm successfully used to identify patients with chronic pain. Specifically, patients must have documented in their VA electronic health record receipt of qualifying pain diagnoses within the same pain category on at least two occasions, at least 90 days apart during the previous 2 years. Pain categories were defined according to the International Classification of Diseases, 10th Revision, Clinical Modification diagnostic codes (ICD-10-CM) and include: Abdominal and bowel pain; Back pain; Bone infections; Fibromyalgia and wide-spread muscle pain; Fractures, contusions, sprains and strains; Headache; Infectious arthritic diseases; Limb extremity pain, joint pain and arthritic disorders; Musculoskeletal chest pain; Neck pain; Neuropathy; Orofacial, ear, and temporomandibular disorder pain; Other painful conditions; Systemic disorders or diseases causing pain; Urogenital, pelvic and menstrual pain.

Patients will be required to have an email address in the EHR. We will use the Health Resources & Services Administration (HRSA) defined Rural-Urban Commuting Areas (RUCA) using zip codes to identify rural patients. The Data & Statistics Teams will then assign these patients a Study ID and create a crosswalk so that identifiable data is kept behind the VA firewall. Introductory postcards will be mailed to these patients. Patients will then be sent emails with a link to the study website, which will include information about the study, instructions for accessing the screener survey, an opt-out option, information about monetary incentives ($25 per survey for the feasibility/pilot; $40 per survey for the RCT), and the study contact information (phone number and email address to contact for help). We anticipate needing to send postcards and emails to up to 30,000 (about 2,000 during the pilot and about 28,000 during the full RCT) people in order to reach our randomization goals. As of October 2022, there were over 50,000 VA patients in the EHR who meet our initial eligibility criteria. Patients who go to the study website will be encouraged to review an information sheet and general introductory information as well as access the initial screener survey using a unique identifier (Qualtrics FedRAMP ID) via either a secure, unique or shortened URL. If participants screen eligible, they will then continue in Qualtrics FedRAMP to complete the baseline survey. This will be followed by a chart review by specially trained staff who will review VA EHR charts for mental health exclusions (see below). Project staff will call eligible participants to verify eligibility, availability, and interest. They will review information sheet details and provide the opportunity for participants to ask

questions before obtaining verbal consent and proceeding to randomization (UH3/Phase 2 only)/full enrollment (both UG3/Phase 1 and UH3/Phase 2).

To facilitate recruitment of patients who may not have reliable access to a device and/or broadband internet, the recruitment materials will: 1) Include instruction on the option to use a smartphone to access the website, and 2) encourage participants who do not have access to a device with internet or a smartphone to call the study phone number to discuss other means to connect and participate. Patients who call the study line will have this information reviewed verbally by project staff, who will then discuss options with interested patients. We will assess the utility of these approaches in the UG3/Phase 1 pilot study, via qualitative feedback. To facilitate recruitment and retention of racial/ethnic minority and female patients we will solicit and incorporate feedback on our recruitment materials and recruitment/retention strategies from patient and community partners/advisors from those groups. If goals for racial/ethnic minority and female patients are not being met, we will adjust our sampling strategy (e.g., increase the proportion of patients from under-supported groups in the subsequent recruitment waves) to achieve our goals, a strategy that was used successfully in the LAMP trial.

RANDOMIZATION
Allocation concealment methods were designed to maximize internal validity within the constraints of the study design.[35,36] The computer-generated randomization list is concealed from the research team conducting eligibility assessments and participant enrollment using a centralized electronic randomization system.

BLINDING
For the UG3, blinding is not possible because of the design (single group). All enrolled participants are assigned to the RAMP intervention.

For the UH3, upcoming treatment assignments will be concealed from study staff involved in screening and enrollment until after randomization through the electronic study application. All investigators will be blinded to the primary and secondary outcomes data until the study database is locked for analysis. Investigators are authorized to be unblinded when needed for safety-related processes (e.g., adjudication of serious adverse events, decisions to withdraw participants from the intervention following adverse events).

RETENTION
We will employ evidence-based retention strategies, which have been successfully used with a similar population of VA patients with chronic pain, participating in a similar trial (LAMP), which had an 86% follow-up rate at 12 months. These include 1) fostering participants' commitment and sense of identification with the study through branded study materials with the study logo, 2) a study newsletter, sent at the start of the study and before each survey, which includes updates about the study from the MPIs, as well as information shown to be motivating to participants (e.g., how they are contributing to research that will help Veterans with pain), 3) asking and using Veterans preferred means of communication (e.g., phone, SMS, email), and 4) multiple follow-up attempts (via phone, SMS, email, mail) if we are not reaching enrolled

participants. Participants also receive monetary incentives ($25 per survey for the feasibility/pilot; $40 per survey for the RCT for each survey completed via pre-paid debit card or physical check) and are sent a reminder postcard shortly before each survey is emailed.

RE-CONTACTING RAMP PARTICIPANTS N THE FUTURE
The project team may re-contact RAMP participants in the future (while the study is still open) if they answer “yes” to the follow-up survey question, “We’d sometimes like to gather more information and opinions, or let you know about other opportunities. Are you willing to be contacted again in the future?” It can be advantageous to reach out to interested participants (e.g., with more information, to ask follow-up questions, to ask for testimonials, to inform of other research opportunities, etc.). Future amendment(s) will describe the specifics of these contacts (e.g., mode of contact, purpose, etc.).

5.3 Informed Consent Procedures

5.3.1 Advisor Engagement

We requested approval for verbal informed consent and waiver of written informed consent from the Minneapolis IRB. Study personnel will review contents of an information sheet with all advisors. The information sheets will explain information typically on a consent form including that the activity is research, participation is voluntary, permission to participate can be withdrawn, permission for use of data can be withdrawn for exempt research activities involving the collection and use of identifiable data, and contact information for the VA Investigator. The information on the sheets will be reviewed with advisors ahead of time, and advisors will have multiple opportunities to ask questions prior to and during study procedures. Advisors will be provided with a paper or electronic copy of the information sheet if they would like one.

A signed HIPAA Authorization form will be obtained in order to 1) disclose the minimum necessary information to the Minneapolis VA Non-Profit Corporation, the Center for Veteran Education and Research (CVRE), for payment to eligible advisors for their time and contributions (VA employees will not be paid if on VA work time); 2) share basic and/or necessary advisor/partner contact information, qualitative data, and limited datasets with study personnel at the (e.g., University of Iowa/Iowa City VA Health Care System and the University of Minnesota); and 3) share required and approved data with study sponsor (e.g., NIH), Data and Safety Monitoring Board (DSMB), IRB, and other federal agency required to monitor or oversee research via VA Box or other approved methods. Signature on the HIPAA Authorization forms will be obtained via electronic signature using DocuSign or via a mailed physical HIPAA Authorization form and a pre-paid return envelope. A HIPAA waiver will be obtained in order to share identifiable information with DocuSign so that an individualized HIPAA form can be generated.

5.3.2 Feasibility/Pilot and RCT

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

Potentially eligible patients will be mailed a postcard describing the study and informing them that the study is voluntary. The postcard will provide instructions for opting out, and at any point during the study, a participant can choose not to be contacted by project staff again. We will provide the study website which includes an Information Sheet (containing information that is typically including in an informed consent document). A hard copy of the Information Sheet will be mailed when a participant is enrolled/randomized into the study.

We received an approval of verbal informed consent over the phone and waiver of written informed consent. We feel this is justified because the study poses minimal risks and waiving documentation of informed consent does not affect the wellbeing of the subject.

A signed HIPAA Authorization form will be obtained in order to 1) disclose the minimum necessary information to the Minneapolis VA Non-Profit Corporation, the Center for Veteran Education and Research (CVRE) and Greenphire, for payment to participants for completing surveys; 2) share data with all approved project team members; and 3) share required and approved data with study sponsor, Data and Safety Monitoring Board (DSMB), IRB, and other federal agencies required to monitor or oversee research via approved methods. Signature on the HIPAA Authorization forms will be obtained via electronic signature using DocuSign or via a mailed physical HIPAA Authorization form and a pre-paid return envelope. The HIPAA waiver will include being allowed to share identifiable information with DocuSign so that an individualized HIPAA form can be generated.

See section 4.1 Study Design for more information on personnel training and human subjects protections.

5.4 Inclusion/Exclusion Criteria

5.4.1 Advisor Engagement

Participants will be interested and willing patients, community partners, and healthcare system leaders and staff.

5.4.2 Feasibility/Pilot and RCT

Inclusion criteria:

- Veteran participants must be rural dwelling

- Email address in EHR.
- Patient's primary care provider is in VISN 7 or VISN 23
- Report pain at least most days in the past 3 months (pain chronicity threshold)
- BPI Pain Interference subscale of 4 or greater (scored by calculating mean of all 7 items; can calculate as long as 4 of 7 are answered).
- Willingness and ability to complete study activities including meeting remotely via videoconferencing when RAMP sessions are held (either at home or another location with internet access).

Exclusion criteria:

- Participated in LAMP study as a randomized participant or VEP member (Award W81XWH-18-2-0003, CIRB 18-21, IRBNet 1613709; led by Dr. Burgess)
- Current RAMP VEP member
- Requested no future follow-up during LAMP recruitment
- Current enrollment in a research study for pain
- Current enrollment in a similar facilitated, multi-week, multi-modal CIH program
- Severe, poorly controlled psychiatric or substance use disorder (based on chart review using structured checklists, conducted by staff who are trained and supervised by a clinical psychologist).

5.5 Study Evaluations

Data Collection. Data will be collected using Qualtrics FedRAMP, VA REDCap, paper surveys, telephone, virtual or in-person meetings, and EHRs.

Survey data will be collected using electronic data capture through Qualtrics FedRAMP or VA REDCap, secure web applications for building and managing online surveys. Qualtrics FedRAMP is VA-approved to collect data from VA patients and store data on VA cloud servers. Qualtrics is accredited by FedRAMP, a government-wide initiative to protect sensitive data in federal agencies, ensuring gold standard security for data collected through Qualtrics. It features data isolation, differentiated user roles and privileges, audit login, multi-factor authentication, single-sign-on and SSL encryption. VA REDCap has an authority to operate (ATO) from VA Office of Information and Technology (OI&T) and is hosted on the VA Enterprise Cloud (VAEC). Login requires a VA Network ID and is accessible only on the VA network, data is backed-up nightly, and audit trails and logging is captured using individualized user rights management. Surveys will contain a study ID number, time of data entry and limited individually identifiable information. Paper surveys will be carefully entered into the VA REDCap or Qualtrics FedRAMP system by project staff. Within the VA firewall, the project team at the VA will create a custom-built tracking app that will track each participant's enrollment and study status. Data will be routinely extracted from Qualtrics FedRAMP and VA REDCap in the VA cloud and stored on secure VINCI, VA Box, and Minneapolis VA CCDOR servers, using SQL database connections.

Qualtrics FedRAMP and VA REDCap will contain the minimal identifying information needed to successfully conduct the study. This will include information that is self-reported by the participants (e.g., phone, email, which is best method of contact). No sensitive data will be stored outside of the VA protected environment. Once data are transferred for data analysis, data will be maintained on password-protected VA computers in the VA environment and on secure VA servers.

Project staff will monitor the functioning of the Qualtrics FedRAMP and VA REDCap applications. Only staff affiliated with this research protocol will have access to Qualtrics FedRAMP and VA REDCap data collected for this study. The MPIs or their designees will be responsible for monitoring data storage location and transfer of data between the VA cloud and VA server.

We will have dedicated research personnel at the Minneapolis VAHCS site to coordinate study data acquisition based on regularly updated reports. We will use several strategies to follow-up with participants who have not completed their assessments. These strategies were used successfully in the LAMP trial, which had an 86% follow-up rate at 12 months. To help decrease the number of participants who don't complete their assessments, we will mail a newsletter between each survey and a reminder postcard shortly before each survey is emailed. After sending assessments, we will contact non-responders via their specified preferred method and using additional contact information they provided. We will encourage online completion but mail paper copies or complete surveys by phone as preferred. We will email, mail, call, and text/SMS participants with reminders to complete the surveys. The emails will be sent using the RAMP study email address or via Qualtrics FedRAMP. Text/SMS messages will be sent via Qualtrics FedRAMP. Participants will be contacted to follow-up on any missing data that doesn't seem deliberate (e.g., if a couple of survey pages are completely blank but the rest of the survey is answered, it is likely the couple pages got stuck together rather than deliberately skipped). Participant flow data using the Consolidated Standards of Reporting Trials (CONSORT) framework[118] will be collected, including recruitment, enrollment, intervention adherence, intervention fidelity, and data collection rates.

All meeting notes will be stored on the VA network.

Data coordination and management. Data collection and management will be overseen at the Minneapolis VA HSR&D Center of Innovation (COIN) by Dr. Brent Taylor. Regular meetings of investigators and project staff within and between sites will take place to routinely review data collection and management issues. To prevent improper use of any data collected for research projects conducted at the Minneapolis COIN we will use a combination of local Minneapolis VA secure servers as well as the national secure VA Informatics and Computing Infrastructure (VINCI) and the secure Qualtrics FedRAMP and VA REDCap systems in the VA cloud. The local VA secure servers facilitate data collection and provide a platform for the customized research tracking application, while the VINCI platform provides a robust environment for pooling the primary research collected data with direct connections to daily or weekly updated

mirrors of nearly the entire VHA EHR. VINCI also provides access to extensive storage area networks, drives, file shares, databases, SharePoint for collaboration and correspondence sites, SAS/Grid, and servers containing virtual machines with an extensive collection of software called the VINCI Workspace. We will request access to the Joint Legacy Viewer (JLV) in order to capture the highest follow-up response rate that is feasible. It is very important that we reach the participants in a timely manner; being able to access current address and phone numbers will help in tracking hard to reach participants. A secure link between local VA secure servers and Qualtrics FedRAMP and VA REDCap will be created. Limited study specific data will be collected on Qualtrics FedRAMP and VA REDCap and will contain a study specific participant ID code. VINCI allows individual researchers and their staff the means to securely conduct their research projects within a secure and well controlled technical environment. All of these VA systems undergo backups of the servers nightly and servers are updated when new security patches become available. All individuals with administrative privileges to the VHA servers have been screened and have been assigned security clearance putting them in trusted positions to work with patient-level data.

Measures
See 2.3 Schedule of Activities.

5.6 Discontinuation & Withdrawal

The reason for participant discontinuation or withdrawal from the study will be recorded in the study tracking database (SQL database) and participants will be notified. Subjects who consent and are randomized but do not receive the study intervention will not be replaced. Subjects who consent, are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

We will not use a participant's data if they request us not to, and we would reassure them, as is in the Information Sheet, that there are no penalties for discontinuing or withdrawing from the study.

5.6.1 Discontinuation of Advisor Engagement

At the point of discussing potential participation, advisors will be informed that this is a multi-year study and asked whether this is a commitment that they want to make. Community organization representatives have the option of naming a second alternate to represent the community (i.e., some community organizations will be represented by only one person and some by two people who will take turns attending meetings and providing feedback). Although the panel meetings will be scheduled well in advance, there will likely be times when a Veteran or community advisor cannot attend a meeting and they will still be part of the panel if this is their preference. Advisors can also decline to provide feedback on any specific topic and remain on the panel. If an advisor no longer wishes to participate, they are of course free to withdraw at any time. Reasons for discontinuation will be recorded. Additional recruitment will be conducted, if necessary, to replace the expertise of advisor(s) that left the study.

5.6.2 Discontinuation of Study Intervention (Feasibility/Pilot Study, RCT)

A study participant may discontinue from the study intervention (i.e., the RAMP program) but not from the research study. In such cases, remaining study procedures will be completed as indicated by the study protocol. If a significant finding (e.g., development of an exclusion criterion) is identified after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new significant findings will be recorded as an adverse event (AE).

All efforts will be taken to facilitate study participants' completion of the study intervention. However, participants may be discontinued from the intervention if, for example:

- They develop an exclusion criterion (new or not previously recognized) that would make it unsafe for them to continue participation.
- Any adverse event (AE), medical condition, or other situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant displays abusive behavior toward other participants and/or the project staff.
- New evidence emerges which suggests it is unsafe for the participant(s) to proceed with the study.
- The participant chooses to withdraw consent.

The data to be collected at the time of study intervention discontinuation, and for the remainder of the study will include the following:

- Reason for intervention discontinuation and methods for determining the need to discontinue.
- Number of completed intervention visits.
- AE/SAE information, if indicated.
- If participant agrees, self-report surveys (to be administered as scheduled), even though the participant has discontinued attending the study intervention.

5.6.3 Withdrawal of Participants (Feasibility/Pilot and RCT)

Participants can initiate withdrawal from participation of the study overall, at any point, upon request. They can withdraw from the study and/or intervention at any time they feel uncomfortable or choose to do so. An investigator may also withdraw a participant from the study for reasons including, but not limited to, the following:

- Participant develops an exclusion criterion (new or not previously recognized) that would make it unsafe for them to continue.
- Participant exhibits significant study intervention non-compliance (e.g., disruptive or unsafe behavior).
- Any adverse event (AE), medical condition, or other situation occurs such that continued participation in the study would not be in the best interest of the participant.

- New evidence emerges which suggests it is unsafe for the participant(s) to proceed with the study.
- A major change occurs in the participant's life (e.g., incarceration, death).
- Study closure by institute or oversight body.
- Participant withdraws consent to continue.

5.7. Adverse Events & Serious Adverse Events

Refer to section 6.0 Reporting and to the Data and Safety Monitoring Plan (DSMP) (Appendix A) for adverse event handling information and details.

Events of Special Interest
Reporting of certain events is required by law (e.g., suspected child abuse, adult abuse or neglect, excessive use of alcohol or use of controlled substances for non-medical reasons during pregnancy) and may be discovered during the study. If information becomes available that may require mandated reporting, project staff will contact the PIs or Project Coordinators (also see https://mn.gov/dhs/general-public/licensing/maltreatment-investigations/mandated-reporter-resources).

Reporting of Pregnancy
Pregnancy, current or planned, at the point of enrollment is not an exclusion criterion for the trial. Enrolled subjects who become pregnant will be monitored for safety and risks the same as all other study subjects.

5.8 Data Analysis

UG3/Phase 1 and UH3/Phase 2 Aim 1a – Advisor Engagement
Quantitative data will be analyzed using descriptive statistics when appropriate (e.g., stakeholder characteristics). For the qualitative analysis, teams of 2-3 will perform rapid deductive, directed content analytic methods to interview notes and text from open-ended surveys; the coding structure and operational definitions will be guided by the study's conceptual models to provide insights into barriers and facilitators to RAMP's future implementation. Directed content analyses will allow for inductive gathering of important themes that might fall outside of our chosen models and frameworks.

We will also apply traditional qualitative methods when more nuanced information would be helpful. In these instances, we will use semi-structured interview guides for individual advisor interviews and focus groups. Teams of 2-3 will perform in-depth, directed content analyses of the meeting notes, applying a codebook in qualitative software (e.g., NVivo). We will use deductive approaches aligned with the study's models and frameworks, as well as inductive thematic coding to document other important information that falls outside the coding structure. Representative quotations will be identified; when useful (e.g., to gain insight as to theme

importance) we will also quantify themes by categorizing them as present or absent for each case and present descriptively as frequencies.

UH3/Phase 2 Aim 1b – Advisor Engagement

We will prepare summaries of the effectiveness and implementation analyses and present them to VA patient, community, and VA stakeholders. This will provide them with the necessary contextual information to meaningfully contribute to participatory research activities focused on problem solving, process mapping, to develop plausible strategies for remaining barriers to implementation of RAMP taking into account internal and external contexts affecting the VA and Whole Health System initiatives at the time. Examples include developing specific facilitation strategies, adapting information and patient-facing resources for particular groups to increase awareness and engagement (i.e., engaging Veterans), tailoring intervention process strategies and resources, identifying and preparing champions to lead, support and marketing implementation efforts, and developing training programs.

UH3/Phase 2 Aim 1c – Advisor Engagement

We will conduct a budget impact analysis synthesizing knowledge gained from stakeholder views/perspectives in Aim 2a, into analytic models that provide viewing of cost implications relevant to particular settings and contexts using recommended methods. This analysis will be performed by investigators with statistical and cost-analyses experience. We will develop models considering both the local facility and national VA perspectives. Model time horizons will be tailored to advisor needs for budget planning. RE-AIM/PRISM data will be used to inform values for model inputs and plausible ranges to consider (e.g., uptake by facilities and patients with chronic pain, training costs, impact on use of other chronic pain interventions, and related costs). Scenario analyses altering values of model inputs and model structure will be conducted to allow the consideration of plausible alternative scenarios. Models will be presented to advisors while in development to ensure face validity.

UG3/Phase 1 – Aim 1 – Feasibility study

The sample size for the proposed feasibility (n=40) was informed by previous feasibility studies by the investigators, who have found this number sufficient for informing the feasibility of larger, randomized clinical trials. The feasibility of recruitment, enrollment, intervention acceptability and credibility, and data collection activities will be assessed using designated feasibility measures and targets, described in. Section 2.4.1 UG3 Milestones, above.

Mixed method analyses will be conducted. Quantitative data will be analyzed using descriptive statistics (e.g., participant characteristics, satisfaction, fidelity rates, etc.). Qualitative data analyses will use a rapid deductive, content analysis approach (directed and summative) informed by the study's conceptual models. We will use the same qualitative methods described above for Advisor Engagement.

UH3/Phase 2 – Aim 1 – RCT

Our randomization goal based on our power calculation is n=500 participants for our UH3/Phase 2 Randomized Clinical Trial. We have chosen a range of biopsychosocial (BPS) outcome measures relevant to Veterans, and which are likely to be affected by the experimental intervention, RAMP. BPS outcome measures will be collected at baseline, 3, and 6 months.

Our power calculation uses the Brief Pain Inventory (BPI) interference scores over the entire follow-up period as the primary outcome measure. The primary outcome uses a repeated measures approach that takes into account assessments at 3 and 6 months with a single test of significance. Secondary outcomes will evaluate the time points separately. For our primary analysis we estimate up to 20% attrition, so at least 500 people will need to be randomized to obtain a sample of 400 people with complete data. 200 participants in each arm will yield 90% power, with an alpha of 0.05, to reject the null hypothesis of equal means over the repeated follow-up time points (i.e., 3 and 6 months) if the arms differ by an effect size of 0.3 or greater. This includes a conservative estimate that the repeated outcome measures are highly correlated (r=0.7) and even with only 1 time point there is power to detect effect sizes of 0.32. Analyses that are stratified by subgroups as small as 70 people per arm (i.e., equivalent to restricting to only women or minority Veterans) would have approximately 90% power to detect differences of 0.50. However, these would only be exploratory in nature and not adjusted for multiple comparisons. While our goal is to achieve 500 randomized participants, our intervention will roll out in large waves so precisely hitting a randomized sample number is difficult. Therefore, we asked for an administrative IRB approval to exceed this goal and enroll up to 550 participants.

We will use an intention-to-treat approach. Preliminary descriptive analyses will summarize the distributions of the baseline measures across treatment arms overall and will similarly assess the outcome distributions across assessment time points (i.e., baseline, 3, and 6 months). We will summarize the completeness of the self-reported outcome assessments and examine associations between completeness and baseline measures as well as the association with secondary outcome assessments that are collected from the electronic medical record (e.g., medications, health care utilization related to pain treatment). Initial analyses will use all available follow-up data and subsequent sensitivity analyses will examine the potential effect of response bias. For analyses of the primary outcome, all repeated measurements of the BPI interference score will be fitted in a mixed model for repeated measures as a function of the group assignment, while controlling for time points and baseline values of the outcome as fixed effects, with participants as random effects. Between-group differences over the entire follow-up period (average of 3 and 6 months) will be the primary test of treatment group differences. Between-group differences will be estimated for each of the individual time points as secondary outcomes. Similar to the methods described above for the primary analyses, weighted selection model analyses will examine the sensitivity of the initial results to response biases. To do this, we will fit a series of weighted selection model analyses. Each analysis will use an expectation-maximization algorithm to estimate weights to assign to potential values of the missing outcomes for use in the regression model. The secondary outcomes will be similarly analyzed

using the same linear mixed effect models for normal continuous measures and appropriate generalized linear mixed effect models for non-normal measures.

Subgroup analyses will explore treatment group effects for individual subgroups. For example, does there appear to be evidence of a benefit in each group (men and women, white and racial/ethnic minorities)? Potential interactions by subgroup type (e.g., sex, race/ethnicity) will also be explored to see if there is evidence that treatment effects depend on subgroup. Only moderately large subgroup differences would be able to be statistically detected, but exploration of subgroup differences is still important for understanding possible mechanisms and barriers. The models described above for the primary analysis will be modified for looking at these subgroup and interaction effects. Additionally, all of these variables can be explored in multivariable models to look at the relative independent relationships between these factors and the primary and secondary outcomes.

Additional exploratory analyses involve the assessment of the extent to which pain catastrophizing, self-efficacy, perceived stress, mindfulness, and body awareness measures mediate the effects of the intervention. We will use the CAUSALMED procedure in SAS/STAT® 14.3 to estimate mediation effects using a counterfactual framework approach (Robins, J. M., and Greenland, S. (1992). Identifiability and Exchangeability for Direct and Indirect Effects. Epidemiology 3:143–155). The overall (total) effect will be decomposed into four component parts. These components include: (i) the effect of the exposure in the absence of the proposed mediators (i.e., controlled direct effect), (ii) the interactive effect when the mediators are left to the levels they would hold in the absence of exposure (i.e., reference interaction), (iii) a mediated interaction, and (iv) a pure indirect (mediated) effect. Four-fold effect decomposition allows for the greatest insight into the causal mechanisms responsible for effect of RAMP on our outcomes by simultaneously assessing the portions of the total effect that are due only to mediation, only to interaction, to both mediation and interaction, and to neither mediation nor interaction. Separate analyses will be conducted pairing each mediator with each outcome.

For the intervention experience responses from intervention participants, we will conduct descriptive analyses of quantitative data and explore differences that may emerge by sex. We will use Rapid Assessment Process (RAP) analyses to analyze open-ended responses.

6.0 Reporting

6.1 Minneapolis VA

We will follow the Minneapolis VA IRB reporting requirements for all issues that must be reported (i.e., unanticipated serious adverse events (U-SAEs), unanticipated problems (UAPs), protocol deviations/violations/noncompliance, and any changes with respect to the protocol). The project staff will remain in regular contact (by phone, email, videoconference, and face-to-face) to discuss study processes, progress, and any issues encountered. Any issues will be reported directly to the MPIs. Data will be reviewed regularly to ensure accuracy and data

privacy. In the case of problems, the project director will immediately discuss with the study MPIs. MPI Dr. Burgess will report any related or possibly related U-SAEs or Deaths to the Minneapolis IRB within 5 business days of learning of the event(s). If there are modifications or amendments to the study MPI Dr. Burgess will also complete the appropriate forms and wait for approval prior to implementation. As described below, IRB notification forms will be completed to notify Data and Safety Monitoring Board (DSMB) of findings.

6.2 NIH

In addition, as guided by the NIH's policy on data and safety monitoring, a detailed data and safety monitoring plan (DSMP) was developed and submitted to NIH program officials for approval prior to data collection. See Appendix A for current DSMP. The DSMP aims to ensure the safety of participants and the validity and integrity of the data collected. A Manual of Operations is also being developed, including standard procedures for protection of all subjects and data collected from participants in both hardcopy and electronic formats, from the point of collection to storage.

NIH advised the project team that a Data and Safety Monitoring Board (DSMB) is required for the UG3/Phase 1 and UH3/Phase 2 of the project. The number of members and specific areas of content expertise for an appointed DSMB was agreed upon with NIH prior to funding. Safety and other data outlined in the DSMP (Appendix A) will be monitored by the MPIs on a monthly basis. The DSMB establishes the frequency of monitoring in the charter agreed upon by the board.

6.2.1 Framework and information monitored

The following information will be collected and monitored as part of the DSMP: participant flow (as per CONSORT recommendations); enrollment; allocation; data collection; findings from quality assurance and quality control procedures; safety (including adverse events described below and in Appendix A); and protocol deviations. No interim analyses are planned given the low expected risks with the study.

6.2.2 Adverse Event Monitoring

We will monitor and report adverse events and unanticipated problems involving risk to subjects or others (UPIRTSO) to our local IRB, DSMB, and the funding agency as required. Active and passive surveillance methods will be used to monitor for adverse events. We will ask about potential adverse events at all study visits and data collection events. Participants will also be asked to notify study personnel (outside of scheduled sessions and reporting) about serious adverse events that occur. Trained project staff will be responsible for documenting adverse events and notifying the principal investigators. The MPIs will have final determination regarding the classification and reporting of adverse events to applicable regulatory bodies (e.g., IRB, DSMB, funding agency). The MPIs will report serious adverse events and unanticipated problems to the appropriate regulatory bodies within 5 business days or other required amount of time.

6.2.3 Adverse events classification

See the Data and Safety Management Plan (DSMP) Appendix A for additional details. The following table summarizes reporting plans.

Table 6. Reporting for Adverse events, Serious adverse events, and Other events

Event	Report to…	Reporting Time
Deaths than are at least possibly related to the research	Minneapolis VA IRB, ACOS-R, NINR, DSMB	- Initial reporting to the Minneapolis IRB within 1 hour of learning of the event. - Follow up with submission of the "Minneapolis IRB Immediate Reporting of Serious Adverse Events or Deaths" written report form will occur within 1 business day. - DSMB and NINR within 3 business days of learning of the event
(non-death) **Unanticipated Serious Adverse Events (U-SAEs)** - unexpected and <u>at least possibly related</u> to the research	Minneapolis VA IRB, NINR, DSMB	- Within 5 business days in writing with submission of the "Minneapolis IRB Immediate Reporting of Serious Adverse Events or Deaths" - DSMB and NINR within 7 business days of learning of the event
Serious Adverse Events (SAEs) – adverse event that is *not* unexpected *and* at least possibly related to the research	Minneapolis VA IRB, NINR, DSMB	- IRB - Summarized at Continuing Review - NINR – annual report - DSMB – annual report
Unanticipated problem involving risk to subjects or others (UPIRTSO)	Minneapolis VA IRB, NINR, DSMB, OHRP	- IRB within 5 business days - NINR and DSMB within 14 business days - OHRP within 21 business days
A summary **of recommendations made by the DSMB** or other monitoring entity as appropriate and (if applicable) the action plan for response.	NINR	- Within 14 business days
Notice of any **actions taken by the IRB or regulatory bodies** regarding the research and any responses to those actions.	NINR	- Within 14 business days
Abbreviations and acronyms: ACOS-R: Associate Chief of Staff for Research; DSMB: Data and Safety Monitoring Board; IRB: Institutional Review Board; NINR: National Institute for Nursing Research; OHRP: Office of Human		

Research Protections; SAE: Serious Adverse Event; UPIRTSO: Unanticipated problem involving risk to subjects or others; U-SAE: Unanticipated Serious Adverse Event; VA: Veterans Health Administration

7.0 Privacy and Confidentiality

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

- Reminders to complete surveys will be sent to the participant's preferred, allowed method of contact: phone, email, mail, SMS, or other secure messenger (e.g., Microsoft Teams chat). Continued non-response will activate reminders sent via other methods, including phone, email, mail, SMS, and secure messenger. Email will be sent using the RAMP study email, via Qualtrics FedRAMP, and/or study personnel email accounts (allowed advisors only). SMSs (text messages) will be sent via Qualtrics FedRAMP.
- ORD Guidelines regarding using email and text messaging for communicating with VA research participants, as drafted in the following document, will be followed: https://www.research.va.gov/resources/policies/guidance/draft-electronic-mailtext.pdf. This includes:
    - No PHI or PII will be transmitted by study personnel through unencrypted email or text message.
    - The following text will be included in all emails and text messages so as to try and prevent participants from including PHI or PII in their responses: "Email and texting is not secure. Please do not reply back to this message with any personal information or personal health information. Please call 877-467-5079."
    - Specific PHI or PII will not be shared in emails from VA staff, but if there is a concern for the participant's immediate safety, and all other forms of communication (phone, emergency contact person's phone) are not successful, emails with general statements like the following will be sent: "My role as your coach is to create a safe space to share and also to make sure you are safe. I have tried reaching you by phone during and after group tonight. To make sure you are safe and doing ok, please reach out to me. My VA cell is xxx-xxx-xxxx. You can also contact the Veteran Crisis line directly by calling 988 and Press 1."
    - If a participant sends PII or PHI as part of a response using the individual's personal email or text messaging, project staff will either respond by telephone to the individual or respond using email or text messaging with redaction of any PII or PHI conveyed by the participant.
    - Email addresses of participants will be kept secure and not shared with other participants.
    - Emails and text messages sent and received for the RAMP study will be saved and maintained in accordance with the VHA Record Control Schedule.
- CCDOR maintains strong protections for coded analysis datasets that will be stored on local VA server space. CCDOR provides protections for research data at least equal to that provided by the Minneapolis VA Health Care System for patients' private health information (PHI). Access to data is on a "need to know" basis. For example, data analysts will not have access to project data unless they can demonstrate that they are somehow needed for a particular analysis.
- Access to project data is obtained through Windows authentication (i.e., PIV card and password to the network). It is virtually impossible for any person without a login name, PIV card and password to the Minneapolis VA hospital's domain network to access data on the

Center's servers. Thus, all data housed on the CCDOR Server is extremely secure. Access by unauthorized persons is highly unlikely.

- CCDOR maintains several secure servers that are located in the Minneapolis VA OIT server room. Physical access to the server room is limited to VA Office of Information and Technology staff. All individuals with administrative access privileges to the Center's servers, including VA OIT personnel and CCDOR programmers, have been screened and assigned a security clearance putting them in trusted positions of the hospital with authorization to work with patient-level data. VA OIT's access to the data is strictly limited to backing up server data, which prevents catastrophic loss of data. Backups are written to tapes that are stored in a secure location accessible only to OIT personnel.
- To share data with non-VA entities, HIPAA authorization forms signed by participants and advisors and/or a Data Use Agreement (DUA) may be put in place and limited datasets will be created for this purpose. Necessary documentation will be determined by Minneapolis regulatory staff.
- Docusign will be used to electronically obtain signed HIPAA authorization. The necessary identifiable information will be shared with Docusign in order for individualized HIPAA forms to be generated.
- VA and NIH regulations require that all investigators and individuals who work on the study undergo comprehensive training annually in research integrity and protection of human subjects. Additionally, all study personnel will be required to complete training in the Responsible Conduct of Research every three years. This includes online CITI training in responsible conduct of research, good clinical practice, and human research protections. The CCDOR data group will ensure that all project staff have proper access to the VA network (i.e., will assist local OIT for project staff not in Minneapolis), so those who require access to study data will have permissions to the data they need.
- Securing Other Physical Confidential Research Data: Primary data (e.g., survey responses, interview transcripts) are identified only by participant number. The original data sources (e.g., paper notes) will either be kept in locked cabinets within a locked room or stored in a secure folder stored on the CCDOR server.
- Only individuals with a need to access the data, as vetted by the project's Principal Investigator are granted access. Even then, only the absolute minimum number of data elements is released. This protects the integrity of the data as well as its confidentiality.
- Study records, including data, will be maintained in a secure location and destroyed in accordance with VA Federal Records requirements in VHA Record Control Schedule (RCS 10-1), currently at 6 fiscal years following the closure of the study. All records, including data will be handled in accordance with all VA and VHA privacy, confidentiality, and information security policies and procedures.
- Dr. Brent Taylor and the CCDOR Data team are responsible for setting up access and creating a personnel list for access to the points on the VA network where documents and/or data are stored (i.e., VINCI, VA Box, local VA servers, VA REDCap, and Qualtrics FedRAMP).

- The current team and other VA investigators have used these procedures in previous studies, and they have proved both feasible to execute and acceptable to multiple Institutional Review Boards (IRBs).

8.0 Communication Plan

MPIs Drs. Burgess, Evans, and Hadlandsmyth will meet regularly with Program Manager, Lee Cross. At these meetings the MPIs will check in with Ms. Cross to ensure that the following key communications occur:

1. Ensure that required local site approvals are obtained and maintained.
2. Notify the Director of any facility where the research in being conducted, but the facility is not engaged.
3. Keep engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization.
4. Inform local sites of any SAEs, UAPs, or interim results that may impact conduct of the study.
5. The project team will review relevant sections of the protocol periodically, so that we can make sure that the different phases of the study are conducted according to the IRB-approved protocol.
6. Notify all local facility directors when the study reaches the point that it no longer requires engagement of the local facility.

Drs. Burgess, Evans, and Hadlandsmyth have a history of prior collaboration. The governance and organizational structure of that project arrangement entails a clear division of the overall responsibilities for the research and frequent contact (weekly and often more frequently). The MPIs will continue to meet no less than weekly via videoconference to collaborate on the project's overall planning, administration, implementation, management, and oversight. If a conflict arises, the MPIs will meet and attempt in good faith to settle any issues. If, in the unlikely event they fail to resolve the dispute, the disagreement will be referred to the Coordinating Center Steering Committee to reach consensus. If, in the unlikely event that the dispute remains unresolved, the Steering Committee will seek input from an arbitration group who are not affiliated with the study and comprised of individuals from CCDOR, the University of Minnesota, and the University of Iowa. No members of the arbitration committee will be directly involved in the research grant or disagreement. This panel will settle any conflict that arises in the performance of the study and the interpretation of the data. The decision of this panel will be final and binding. Publication authorship will be based on the relative contributions of participating research and community team members.

9.0 Repository/Data Banking

UG3/Phase 1 feasibility and UH3/Phase 2 RCT data will be shared with an external NIH HEAL-approved data repository called National Institute of Mental Health (NIMH) Data Archive (NDA). The data will be anonymized as much as possible. All required documentation and agreements will be put in place prior to actually sharing any data.

As with the rest of the RAMP data, the repository/data banking will be handled in accordance with all VA and VHA privacy, confidentiality, and information security policies and procedures.

10.0 References

1. Giummarra MJ, Arnold CA, Beck BB. Evaluation of the Relationship Between Geographic Proximity and Treatment for People Referred to a Metropolitan Multidisciplinary Pain Clinic. *Pain Med*. Sep 8 2021;22(9):1993-2006. doi:10.1093/pm/pnab011
2. Le Lait MC, Martinez EM, Severtson SG, Lavery SA, Bucher-Bartelson B, Dart RC. Assessment of prescription opioid intentional exposures across the rural-urban continuum in the United States using both population and drug availability rates. *Pharmacoepidemiol Drug Saf*. Dec 2014;23(12):1334-7. doi:10.1002/pds.3653
3. Office of Rural Health. U.S. Department of Veterans Affairs. Accessed 09/09/2022, 2022. https://www.ruralhealth.va.gov/aboutus/ruralvets.asp
4. Nahin RL. Severe Pain in Veterans: The Effect of Age and Sex, and Comparisons With the General Population. *J Pain*. Mar 2017;18(3):247-254. doi:10.1016/j.jpain.2016.10.021
5. Bohnert AS, Ilgen MA, Galea S, McCarthy JF, Blow FC. Accidental poisoning mortality among patients in the Department of Veterans Affairs Health System. *Med Care*. Apr 2011;49(4):393-6. doi:10.1097/MLR.0b013e318202aa27
6. Hadlandsmyth K, Driscoll MA, Mares JG, Au V, Miell KR, Lund BC. Rurality impacts pain care for female veterans similarly to male veterans. *J Rural Health*. Feb 16 2022;doi:10.1111/jrh.12646
7. Arout CA, Sofuoglu M, Rosenheck RA. Rates and Correlates of Pain Specialty Clinic Use Nationally in the Veterans Health Administration. *Pain Med*. Apr 1 2017;18(4):702-710. doi:10.1093/pm/pnw206
8. Lund BC, Ohl ME, Hadlandsmyth K, Mosher HJ. Regional and Rural-Urban Variation in Opioid Prescribing in the Veterans Health Administration. *Mil Med*. Dec 1 2019;184(11-12):894-900. doi:10.1093/milmed/usz104
9. Eaton LH, Langford DJ, Meins AR, Rue T, Tauben DJ, Doorenbos AZ. Use of Self-management Interventions for Chronic Pain Management: A Comparison between Rural and Nonrural Residents. *Pain Manag Nurs*. Feb 2018;19(1):8-13. doi:10.1016/j.pmn.2017.09.004
10. Stubbs D, Krebs E, Bair M, et al. Sex Differences in Pain and Pain-Related Disability among Primary Care Patients with Chronic Musculoskeletal Pain. *Pain Med*. Feb 2010;11(2):232-9. doi:10.1111/j.1526-4637.2009.00760.x
11. Skinner K, Sullivan LM, Tripp TJ, et al. Comparing the health status of male and female veterans who use VA health care: results from the VA Women's Health Project. *Women Health*. 1999;29(4):17-33. doi:10.1300/J013v29n04_02
12. McClendon J, Essien UR, Youk A, et al. Cumulative Disadvantage and Disparities in Depression and Pain among Veterans with Osteoarthritis: The Role of Perceived Discrimination. *Arthritis care & research*. 2021;73(1):11-17.

13. Evans EA, Herman PM, Washington DL, et al. Gender differences in use of complementary and integrative health by US military veterans with chronic musculoskeletal pain. *Women's Health Issues*. 2018;28(5):379-386.
14. Morales ME, Yong RJ. Racial and ethnic disparities in the treatment of chronic pain. *Pain Medicine*. 2021;22(1):75-90.
15. Bove AM, Dong E, Hausmann LRM, et al. Exploring Race Differences in Satisfaction With Rehabilitation Following Total Knee Arthroplasty: A Qualitative Study. *J Gerontol A Biol Sci Med Sci*. Feb 3 2022;77(2):e48-e55. doi:10.1093/gerona/glab132
16. Mares J, Adamowicz J, Lund BC, Burgess DJ, Rothmiller SJ, Hadlandsmyth K. Differences in Chronic Pain Care among Veterans from Differing Racial and Ethnic Groups: Primary Care, Pain Clinic, Physical Therapy and Emergency/urgent Care Visits. *The Journal of Pain*. 2022;23(5):35-36.
17. Knoebel RW, Starck JV, Miller P. Treatment disparities among the Black population and their influence on the equitable management of chronic pain. *Health Equity*. 2021;5(1):596-605.
18. Pincus T, Kent P, Bronfort G, Loisel P, Pransky G, Hartvigsen J. Twenty-five years with the biopsychosocial model of low back pain-is it time to celebrate? A report from the twelfth international forum for primary care research on low back pain. *Spine (Phila Pa 1976)*. Nov 15 2013;38(24):2118-23. doi:10.1097/BRS.0b013e3182a8c5d6
19. Hush JM. Low back pain: it is time to embrace complexity. *PAIN*. 2020;161(10):2248-2251. doi:10.1097/j.pain.0000000000001933
20. Becker WC, DeBar LL, Heapy AA, et al. A Research Agenda for Advancing Non-pharmacological Management of Chronic Musculoskeletal Pain: Findings from a VHA State-of-the-art Conference. *J Gen Intern Med*. May 2018;33(Suppl 1):11-15. doi:10.1007/s11606-018-4345-6
21. National Academies of Sciences E, Medicine, Health, et al. The National Academies Collection: Reports funded by National Institutes of Health. In: Stroud C, Posey Norris SM, Bain L, eds. *The Role of Nonpharmacological Approaches to Pain Management: Proceedings of a Workshop*. National Academies Press (US) Copyright 2019 by the National Academy of Sciences. All rights reserved.; 2019.
22. Goldsmith E, Koffel E, Ackland P, et al. *Implementation of Psychotherapies and Mindfulness-based Stress Reduction for Chronic Pain and Chronic Mental Health Conditions*. 2021.
23. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. National Academies Press; 2011.
24. Silvestrini M, Indresano J, Zeliadt SB, Chen JA. "There's a huge benefit just to know that someone cares:" a qualitative examination of rural veterans' experiences with TelePain. *BMC Health Serv Res*. Oct 16 2021;21(1):1111. doi:10.1186/s12913-021-07133-5
25. Burgess DJ ER, Allen KD, Bangerter A, Bronfort G, Cross LJ, Ferguson JE, Haley A, Hagel EM, Mahaffey MR, Matthias MS, Meis LA, Polusny MA, Serpa JG, Taylor SL, Taylor, BC. Learning to Apply Mindfulness to Pain (LAMP): Design for a pragmatic clinical trial of two mindfulness-based interventions for chronic pain. . *Pain Medicine*. 2020;21:S29–S36.
26. Maiers M, Bronfort G, Evans R, et al. Spinal manipulative therapy and exercise for seniors with chronic neck pain. *Spine J*. Sep 1 2014;14(9):1879-89. doi:10.1016/j.spinee.2013.10.035
27. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. *Chiropr Man Therap*. 2019;27:21. doi:10.1186/s12998-019-0243-1

28. Maiers M, Hartvigsen J, Evans R, et al. Short- or Long-Term Treatment of Spinal Disability in Older Adults With Manipulation and Exercise. *Arthritis Care Res (Hoboken)*. Nov 2019;71(11):1516-1524. doi:10.1002/acr.23798
29. Bronfort G, Maiers M, Schulz C, et al. Multidisciplinary integrative care versus chiropractic care for low back pain: a randomized clinical trial. *Chiropr Man Therap*. Mar 1 2022;30(1):10. doi:10.1186/s12998-022-00419-3
30. Hadlandsmyth K, Conrad M, Steffensmeier KS, et al. Enhancing the Biopsychosocial Approach to Perioperative Care: A Pilot Randomized Trial of the Perioperative Pain Self-management (PePS) Intervention. *Ann Surg*. Jan 1 2022;275(1):e8-e14. doi:10.1097/SLA.0000000000004671
31. Dindo L, Zimmerman MB, Hadlandsmyth K, et al. Acceptance and Commitment Therapy for Prevention of Chronic Postsurgical Pain and Opioid Use in At-Risk Veterans: A Pilot Randomized Controlled Study. *J Pain*. Oct 2018;19(10):1211-1221. doi:10.1016/j.jpain.2018.04.016
32. Steffensmeier KS, Van Tiem J, Obrecht A, Conrad M, Vander Weg MW, Hadlandsmyth K. The Impact of Preoperative Distress: A Qualitative analysis of the Perioperative Pain Self-Management Intervention. *Pain Manag Nurs*. Apr 2022;23(2):212-219. doi:10.1016/j.pmn.2021.05.010
33. Bokhour BG, Haun JN, Hyde J, Charns M, Kligler B. Transforming the Veterans Affairs to a Whole Health System of Care: Time for Action and Research. *Med Care*. Apr 2020;58(4):295-300. doi:10.1097/MLR.0000000000001316
34. Veterans Health Administration. Accessed October 12, 2022. https://www.va.gov/health/aboutVHA.asp#:~:text=The%20Veterans%20Health%20Administration%20(VHA,Veterans%20enrolled%20in%20the%20VA
35. Kerns RD, Otis J, Rosenberg R, Reid MC. Veterans' reports of pain and associations with ratings of health, health-risk behaviors, affective distress, and use of the healthcare system. *J Rehabil Res Dev*. Sep-Oct 2003;40(5):371-9.
36. Goulet JL, Kerns RD, Bair M, et al. The musculoskeletal diagnosis cohort: examining pain and pain care among veterans. *Pain*. Aug 2016;157(8):1696-703. doi:10.1097/j.pain.0000000000000567
37. Gellad WF, Good CB, Shulkin DJ. Addressing the Opioid Epidemic in the United States: Lessons From the Department of Veterans Affairs. *JAMA Intern Med*. May 1 2017;177(5):611-612. doi:10.1001/jamainternmed.2017.0147
38. Hadlandsmyth K, Mosher H, Vander Weg MW, Lund BC. Decline in Prescription Opioids Attributable to Decreases in Long-Term Use: A Retrospective Study in the Veterans Health Administration 2010-2016. *J Gen Intern Med*. Jun 2018;33(6):818-824. doi:10.1007/s11606-017-4283-8
39. Bennett AS, Elliott L, Golub A. Veterans' Health and Opioid Safety-Contexts, Risks, and Outreach Implications. *Fed Pract*. Jun 2015;32(6):4-7.
40. Hudson TJ, Painter JT, Martin BC, et al. Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans. *Pain*. Jun 2017;158(6):1039-1045. doi:10.1097/j.pain.0000000000000874
41. Prunuske JP, St Hill CA, Hager KD, et al. Opioid prescribing patterns for non-malignant chronic pain for rural versus non-rural US adults: a population-based study using 2010 NAMCS data. *BMC Health Serv Res*. Nov 19 2014;14:563. doi:10.1186/s12913-014-0563-8
42. Garcia MC, Heilig CM, Lee SH, et al. Opioid Prescribing Rates in Nonmetropolitan and Metropolitan Counties Among Primary Care Providers Using an Electronic Health Record System - United States, 2014-2017. *MMWR Morb Mortal Wkly Rep*. Jan 18 2019;68(2):25-30. doi:10.15585/mmwr.mm6802a1

43. Karran EL, Grant AR, Moseley GL. Low back pain and the social determinants of health: a systematic review and narrative synthesis. *Pain*. Nov 2020;161(11):2476-2493. doi:10.1097/j.pain.0000000000001944
44. Higgins DM, Fenton BT, Driscoll MA, et al. Gender Differences in Demographic and Clinical Correlates among Veterans with Musculoskeletal Disorders. *Womens Health Issues*. Jul - Aug 2017;27(4):463-470. doi:10.1016/j.whi.2017.01.008
45. Pinheiro MB, Ferreira ML, Refshauge K, et al. Symptoms of depression as a prognostic factor for low back pain: a systematic review. *Spine J*. Jan 1 2016;16(1):105-16. doi:10.1016/j.spinee.2015.10.037
46. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA*. Apr 7 2010;303(13):1295-302. doi:10.1001/jama.2010.344
47. Karran E, Grant A, Moseley L. Low back pain and the social determinants of health: a systematic review and narrative synthesis. *Pain*. 08/16 2020;161doi:10.1097/j.pain.0000000000001944
48. Janevic MR, McLaughlin SJ, Heapy AA, Thacker C, Piette JD. Racial and Socioeconomic Disparities in Disabling Chronic Pain: Findings From the Health and Retirement Study. *J Pain*. Dec 2017;18(12):1459-1467. doi:10.1016/j.jpain.2017.07.005
49. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. *MMWR Morb Mortal Wkly Rep*. Sep 14 2018;67(36):1001-1006. doi:10.15585/mmwr.mm6736a2
50. Ashworth J, Konstantinou K, Dunn KM. Prognostic factors in non-surgically treated sciatica: a systematic review. *BMC Musculoskelet Disord*. Sep 25 2011;12:208. doi:10.1186/1471-2474-12-208
51. Hasenbring M, Marienfeld G, Kuhlendahl D, Soyka D. Risk factors of chronicity in lumbar disc patients. A prospective investigation of biologic, psychologic, and social predictors of therapy outcome. *Spine*. Dec 15 1994;19(24):2759-65. doi:10.1097/00007632-199412150-00004
52. Cook CE, Taylor J, Wright A, Milosavljevic S, Goode A, Whitford M. Risk factors for first time incidence sciatica: a systematic review. *Physiother Res Int*. Jun 2014;19(2):65-78. doi:10.1002/pri.1572
53. Karos K, Williams ACC, Meulders A, Vlaeyen JWS. Pain as a threat to the social self: a motivational account. *Pain*. Sep 2018;159(9):1690-1695. doi:10.1097/j.pain.0000000000001257
54. Sturgeon JA, Zautra AJ. Social pain and physical pain: shared paths to resilience. *Pain Manag*. 2016;6(1):63-74. doi:10.2217/pmt.15.56
55. Reeves E. A synthesis of the literature on trauma-informed care. *Issues Ment Health Nurs*. 2015;36(9):698-709. doi:10.3109/01612840.2015.1025319
56. Landes SD, London AS, Wilmoth JM. Mortality among veterans and non-veterans: Does type of health care coverage matter? *Population Research and Policy Review*. 2018;37(4):517-537.
57. Duan-Porter W, Martinson BC, Greer N, et al. Evidence Review-Social Determinants of Health for Veterans. *J Gen Intern Med*. Oct 2018;33(10):1785-1795. doi:10.1007/s11606-018-4566-8
58. Driscoll MA, Higgins DM, Seng EK, et al. Trauma, social support, family conflict, and chronic pain in recent service veterans: does gender matter? *Pain Med*. Jun 2015;16(6):1101-11. doi:10.1111/pme.12744
59. Foster NE, Delitto A. Embedding psychosocial perspectives within clinical management of low back pain: integration of psychosocially informed management principles into physical therapist practice--challenges and opportunities. *Phys Ther*. May 2011;91(5):790-803. doi:10.2522/ptj.20100326

60. Foster NE, Delitto A. Embedding psychosocial perspectives within clinical management of low back pain: integration of psychosocially informed management principles into physical therapist practice—challenges and opportunities. *Physical therapy*. 2011;91(5):790-803.
61. Craig KD, Holmes C, Hudspith M, et al. Pain in persons who are marginalized by social conditions. *Pain*. Feb 2020;161(2):261-265. doi:10.1097/j.pain.0000000000001719
62. Foster NE, Anema JR, Cherkin D, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet*. Jun 9 2018;391(10137):2368-2383. doi:10.1016/s0140-6736(18)30489-6
63. Mansell G, Hall A, Toomey E. Behaviour change and self-management interventions in persistent low back pain. *Best Pract Res Clin Rheumatol*. Dec 2016;30(6):994-1002. doi:10.1016/j.berh.2017.07.004
64. Bair MJ, Matthias MS, Nyland KA, et al. Barriers and facilitators to chronic pain self-management: a qualitative study of primary care patients with comorbid musculoskeletal pain and depression. *Pain Med*. Oct 2009;10(7):1280-90. doi:10.1111/j.1526-4637.2009.00707.x
65. Upshur CC, Bacigalupe G, Luckmann R. "They Don't Want Anything to Do with You": Patient Views of Primary Care Management of Chronic Pain. *Pain Med*. 2010/12 2010;11(12):1791-1798. doi:10.1111/j.1526-4637.2010.00960.x
66. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep*. Mar 18 2016;65(1):1-49. doi:10.15585/mmwr.rr6501e1
67. VA/DoD. *VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain*. 2017.
68. Kroesen K, Baldwin CM, Brooks AJ, Bell IR. US military veterans' perceptions of the conventional medical care system and their use of complementary and alternative medicine. *Fam Pract*. Feb 2002;19(1):57-64.
69. Fletcher CE, Mitchinson AR, Trumble E, Hinshaw DB, Dusek JA. Providers' and Administrators' Perceptions of Complementary and Integrative Health Practices Across the Veterans Health Administration. *J Altern Complement Med*. Jan 2017;23(1):26-34. doi:10.1089/acm.2016.0236
70. Elwy AR, Johnston JM, Bormann JE, Hull A, Taylor SL. A systematic scoping review of complementary and alternative medicine mind and body practices to improve the health of veterans and military personnel. *Med Care*. Dec 2014;52(12 Suppl 5):S70-82. doi:10.1097/MLR.0000000000000228
71. Denneson LM, Corson K, Dobscha SK. Complementary and alternative medicine use among veterans with chronic noncancer pain. *J Rehabil Res Dev*. 2011;48(9):1119-28.
72. Bolton RE, Bokhour BG, Dvorin K, et al. Garnering Support for Complementary and Integrative Health Implementation: A Qualitative Study of VA Healthcare Organization Leaders. *J Altern Complement Med*. Mar 2021;27(S1):S81-S88. doi:10.1089/acm.2020.0383
73. Taylor SL, Bolton R, Huynh A, et al. What Should Health Care Systems Consider When Implementing Complementary and Integrative Health: Lessons from Veterans Health Administration. *J Altern Complement Med*. Mar 2019;25(S1):S52-S60. doi:10.1089/acm.2018.0445
74. Kligler B. Integrative Health in the Veterans Health Administration. *Med Acupunct*. Aug 1 2017;29(4):187-188. doi:10.1089/acu.2017.29055.bkl
75. Administration DoVAVH. *Whole Health System Implementation Guide*. 2021.
76. Tegner H, Frederiksen P, Esbensen BA, Juhl C. Neurophysiological Pain Education for Patients With Chronic Low Back Pain: A Systematic Review and Meta-Analysis. *Clin J Pain*. Aug 2018;34(8):778-786. doi:10.1097/AJP.0000000000000594

77. Morone NE, Greco CM, Moore CG, et al. A mind-body program for older adults with chronic low back pain: a randomized clinical trial. *JAMA Internal Medicine*. 2016;doi:10.1001/jamainternmed.2015.8033
78. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA*. Mar 22-29 2016;315(12):1240-9. doi:10.1001/jama.2016.2323
79. Wood L, Hendrick PA. A systematic review and meta-analysis of pain neuroscience education for chronic low back pain: Short-and long-term outcomes of pain and disability. *Eur J Pain*. Feb 2019;23(2):234-249. doi:10.1002/ejp.1314
80. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. 2020;
81. Meng XG, Yue SW. Efficacy of aerobic exercise for treatment of chronic low back pain: a meta-analysis. *Am J Phys Med Rehabil*. May 2015;94(5):358-65. doi:10.1097/PHM.0000000000000188
82. Carnes D, Homer KE, Miles CL, et al. Effective delivery styles and content for self-management interventions for chronic musculoskeletal pain: a systematic literature review. *Clin J Pain*. May 2012;28(4):344-54. doi:10.1097/AJP.0b013e31822ed2f3
83. Ghildayal N, Johnson PJ, Evans RL, Kreitzer MJ. Complementary and Alternative Medicine Use in the US Adult Low Back Pain Population. *Glob Adv Health Med*. Jan 2016;5(1):69-78. doi:10.7453/gahmj.2015.104
84. Hilton L, Hempel S, Ewing BA, et al. Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Ann Behav Med*. Apr 2017;51(2):199-213. doi:10.1007/s12160-016-9844-2
85. McClintock AS, McCarrick SM, Garland EL, Zeidan F, Zgierska AE. Brief Mindfulness-Based Interventions for Acute and Chronic Pain: A Systematic Review. *J Altern Complement Med*. Mar 2019;25(3):265-278. doi:10.1089/acm.2018.0351
86. Jackson W, Zale EL, Berman SJ, et al. Physical functioning and mindfulness skills training in chronic pain: a systematic review. *J Pain Res*. 2019;12:179-189. doi:10.2147/JPR.S172733
87. Polusny MA, Erbes CR, Thuras P, et al. Mindfulness-Based Stress Reduction for Posttraumatic Stress Disorder Among Veterans: A Randomized Clinical Trial. *JAMA*. Aug 04 2015;314(5):456-65. doi:10.1001/jama.2015.8361
88. Goldberg SB, Tucker RP, Greene PA, et al. Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. *Clin Psychol Rev*. Feb 2018;59:52-60. doi:10.1016/j.cpr.2017.10.011
89. Garland EL, Hanley AW, Nakamura Y, et al. Mindfulness-Oriented Recovery Enhancement vs Supportive Group Therapy for Co-occurring Opioid Misuse and Chronic Pain in Primary Care: A Randomized Clinical Trial. *JAMA Internal Medicine*. 2022;doi:10.1001/jamainternmed.2022.0033
90. Garland EL, Brintz CE, Hanley AW, et al. Mind-Body Therapies for Opioid-Treated Pain: A Systematic Review and Meta-analysis. *JAMA Intern Med*. Jan 1 2020;180(1):91-105. doi:10.1001/jamainternmed.2019.4917
91. Goldsmith E, Koffel E, Ackland P, et al. Implementation of Psychotherapies and Mindfulness-based Stress Reduction for Chronic Pain and Chronic Mental Health Conditions: A Systematic Review. 2021;
92. Du S, Hu L, Dong J, et al. Self-management program for chronic low back pain: A systematic review and meta-analysis. *Patient Education and Counseling*. Jan 2017;100(1):37-49. doi:10.1016/j.pec.2016.07.029

93. van Erp RMA, Huijnen IPJ, Jakobs MLG, Kleijnen J, Smeets R. Effectiveness of Primary Care Interventions Using a Biopsychosocial Approach in Chronic Low Back Pain: A Systematic Review. *Pain Pract*. Feb 2019;19(2):224-241. doi:10.1111/papr.12735
94. Hall A, Richmond H, Copsey B, et al. Physiotherapist-delivered cognitive-behavioural interventions are effective for low back pain, but can they be replicated in clinical practice? A systematic review. *Disabil Rehabil*. Jan 2018;40(1):1-9. doi:10.1080/09638288.2016.1236155
95. Foster G, Taylor SJC, Eldridge S, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database of Systematic Reviews*. 2007;(4)doi:10.1002/14651858.CD005108.pub2
96. Du S, Hu L, Dong J, et al. Self-management program for chronic low back pain: A systematic review and meta-analysis. *Patient Educ Couns*. Jan 2017;100(1):37-49. doi:10.1016/j.pec.2016.07.029
97. Foster G, Taylor SJ, Eldridge S, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane database of systematic reviews*. 2007;(4)
98. Michie S AL, West R. *The Behaviour Change Wheel: A Guide to Designing Interventions.* Silverback Publishing; 2014.
99. Kligler B, Bair MJ, Banerjea R, et al. Clinical Policy Recommendations from the VHA State-of-the-Art Conference on Non-Pharmacological Approaches to Chronic Musculoskeletal Pain. *J Gen Intern Med*. May 2018;33(Suppl 1):16-23. doi:10.1007/s11606-018-4323-z
100. Farmer MM, McGowan M, Yuan AH, Whitehead AM, Osawe U, Taylor SL. Complementary and Integrative Health Approaches Offered in the Veterans Health Administration: Results of a National Organizational Survey. *J Altern Complement Med*. Mar 2021;27(S1):S124-S130. doi:10.1089/acm.2020.0395
101. Taylor SL, Hoggatt KJ, Kligler B. Complementary and Integrated Health Approaches: What Do Veterans Use and Want. *J Gen Intern Med*. Jul 2019;34(7):1192-1199. doi:10.1007/s11606-019-04862-6
102. Giannitrapani K, McCaa M, Haverfield M, et al. Veteran Experiences Seeking Non-pharmacologic Approaches for Pain. *Mil Med*. Nov 1 2018;183(11-12):e628-e634. doi:10.1093/milmed/usy018
103. Giannitrapani KF, Ahluwalia SC, McCaa M, Pisciotta M, Dobscha S, Lorenz KA. Barriers to Using Nonpharmacologic Approaches and Reducing Opioid Use in Primary Care. *Pain Med*. Jul 1 2018;19(7):1357-1364. doi:10.1093/pm/pnx220
104. Purcell N, Zamora K, Gibson C, et al. Patient Experiences With Integrated Pain Care: A Qualitative Evaluation of One VA's Biopsychosocial Approach to Chronic Pain Treatment and Opioid Safety. *Glob Adv Health Med*. 2019;8:2164956119838845. doi:10.1177/2164956119838845
105. Matthias MS, Miech EJ, Myers LJ, Sargent C, Bair MJ. An expanded view of self-management: patients' perceptions of education and support in an intervention for chronic musculoskeletal pain. *Pain Med*. Aug 2012;13(8):1018-28. doi:10.1111/j.1526-4637.2012.01433.x
106. Matthias MS, Miech EJ, Myers LJ, Sargent C, Bair MJ. A qualitative study of chronic pain in Operation Enduring Freedom/Operation Iraqi Freedom veterans: "A burden on my soul". *Mil Med*. Jan 2014;179(1):26-30. doi:10.7205/MILMED-D-13-00196
107. Taylor SL, Giannitrapani KF, Yuan A, Marshall N. What Patients and Providers Want to Know About Complementary and Integrative Health Therapies. *J Altern Complement Med*. Jan 2018;24(1):85-89. doi:10.1089/acm.2017.0074

108. Glynn LH, Chen JA, Dawson TC, Gelman H, Zeliadt SB. Bringing chronic-pain care to rural veterans: A telehealth pilot program description. *Psychol Serv*. Aug 2021;18(3):310-318. doi:10.1037/ser0000408
109. Burgess DJ, Hagel Campbell E, Hammett P, et al. Taking ACTION to Reduce Pain: a Randomized Clinical Trial of a Walking-Focused, Proactive Coaching Intervention for Black Patients with Chronic Musculoskeletal Pain. *J Gen Intern Med*. Feb 7 2022;doi:10.1007/s11606-021-07376-2
110. Joseph A, Fu S. Proactive outreach strategies to connect smokers with tobacco cessation treatment. *JAMA Intern Med*. Feb 2015;175(2):226-7. doi:10.1001/jamainternmed.2014.5291
111. Klap R, Darling JE, Hamilton AB, et al. Prevalence of Stranger Harassment of Women Veterans at Veterans Affairs Medical Centers and Impacts on Delayed and Missed Care. *Womens Health Issues*. Mar-Apr 2019;29(2):107-115. doi:10.1016/j.whi.2018.12.002
112. Kelly MM, Vogt DS, Scheiderer EM, Ouimette P, Daley J, Wolfe J. Effects of military trauma exposure on women veterans' use and perceptions of Veterans Health Administration care. *J Gen Intern Med*. Jun 2008;23(6):741-7. doi:10.1007/s11606-008-0589-x
113. Chen CK, Palfrey A, Shreck E, et al. Implementation of Telemental Health (TMH) psychological services for rural veterans at the VA New York Harbor Healthcare System. *Psychol Serv*. Feb 2021;18(1):1-10. doi:10.1037/ser0000323
114. Veazie S, Bourne D, Peterson K, Anderson J. Evidence brief: video telehealth for primary care and mental health services. 2019;
115. Mochari-Greenberger H, Peters A, Vue L, Pande RL. A Nationally Scaled Telebehavioral Health Program for Chronic Pain: Characteristics, Goals, and Psychological Outcomes. *Telemed J E Health*. Aug 2017;23(8):640-648. doi:10.1089/tmj.2016.0188
116. Mathews CP, Convoy S, Heyworth L, Knisely M. Evaluation of the Use of Telehealth Video Visits for Veterans With Chronic Pain. *Pain Manag Nurs*. Aug 2022;23(4):418-423. doi:10.1016/j.pmn.2022.02.006
117. Elliott VL. Telehealth and telemedicine: description and issues. *United States Senate*. 2016;
118. Ferguson JM, Jacobs J, Yefimova M, Greene L, Heyworth L, Zulman DM. Virtual care expansion in the Veterans Health Administration during the COVID-19 pandemic: clinical services and patient characteristics associated with utilization. *J Am Med Inform Assoc*. Mar 1 2021;28(3):453-462. doi:10.1093/jamia/ocaa284
119. VA. With telehealth, Veterans can access care when and where they need it. 2022. https://news.va.gov/108453/telehealth-access-care-when-where-need/#:~:text=Last%20year%2C%20more%20than%202.3%20million%20Veterans%20used%20telehealth%20to,facility%20or%20wherever%20they%20are.
120. Kobe EA, Lewinski AA, Jeffreys AS, et al. Implementation of an Intensive Telehealth Intervention for Rural Patients with Clinic-Refractory Diabetes. *J Gen Intern Med*. Sep 2022;37(12):3080-3088. doi:10.1007/s11606-021-07281-8
121. Day SC, Day G, Keller M, et al. Personalized implementation of video telehealth for rural veterans (PIVOT-R). *Mhealth*. 2021;7:24. doi:10.21037/mhealth.2020.03.02
122. Chen JA, DeFaccio RJ, Gelman H, et al. Telehealth and Rural-Urban Differences in Receipt of Pain Care in the Veterans Health Administration. *Pain Med*. Mar 2 2022;23(3):466-474. doi:10.1093/pm/pnab194
123. Jacobs J, Ferguson JM, Van Campen J, et al. Organizational and External Factors Associated with Video Telehealth Use in the Veterans Health Administration Before and During the COVID-19 Pandemic. *Telemed J E Health*. Feb 2022;28(2):199-211. doi:10.1089/tmj.2020.0530

124. Office of Connected Care. October 12, 2022. https://connectedcare.va.gov/partners/atlas
125. Zulman DM, Wong EP, Slightam C, et al. Making connections: nationwide implementation of video telehealth tablets to address access barriers in veterans. *JAMIA Open*. Oct 2019;2(3):323-329. doi:10.1093/jamiaopen/ooz024
126. Burris JL, Borger TN, Baker TB, et al. Proposing a Model of Proactive Outreach to Advance Clinical Research and Care Delivery for Patients Who Use Tobacco. *J Gen Intern Med*. Aug 2022;37(10):2548-2552. doi:10.1007/s11606-022-07553-x
127. Holtrop JS, Estabrooks PA, Gaglio B, et al. Understanding and applying the RE-AIM framework: Clarifications and resources. *Journal of Clinical and Translational Science*. 2021;5(1):e126. e126. doi:10.1017/cts.2021.789
128. Lehman BJ, David DM, Gruber JA. Rethinking the biopsychosocial model of health: Understanding health as a dynamic system. *Soc Personal Psychol*. Aug 2017;11(8)doi:ARTN e12328
10.1111/spc3.12328
129. Alcaraz KI, Sly J, Ashing K, et al. The ConNECT Framework: a model for advancing behavioral medicine science and practice to foster health equity. *J Behav Med*. Feb 2017;40(1):23-38. doi:10.1007/s10865-016-9780-4
130. Pearson N, Naylor P-J, Ashe MC, Fernandez M, Yoong SL, Wolfenden L. Guidance for conducting feasibility and pilot studies for implementation trials. *Pilot and feasibility studies*. 2020;6(1):1-12.
131. Landes SJ, McBain SA, Curran GM. Reprint of: An introduction to effectiveness-implementation hybrid designs. *Psychiatry Research*. 2020/01/01/ 2020;283:112630. doi:https://doi.org/10.1016/j.psychres.2019.112630
132. Burgess DJ, Evans R, Allen KD, et al. Learning to Apply Mindfulness to Pain (LAMP): Design for a Pragmatic Clinical Trial of Two Mindfulness-Based Interventions for Chronic Pain. *Pain Medicine*. 2020;21(Supplement_2):S29-S36. doi:10.1093/pm/pnaa337
133. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*. Mar 2012;50(3):217-26. doi:10.1097/MLR.0b013e3182408812
134. Burgess DJ, Hagel Campbell E, Hammett P, et al. Taking ACTION to Reduce Pain: a Randomized Clinical Trial of a Walking-Focused, Proactive Coaching Intervention for Black Patients with Chronic Musculoskeletal Pain. *Journal of General Internal Medicine*. 2022:1-9.
135. Hadlandsmyth K, Driscoll M, Burgess DJ, Hadlandsmyth K, Goulet JL. Providing quality pain care to United States Military Veterans: Reaching the marginalized and under-served. LIPPINCOTT WILLIAMS & WILKINS TWO COMMERCE SQ, 2001 MARKET ST, PHILADELPHIA …; 2020:A150-A150.
136. Bhimani RH, Cross LJ, Taylor BC, et al. Taking ACTION to reduce pain: ACTION study rationale, design and protocol of a randomized trial of a proactive telephone-based coaching intervention for chronic musculoskeletal pain among African Americans. *BMC Musculoskelet Disord*. Jan 13 2017;18(1):15. doi:10.1186/s12891-016-1363-6
137. Hammett PJ, Eliacin J, Makris UE, et al. An Analysis of the Role of Mental Health in a Randomized Trial of a Walking Intervention for Black Veterans with Chronic Pain. *J Pain*. Sep 23 2022;doi:10.1016/j.jpain.2022.07.002
138. Evans R, Bronfort G, Schulz C, et al. Supervised exercise with and without spinal manipulation performs similarly and better than home exercise for chronic neck pain: a randomized controlled trial. *Spine (Phila Pa 1976)*. May 15 2012;37(11):903-14. doi:10.1097/BRS.0b013e31823b3bdf

139. Evans R, Haas M, Schulz C, Leininger B, Hanson L, Bronfort G. Spinal manipulation and exercise for low back pain in adolescents: a randomized trial. *Pain*. Jul 2018;159(7):1297-1307. doi:10.1097/j.pain.0000000000001211
140. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. journal article. *Chiropractic & Manual Therapies*. May 15 2019;27(1):21. doi:10.1186/s12998-019-0243-1
141. Nevedal AL, Reardon CM, Opra Widerquist MA, et al. Rapid versus traditional qualitative analysis using the Consolidated Framework for Implementation Research (CFIR). *Implement Sci*. Jul 2 2021;16(1):67. doi:10.1186/s13012-021-01111-5
142. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. Nov 2005;15(9):1277-88. doi:10.1177/1049732305276687
143. Glasgow RE, Harden SM, Gaglio B, et al. *Use of the RE-AIM Framework: Translating Research to Practice with Novel Applications and Emerging Directions*. Frontiers Media SA; 2021.
144. Matthias MS, Donaldson MT, Jensen AC, Krebs EE. "I Was a Little Surprised": Qualitative Insights From Patients Enrolled in a 12-Month Trial Comparing Opioids With Nonopioid Medications for Chronic Musculoskeletal Pain. *J Pain*. Sep 2018;19(9):1082-1090. doi:10.1016/j.jpain.2018.04.008
145. Matthias MS, Miech EJ, Myers LJ, Sargent C, Bair MJ. "There's more to this pain than just pain": how patients' understanding of pain evolved during a randomized controlled trial for chronic pain. *The journal of pain*. 2012/06// 2012;13(6):571-578. doi:10.1016/j.jpain.2012.03.007
146. Matthias MS, Bair MJ, Nyland KA, et al. Self-management support and communication from nurse care managers compared with primary care physicians: a focus group study of patients with chronic musculoskeletal pain. *Pain Manag Nurs*. Mar 2010;11(1):26-34. doi:10.1016/j.pmn.2008.12.003
147. Matthias MS, Henry SG. Reducing Frustration and Improving Management of Chronic Pain in Primary Care: Is Shared Decision-making Sufficient? *J Gen Intern Med*. Jan 2022;37(1):227-228. doi:10.1007/s11606-021-06967-3
148. Matthias MS, Talib TL, Huffman MA. Managing Chronic Pain in an Opioid Crisis: What Is the Role of Shared Decision-Making? *Health Commun*. Sep 2020;35(10):1239-1247. doi:10.1080/10410236.2019.1625000
149. Shields CG, Fuzzell LN, Christ SL, Matthias MS. Patient and provider characteristics associated with communication about opioids: An observational study. *Patient Educ Couns*. May 2019;102(5):888-894. doi:10.1016/j.pec.2018.12.005
150. Matthias MS, Adams J, Burgess D, et al. Corrigendum to: Communication and Activation in Pain to Enhance Relationships and Treat Pain with Equity (COOPERATE): Rationale, study design, methods, and sample characteristics (Contemporary Clinical Trials, volume 118, article number 106790). *Contemp Clin Trials*. Sep 2022;120:106883. doi:10.1016/j.cct.2022.106883
151. Matthias MS, Adams J, Burgess DJ, et al. Communication and Activation in Pain to Enhance Relationships and Treat Pain with Equity (COOPERATE): Rationale, study design, methods, and sample characteristics. *Contemp Clin Trials*. Jul 2022;118:106790. doi:10.1016/j.cct.2022.106790
152. Rich TL, Voss G, Fairhurst S, et al. Feasibility testing of a novel prosthetic socket sensor system. *Disabil Rehabil*. Jul 7 2022:1-8. doi:10.1080/09638288.2022.2093997
153. Olney CM, Ferguson JE, Voss G, et al. Supine arm cycling during the post-flap recovery period for persons with spinal cord injuries: The multi-purpose arm cycle ergometer (M-PACE) safety and pilot testing. *J Spinal Cord Med*. Nov 2 2021:1-8. doi:10.1080/10790268.2021.1975082

154. Bernstein JPK, Mattek N, Dorociak KE, et al. Age Predicts Older Adults' Driving Self-Regulation but Not Dangerous Driving Behaviors after Controlling for Executive Function. *Gerontology*. 2022;68(1):98-105. doi:10.1159/000515497
155. Dorociak KE, Mattek N, Ferguson JE, et al. Subtle Changes in Medication-taking Are Associated With Incident Mild Cognitive Impairment. *Alzheimer Dis Assoc Disord*. Jul-Sep 01 2021;35(3):237-243. doi:10.1097/WAD.0000000000000439
156. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ*. May 8 2015;350:h2147. doi:10.1136/bmj.h2147
157. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH Task Force on research standards for chronic low back pain. *J Pain*. Jun 2014;15(6):569-85. doi:10.1016/j.jpain.2014.03.005
158. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. Dec 2003;106(3):337-45.
159. Joosten YA, Israel TL, Williams NA, et al. Community Engagement Studios: A Structured Approach to Obtaining Meaningful Input From Stakeholders to Inform Research. *Acad Med*. Dec 2015;90(12):1646-50. doi:10.1097/ACM.0000000000000794
160. Forsythe LP, Ellis LE, Edmundson L, et al. Patient and Stakeholder Engagement in the PCORI Pilot Projects: Description and Lessons Learned. *J Gen Intern Med*. Jan 2016;31(1):13-21. doi:10.1007/s11606-015-3450-z
161. McCreight MS, Rabin BA, Glasgow RE, et al. Using the Practical, Robust Implementation and Sustainability Model (PRISM) to qualitatively assess multilevel contextual factors to help plan, implement, evaluate, and disseminate health services programs. *Translational Behavioral Medicine*. 2019;9(6):1002-1011. doi:10.1093/tbm/ibz085
162. Palinkas LA, Zatzick D. Rapid Assessment Procedure Informed Clinical Ethnography (RAPICE) in Pragmatic Clinical Trials of Mental Health Services Implementation: Methods and Applied Case Study. *Adm Policy Ment Health*. Mar 2019;46(2):255-270. doi:10.1007/s10488-018-0909-3
163. Evans R, Bronfort G, Maiers M, Schulz C, Hartvigsen J. "I know it's changed": a mixed-methods study of the meaning of Global Perceived Effect in chronic neck pain patients. *Eur Spine J*. Apr 2014;23(4):888-97. doi:10.1007/s00586-013-3149-y
164. Maiers M, Hondras MA, Salsbury SA, Bronfort G, Evans R. What do patients value about spinal manipulation and home exercise for back-related leg pain? A qualitative study within a controlled clinical trial. *Manual Therapy*. 2016;26:183-191. doi:10.1016/j.math.2016.09.008
165. Bronfort G, Evans RL, Anderson AV, et al. Nonoperative treatments for sciatica: a pilot study for a randomized clinical trial. *Journal of manipulative and physiological therapeutics*. Oct 2000;23(8):536-44. doi:10.1067/mmt.2000.109678
166. Bronfort G, Evans RL, Maiers M, Anderson AV. Spinal manipulation, epidural injections, and self-care for sciatica: a pilot study for a randomized clinical trial. *Journal of manipulative and physiological therapeutics*. Oct 2004;27(8):503-8. doi:10.1016/j.jmpt.2004.08.002
167. Evans R, Bronfort G, Bittell S, Anderson AV. A pilot study for a randomized clinical trial assessing chiropractic care, medical care, and self-care education for acute and subacute neck pain patients. *Journal of manipulative and physiological therapeutics*. Sep 2003;26(7):403-11. doi:10.1016/s0161-4754(03)00093-9
168. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *Morbidity and Mortality Weekly Report*. 2018;67(36):1001.

169. NIH-DOD-VA Pain Management Collaboratory Phenotypes Work Group. Tools & Measures for Researchers. Pain Management Collaboratory Coordinating Center, Yale University. Accessed 02/27/2022,
170. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain*. Jun 2012;153(6):1148-1158. doi:10.1016/j.pain.2012.03.003
171. Rief W, Kopp M, Awarzamani R, Weise C. Selected trends in psychotherapy research: an index analysis of RCTs. *Clinical Psychology in Europe*. 2022;4(2):1-15.
172. Crane RS, Hecht FM. Intervention Integrity in Mindfulness-Based Research. *Mindfulness (N Y)*. 2018;9(5):1370-1380. doi:10.1007/s12671-018-0886-3
173. Michie S, Wood CE, Johnston M, Abraham C, Francis JJ, Hardeman W. Behaviour change techniques: the development and evaluation of a taxonomic method for reporting and describing behaviour change interventions (a suite of five studies involving consensus methods, randomised controlled trials and analysis of qualitative data). *Health technology assessment*. Nov 2015;19(99):1-188. doi:10.3310/hta19990
174. Serpa JG, Atwood K, Shamblen SR, Sangpukdee A, Jents MA, Wolf C. Training Mindfulness Facilitators: Evaluating the VA CALM Program at the Veterans Health Administration. *Mindfulness*. 2022;13(7):1662-1670.
175. Crane RS, Kuyken W. The Mindfulness-Based Interventions: Teaching Assessment Criteria (MBI:TAC): reflections on implementation and development. *Curr Opin Psychol*. Aug 2019;28:6-10. doi:10.1016/j.copsyc.2018.10.004
176. Skelly AC, Chou R, Dettori JR, et al. AHRQ Comparative Effectiveness Reviews. *Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update*. Agency for Healthcare Research and Quality (US); 2020.
177. Bronfort G, Evans R, Nelson B, Aker PD, Goldsmith CH, Vernon H. A randomized clinical trial of exercise and spinal manipulation for patients with chronic neck pain. *Spine*. Apr 1 2001;26(7):788-97; discussion 798-9.
178. Bronfort G, Maiers MJ, Evans RL, et al. Supervised exercise, spinal manipulation, and home exercise for chronic low back pain: a randomized clinical trial. *Spine J*. Jul 2011;11(7):585-98. doi:10.1016/j.spinee.2011.01.036
179. Mehling WE, Acree M, Stewart A, Silas J, Jones A. The Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2). *PLoS One*. 2018;13(12):e0208034. doi:10.1371/journal.pone.0208034
180. Michie S, Carey RN, Johnston M, et al. From Theory-Inspired to Theory-Based Interventions: A Protocol for Developing and Testing a Methodology for Linking Behaviour Change Techniques to Theoretical Mechanisms of Action. *Ann Behav Med*. Jul 11 2016;doi:10.1007/s12160-016-9816-6
181. Creswell JW. *Research Design: Qualitative, Quantitative, and Mixed Methods Approaches*. SAGE Publications; 2013.
182. Freedland KE, King AC, Ambrosius WT, et al. The selection of comparators for randomized controlled trials of health-related behavioral interventions: recommendations of an NIH expert panel. *Journal of clinical epidemiology*. 2019/06/01/ 2019;110:74-81. doi:https://doi.org/10.1016/j.jclinepi.2019.02.011
183. Ziouani S, Granados D, Borget I. How to select the best comparator? An international economic evaluation guidelines comparison. *Value in Health*. 2016;19(7):A471-A472.
184. Wandner LD, Domenichiello AF, Beierlein J, et al. NIH's Helping to End Addiction Long-term(SM) Initiative (NIH HEAL Initiative) Clinical Pain Management Common Data Element Program. *J Pain*. Sep 9 2021;doi:10.1016/j.jpain.2021.08.005

185. Cox LA, Hwang S, Haines J, et al. Using the PhenX Toolkit to Select Standard Measurement Protocols for Your Research Study. *Curr Protoc*. May 2021;1(5):e149. doi:10.1002/cpz1.149
186. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. Jan 2005;113(1-2):9-19. doi:10.1016/j.pain.2004.09.012
187. Kroenke K, Krebs EE, Turk D, et al. Core Outcome Measures for Chronic Musculoskeletal Pain Research: Recommendations from a Veterans Health Administration Work Group. *Pain Med*. Aug 1 2019;20(8):1500-1508. doi:10.1093/pm/pny279
188. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*. Mar 1994;23(2):129-38.
189. Kean J, Monahan PO, Kroenke K, et al. Comparative Responsiveness of the PROMIS Pain Interference Short Forms, Brief Pain Inventory, PEG, and SF-36 Bodily Pain Subscale. *Med Care*. Apr 2016;54(4):414-21. doi:10.1097/mlr.0000000000000497
190. Chen CX, Kroenke K, Stump T, et al. Comparative Responsiveness of the PROMIS Pain Interference Short Forms With Legacy Pain Measures: Results From Three Randomized Clinical Trials. *The journal of pain : official journal of the American Pain Society*. Jun 2019;20(6):664-675. doi:10.1016/j.jpain.2018.11.010
191. Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *JAMA*. Mar 6 2018;319(9):872-882. doi:10.1001/jama.2018.0899
192. Von Korff M, DeBar LL, Krebs EE, Kerns RD, Deyo RA, Keefe FJ. Graded chronic pain scale revised: mild, bothersome, and high-impact chronic pain. *Pain*. Mar 2020;161(3):651-661. doi:10.1097/j.pain.0000000000001758
193. Cook KF, Jensen SE, Schalet BD, et al. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. *J Clin Epidemiol*. May 2016;73:89-102. doi:10.1016/j.jclinepi.2015.08.038
194. Deyo RA, Katrina R, Buckley DI, et al. Performance of a Patient Reported Outcomes Measurement Information System (PROMIS) Short Form in Older Adults with Chronic Musculoskeletal Pain. *Pain Med*. Feb 2016;17(2):314-24. doi:10.1093/pm/pnv046
195. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. Apr 2009;114(1-3):163-73. doi:10.1016/j.jad.2008.06.026
196. Bovin MJ, Marx BP, Weathers FW, et al. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychological assessment*. Nov 2016;28(11):1379-1391. doi:10.1037/pas0000254
197. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *J Man Manip Ther*. 2009;17(3):163-70. doi:10.1179/jmt.2009.17.3.163
198. McWilliams LA, Kowal J, Wilson KG. Development and evaluation of short forms of the Pain Catastrophizing Scale and the Pain Self-efficacy Questionnaire. *Eur J Pain*. Oct 2015;19(9):1342-9. doi:10.1002/ejp.665
199. Gruber-Baldini AL, Velozo C, Romero S, Shulman LM. Validation of the PROMIS((R)) measures of self-efficacy for managing chronic conditions. *Qual Life Res*. Jul 2017;26(7):1915-1924. doi:10.1007/s11136-017-1527-3
200. Kupst MJ, Butt Z, Stoney CM, et al. Assessment of stress and self-efficacy for the NIH Toolbox for Neurological and Behavioral Function. *Anxiety Stress Coping*. 2015;28(5):531-44. doi:10.1080/10615806.2014.994204

201. Li MJ, Black DS, Garland EL. The Applied Mindfulness Process Scale (AMPS): A process measure for evaluating mindfulness-based interventions. *Pers Individ Dif*. Apr 01 2016;93:6-15. doi:10.1016/j.paid.2015.10.027
202. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. Mar 1992;3(2):143-55. doi:10.1097/00001648-199203000-00013
203. Pope C, Mays N. Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ*. 1995/07/01 1995;311(6996):42-45. doi:10.1136/bmj.311.6996.42
204. Creswell J, Plano-Clark V. *Designing and Conducting Mixed Methods Research*. vol 2nd ed. Sage Publications; 2011.
205. Lu AD, Kaul B, Reichert J, Kilbourne AM, Sarmiento KF, Whooley MA. Implementation Strategies for Frontline Healthcare Professionals: People, Process Mapping, and Problem Solving. *J Gen Intern Med*. Feb 2021;36(2):506-510. doi:10.1007/s11606-020-06169-3
206. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health*. Jan-Feb 2014;17(1):5-14. doi:10.1016/j.jval.2013.08.2291
207. Jones Rhodes WC, Ritzwoller DP, Glasgow RE. Stakeholder perspectives on costs and resource expenditures: tools for addressing economic issues most relevant to patients, providers, and clinics. *Translational behavioral medicine*. 2018;8(5):675-682.
208. Reilly KL, Kennedy S, Porter G, Estabrooks P. Comparing, Contrasting, and Integrating Dissemination and Implementation Outcomes Included in the RE-AIM and Implementation Outcomes Frameworks. *Front Public Health*. 2020;8:430. doi:10.3389/fpubh.2020.00430
209. Dopp AR, Mundey P, Beasley LO, Silovsky JF, Eisenberg D. Mixed-method approaches to strengthen economic evaluations in implementation research. *Implement Sci*. Jan 11 2019;14(1):2. doi:10.1186/s13012-018-0850-6

Appendix A – DSMP

Data and Safety Monitoring Plan (DSMP)

Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP)

NIH Institute or Center:	National Institutes of Health National Institute of Nursing Research (NINR)
Grant Number:	1UG3NR020929
Version Date:	February 2025
NINR Approval Date	
IRB Approval Date	

National Center for Complementary and Integrative Health

1 Study Overview

1.1 Purpose of Study

This research is part of a two-phase project (UG3/UH3) supported through the National Institutes of Health's Helping to End Addiction Long-term (HEAL) Initiative.

In UG3/Phase 1, we will prepare for the future UH3/Phase 2 trial. This phase focuses on advisor engagement activities (Aim 1) and a single arm pilot study (Aim 2) to assess feasibility.

In the UH3/Phase 2 we will conduct a randomized hybrid type 2 effectiveness-implementation multi-site pragmatic clinical trial of RAMP compared to Usual Care, enrolling 500 rural VA patients from the VA healthcare system, oversampling female and racial/ethnic minority patients.

1.1.1 *Project Aims*

Phase I

a. UG3/Phase 1 Aim 1: We will conduct advisor engagement activities including identifying and developing new community partnerships and using mixed methods data collection from multiple levels of advisors (n=35-50 patients, community partners, VA healthcare system leaders and staff), guided by the established REAIM/PRISM framework, to learn about key factors that can affect long-term adoption.

b. UG3/Phase 1 Aim 2: We will conduct a feasibility study of 40 rural VA patients with chronic pain to assess the feasibility of delivering RAMP (pilot) in terms of recruitment and engagement, intervention fidelity and adherence, data collection, and other key metrics.

Phase II

UH3/Phase 2 Aim 1 (Effectiveness): To assess the relative effectiveness of RAMP in rural VA patients in terms of pain interference (primary outcome) at 3 and 6 months and secondary outcomes of opioid use and other HEAL recommended outcomes. We will also perform additional exploratory analyses of women and minority Veterans' primary and secondary outcomes.

UH3/Phase 2 Aim 2 (Implementation): To work iteratively with multiple levels of advisors (n=35-50 patients, community advisors, VA healthcare system leaders and staff) to evaluate intervention implementation strategies used in the trial and adapt these strategies to scale up RAMP within the national VA healthcare system. This will include:

a. Conducting mixed-methods assessments of advisor and randomized trial participant views of implementation-related barriers and facilitators, resource needs, and other RE-AIM/PRISM domains.

b. Working with advisors to co-create additional plausible strategies for overcoming barriers to implementation of RAMP in the national VA healthcare system.

c. Conducting budget impact analyses using models informed by advisor views to inform future decision making.

The Data and Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the Minneapolis VA IRB.

2 Protocol Amendments

We have used the NCCIH Guidance on Changes in Clinical Studies in Active Awards to define protocol amendments. These include:

- Any change that may affect patient safety (e.g., change in eligibility criteria; change in risk, regardless of whether risk is increased or decreased)
- Any change that changes scientific intent or study design, or affects human subject protection
- Addition/deletion of a site
- Addition/deletion of key study personnel
- A change of institution for key study personnel
- A change in enrollment targets.

Protocol amendments will be submitted to NINR and the IRB for approval prior to implementation except when necessary to protect the safety, rights, or welfare of participants. All protocol amendments will be provided to the DSMB in semi-annual reports (or sooner if directed by NINR, the IRB or other regulatory bodies).

Protocol changes that do not meet the definitions described above are considered editorial or administrative and do not require approval. Protocol amendments not submitted for prior approval will be reported to NINR within 5 business days.

3 Multi-site Studies

This is a multi-site study with the Center for Care Delivery and Outcomes Research (CCDOR) at the Minneapolis VA Healthcare System serving as the Coordinating Center Institution. All screening, enrollment, intervention, and data collection procedures will occur using remote methods (e.g., videoconferencing). Trained personnel at CCDOR will conduct all screening, enrollment, intervention, and data collection activities during both phases of the project.

There are multiple responsibilities associated with serving in the capacity of a coordinating center. The Coordinating Center will perform the following:

- Design and develop the protocol and template informed consent documents (i.e., Information Sheets)
- Review and approve all study-related documents
- Ensure the protocol is reviewed and approved by the Minneapolis VA IRB prior to enrollment of participants
- Collect and maintain critical documents from affiliated investigators (e.g. resume/CV, professional license, certification of completion of training, signed COI disclosure forms)
- Store and/or manage data, data analysis, and data and safety monitoring activities
- Comply with necessary protocols and maintain consistency with the HEAL Initiative Public Access and Data Sharing Policy.
- Ensure informed consent is obtained and documented from each participant in compliance with federal regulations as described in the Minneapolis VA IRB-approved protocol.
- Maintain documentation of all IRB approvals for the protocol
- Provide study specific training to the research personnel
- Develop and provide protocol specific case report forms
- Coordinate randomization as applicable
- Register participants and track participant enrollment
- Ensure use of the correct version of the protocol and consent document.
- Ensure the use of quality control measures to assure data accuracy and completeness.
- Track, report and maintain documentation of all serious adverse events and unanticipated problems and disseminating the information
- Provide periodic updates to affiliated investigators on participant enrollment, general study progress, and relevant scientific advances
- Assure that all relevant IRB correspondence (e.g., amendments) and study status changes are communicated
- Protect participants' rights in regard to research participation
- Monitor protocol compliance, track protocol deviations and report as needed

4 Confidentiality

4.1 Protection of Participant Privacy

Participant confidentiality is strictly held in trust by the investigators, project staff, the sponsor and their agents. This confidentiality covers any study information relating to participants. All published reports will be of summary nature and no individual participants will be identified. Access to identifiable participant information will be limited to study personnel with authorized access.

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

4.2 Confidentiality During Adverse Event (AE) Reporting

AE reports and annual summaries will not include participant identifiable material.

5 Expected Risks

5.1 Advisors (Non-Feasibility/RCT) Expected Risks

New information will be gathered from advisors and is not anticipated to place them at risk of criminal or civil liability or be damaging to their financial standing, employability, educational advancement, or reputation.

5.1.1 Advisors (Non-Feasibility/RCT) Protections Against Risks

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

5.2 Research Participants Expected Risks

The potential risks are considered minimal for research participants in both the active and control groups. These include risks associated with the following:

- ***Completing Health Surveys*.** Participants will be asked to complete health surveys as part of the screening and follow up data collection. The nature of the questions might be distressing to some individuals.
- ***Breach of Confidentiality.*** There is a very small risk of breach of confidentiality and privacy. New information will be gathered from participants and is not anticipated to place individuals at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, educational advancement, or reputation.

The fluctuations associated with the natural history of pain and mental health conditions that co-occur with pain may be associated with some risk.

- ***Natural History of Pain.*** People with pain that is chronic in nature often experience fluctuations in pain severity, location, character, and quality unrelated to study participation (e.g., aggravated by lifting at work or home).
- ***Natural History of Mental Health Conditions in People with Pain:*** People with chronic pain often experience fluctuations in their levels of distress or aggravation of mental health conditions unrelated to study participation (e.g., stressful life events).

Additional Risk Associated with RAMP Program (active intervention).

The additional potential risks associated with the RAMP Program are considered minimal. All Veteran patients in the VA health system have a primary health care provider; they will not be asked to limit any other treatment they might be receiving for their pain. Participants will be asked to take part in a group behavioral intervention via a VA-approved videoconferencing program (for example, Webex). Minimal risks associated with the experimental educational intervention may occur in program sessions and practicing on one's own. The intervention is not physically invasive, embarrassing, or offensive, and not expected to have adverse lasting impact. Expected risks include:

- Experiencing some anxiety or nervousness when participating in group activities (e.g., discussions); mild short-lasting physical discomfort (e.g., muscle and joint soreness) as a result of performing short periods of exercises (~5-10 minutes); and feeling emotional when doing the brief mind-body practices (~5-10 minutes), which include mindfulness and behavioral coping strategies (e.g., relaxed breathing, guided imagery, progressive muscle relaxation).

Additional Risk Associated with Usual Care (control group, UH3/Phase II only).

The additional potential risks associated with being randomly assigned to Usual Care are considered minimal. As noted previously, all Veteran patients in the VA health system have a primary health care provider. Participants in the Usual Care condition will be instructed to do what they normally would, on their own. Patients will not be asked to limit any other treatment they might be receiving for their pain. After completing the final follow-up survey, they will be mailed information about how to access the intervention materials online, which they can use on their own if they wish.

5.2.1 Research Participants Protections Against Risks

The expected risks associated with this research have been deemed minimal by the Minneapolis VA IRB. All potential participants will be actively engaged in healthcare; they will have been identified through the electronic record in which they have had at least two visits with a provider in the past year. Also, as part of standard VA policy, Veteran patients complete annual suicidality screening. The project team has developed

plans for risk mitigation that meet or exceed what currently exists within the VA health system. See Table 1 for plans to protect participants against risks and Sections 5 and 6 for monitoring and reporting plans.

As part of the study, we will monitor safety after consent has been secured (e.g. screening, intervention, follow up). Safety concerns may be learned of actively (e.g. through querying at screening or in surveys) or passively (e.g. participant discloses during any communication at any point on Webex, by email or on phone).

All participant facing staff will be trained, certified and monitored by investigators to ensure the satisfactory implementation of safety and monitoring procedures. In the event a staff member learns a participant is at risk of experiencing a serious adverse event (e.g., suicidality) they will implement safety procedures developed by our team's clinical health experts (summarized in Table 1 and detailed in the manual of operations).

MPIs and Co-Investigators will conduct, at least monthly, a review of safety data and meet with project staff to discuss any problems or concerns that arise; additional training to implement risk monitoring, documentation and implementation of safety procedures will occur as necessary.

Table 1. Protection Against Risks

Type of Risk	**Risk Mitigation**
Confidentiality and Data Safety	● All staff receive HIPAA and data safety training that includes maintaining the confidentiality and security of research records and information. ● Details regarding the protection of study databases and source documentation is provided in sections 8.
Health Surveys ***(All)***	● All participants will have the option of skipping any interview or questionnaire questions they do not wish to answer. ● All surveys will be prefaced by the following*: *"Our first priority is your safety. The following questions relate to your emotional and mental wellbeing. We recognize that sharing this information can be challenging. Please remember while answering these questions to take care of yourself and if you are feeling upset and*

	would like help, please call the Veterans Crisis line by dialing 988 and pressing 1." ● All surveys will have the following message at the end*: *"Our first priority is your safety. The previous questions relate to your emotional and mental wellbeing. We recognize that sharing this information can be challenging. Please remember to take care of yourself, and if you are feeling upset and would like help, please call the Veterans Crisis Line by dialing 988 and pressing 1.* *Language based on suggestions by our Veteran Advisors
Health Surveys ***(Follow Up Only)***	● All participants will be queried for Serious Adverse Events. *"Since your last survey, have you experienced a NEW or WORSENING medical issue or event which resulted in any of the following:* *a. Overnight stay in a hospital?" (no, yes with open fields to describe when it occurred, what happened, if still being treated)* *b. Problem that results in a severe or permanent disability?" (no, yes with open fields to describe when it occurred, what happened, if still being treated)* *c. A life-threatening injury or event? (no, yes with open fields to describe when it occurred, what happened, if still being treated)*
Screening procedures	● Potential research participants will undergo baseline screening to ensure they meet eligibility criteria and it is safe for them to participate. ● Baseline screening will be conducted by staff applying structured checklists to existing electronic medical records review ● Screening staff will be trained and supervised by the clinical psychologist MPI and Co-Is responsible for data collection. The following is considered <u>exclusionary</u>: ● Hospitalization for a severe mental illness-related issue in the past 6 months; active psychotic symptoms, suicidal ideation, or manic episodes; active substance use disorder that is poorly controlled. ● Staff will be trained to actively monitor for potential emotional distress during baseline eligibility calls and to implement safety procedures if needed. The manual of operations details steps for assessing the nature of the situation, responding appropriately to ensure participant safety, documenting the event and notifying the Project Director and the MPIs (see Section 6). Participants in which imminent risk for suicidality is possible will be offered a warm handoff to the Veterans Crisis Line; if they decline, or disconnect, staff will immediately 1) contact the local police department to conduct a wellness check, then 2) contact the Veterans Crisis line to report event and 3) contact the participants' local suicide prevention team.

Intervention	● The RAMP intervention has been designed to include activities and exercises that are suitable for a range of abilities and preferences. The mind-body skill practices are short in duration (~5-10 minutes), lowering the risk of emotional discomfort or psychological events. ● Participants will also be given the option to refrain from participating in activities that feel uncomfortable. ● Facilitators will be trained and supervised by the clinical psychologist MPI, chiropractic MPI, and Co-Is with clinical pain management experience to actively monitor for potential emotional or physical distress during session activities and how to implement safety procedures. The manual of operations details steps for assessing the nature of the situation, responding appropriately to ensure participant safety, documenting the event and notifying the Project Director and the MPIs (see Section 6). ● Participants in which imminent risk for suicidality is possible will be offered a warm hand off to the Veterans Crisis Line; if they decline, or disconnect, staff will immediately 1) contact the local police department to conduct a wellness check, then 2) contact the Veterans Crisis line to report event and 3) contact the participants' local suicide prevention team.

6 Adverse Event/ Unanticipated Problems

All project team members will undergo project-specific human subjects training that addresses risks to subjects; protection against risks; potential benefits of research to subjects and others; and the importance of knowledge to be gained. Additionally, all study personnel will be required to complete training in the Responsible Conduct of Research every three years. This includes online CITI training in responsible conduct of research, good clinical practice, and human research protections. Current human subjects training records are regularly updated by the Minneapolis VA IRB and checked annually at Continuing Review.

All project team members will be trained in study specific protocols relevant to their role, including detailed safety procedures to mitigate risk to participants (see Section 5 and Table 1 above). We will use active and passive monitoring of adverse events and unanticipated problems in the study. Serious or possibly related adverse events and unanticipated problems can be learned about in the following ways:

- From participants, who will be encouraged to contact the Project Director or an MPI
- From direct queries in the self-report surveys
- From observations by project staff during baseline screening calls, interventions, and other interactions with participants

Participants who experience possibly related serious adverse events and unanticipated problems will be contacted by the Project Director or delegate to gather information for adverse event reporting (see Section 6.1 below) and ensure safety procedures are followed (see Section 5 above).

Events identified as serious adverse events or unanticipated problems will be adjudicated by the MPIs and Co-Is for: confirmation of severity, relatedness and expectedness based on the definitions below.

6.1 Definitions

6.1.1 Adverse Event (AE)

An adverse event (AE) is defined as any reaction or undesirable event that occurs while a subject is on the research protocol whether or not it is considered related to the study intervention. Such events could include illness, signs, symptoms, or abnormal laboratory tests that have appeared or worsened during the course of the trial, regardless of whether causal relationship to the study can be made.

6.1.2 Unanticipated problem involving risk to subjects or others (UPIRTSO)

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 participant 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.

6.2 Time Period and Frequency for Event Assessment and Follow-Up

The Project Director or designee will record all adverse events or UPIRTSOs the project team is made aware of occurring any time after consent until 30 days after the last day of study participation. Study related SAEs will be followed to stabilization/resolution.

Characteristics of an Adverse Event

6.2.1 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
4) **Serious:** results in any of the following:

   Death – death due to any cause

   Life-threatening condition – the subject was at potential risk of dying at the time of the AE or if it is suspected that the use of the study interventions would result in the subject's death.

   Hospitalization – this indicated the initial admission to the hospital or prolongation of a hospital stay that resulted from the AE.

   Disability – the AE has resulted in a significant, persistent or permanent change, impairment, damage, or disruptions in the subject's body function/structure, physical activities, or quality of life.

6.2.2 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used (see Table 2).

Table 2. Relationship of Adverse Events to Study Procedures

Relatedness	Definition
Definitely Related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

Possibly Related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
Unlikely to be related	A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
Not Related	The AE is completely independent of study procedures administration, and/or evidence exists that the event is related to another etiology. There must be an alternative, definitive etiology documented.

6.2.3 Expectedness of SAEs

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.

6.3 Reporting Procedures

6.3.1 Serious adverse events (SAEs) and Unanticipated Problems.

These will be reported to the IRB, NINR, DSMB and others as described in Table 3. Reporting will include a detailed description of the event, incident, experience, or outcome; an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response.

Table 3. Reporting of Serious Adverse Events and Unanticipated Problems

Event	Report to…	Reporting Time
Deaths that are at least possibly related to the research	Minneapolis VA IRB, ACOS-R, NINR, DSMB	- Initial reporting to the Minneapolis IRB within 1 hour of learning of the event. - Follow up with submission of the "Minneapolis IRB Immediate Reporting of Serious Adverse Events or Deaths" written report

		form will occur within 1 business day. - DSMB and NINR within 3 business days of learning of the event
(non-death) **Unanticipated Serious Adverse Events (U-SAEs)** - unexpected and at <u>least possibly related</u> to the research	Minneapolis VA IRB, NINR, DSMB	- Within 5 business days in writing with submission of the "Minneapolis IRB Immediate Reporting of Serious Adverse Events or Deaths" - DSMB and NINR within 7 business days of learning of the event
Serious Adverse Events (SAEs) – adverse event that is *not* unexpected *and* at least possibly related to the research	Minneapolis VA IRB, NINR, DSMB	- IRB - Summarized at Continuing Review - NINR – annual report - DSMB – annual report
Unanticipated problem involving risk to subjects or others (UPIRTSO)	Minneapolis VA IRB, NINR, DSMB, OHRP	- IRB within 5 business days - NINR and DSMB within 14 business days - OHRP within 21 business days
ACOS-R: Associate Chief of Staff for Research; DSMB: Data and Safety Monitoring Board; IRB: Institutional Review Board; NINR: National Institute for Nursing Research; OHRP: Office of Human Research Protections; SAE: Serious Adverse Event; UPIRTSO: Unanticipated problem involving risk to subjects or others; U-SAE: Unanticipated Serious Adverse Event; VA: Veterans Health Administration		

6.3.2 Other reporting

The following will be reported to NINR within 14 business days:

- Summary **of recommendations made by the DSMB** or other monitoring entity as appropriate and (if applicable), as well as the action plan for response.
- Notice of any **actions taken by the IRB or regulatory bodies** regarding the research and any responses to those actions.

6.4 Halting Rules

The study may be temporarily suspended or prematurely closed if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or

termination, will be provided to study participants, investigators and study collaborators, funding agency, and regulatory authorities, including the IRB, by the MPIs or designee.

In the event of any type of closure, the MPIs, or designee, will inform ongoing study participants, the IRB, and NINR and provide the reason(s) for the termination or temporary suspension within 14 business days.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of project staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Natural disaster, public health crisis

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy regulatory bodies (e.g., NINR, IRB, DSMB).

7 Quality Control and Quality Assurance

Quality assurance and control procedures will be implemented as follows.

Investigator and Staff Compliance: Research staff will undergo project-specific training in informed consent, screening and enrollment procedures, data collection, safety assessment, and adverse event protocols prior to study enrollment. Study intervention facilitators will undergo project-specific training, and safety assessment and adverse event protocols prior to study enrollment. Certification by a MPI (or designee) requires adherence to standard operating procedures outlined in the manual of operations. Training and certification will be logged. The Project Director will track all team members' human subjects training to ensure it is current and will notify each person when renewal deadlines are approaching to ensure that they complete these renewals prior to expiration.

Informed consent: The Project Director (and other team members, as required) will follow IRB guidelines when preparing for compliance audits of the study overall and informed consent documentation. The Minneapolis VA IRB reviews 100% of documentation of verbal informed consent and HIPAA authorization forms for completion and accuracy. Triennially the Minneapolis VA IRB reviews whether all study materials are properly and securely stored, IRB correspondence and approvals are up-to-date, and personnel training is current.

Outcome data collection: The primary method of data collection for participant self-reported outcomes will be direct electronic entry through a survey interface with Qualtrics FedRAMP. Logic rules specifying the type and range of acceptable responses will be programmed into Qualtrics FedRAMP. Participants will receive an error message

if they enter an invalid response. The MPIs will review reports on data capture and quality on a monthly basis. Missing data reporting and other customized reports will be developed in order to facilitate efficient workflow and high-quality data capture. Data collection instrument specific follow-up rates will be tabulated and reviewed during meetings between the MPIs and project staff. Additional training will be provided as needed based on the findings.

Intervention Fidelity: Consistent delivery of the study intervention will be monitored throughout the intervention phase of the study. Facilitators will use standardized checklists at each session to document the delivery of session activities. In addition, a total of 15% of intervention sessions will be assessed by an MPI (or designee) to ensure session activities are delivered as intended (goal: 90% of all activities are delivered). The MPIs will meet at least two times per month to review barriers to session activities and implement additional training as needed.

Protocol Deviations: Protocol deviations will be documented by the Project Director and designees. The MPIs will review protocol deviations at least two times per month, and will implement corrective actions, as appropriate, or when the quantity or nature of deviations are deemed to be at a level of concern. Protocol deviations will be reported to NINR and the DSMB in the semi-annual reports.

Verification of Source Documents: All project staff will engage in training related to proper documentation during the trial. Best practices of source document verification will be utilized. Original electronic copies of data will be saved where regular backups occur. Hard copy assessments and notes will be kept in locked cabinets in locked offices in locked buildings. At the triennial audit, the IRB Research Compliance Officer (RCO) will select and review 10-30 participant files.

7.1 Subject Accrual and Compliance

7.1.1 Measurement and Reporting of Subject Accrual

Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur routinely (at least monthly) during the recruitment phase to ensure participant enrollment aligns with proposed recruitment projections and targeted diversity goals are met.

7.1.2 Measurement and Reporting of Participant Adherence to Treatment Protocol

Participant adherence to the RAMP Program intervention will be assessed through documentation of attendance/engagement in study sessions. Adherence is defined as attending/engaging in $\geq$6/9 session activities. These rates will be monitored routinely (at least monthly). Operating procedures will be reassessed and refined if the rates drop below study goals.

7.2 Justification of Sample Size

a. UG3/Phase 1 – Aim 1 – Feasibility study

The sample size for the proposed feasibility study (n=40) was informed by previous studies by the investigators, who have found this number sufficient for informing the feasibility of larger, randomized clinical trials.

b. UH3/Phase 2 – Aim 1 – RCT

We plan to randomize n=500 participants for our UH3/Phase 2 Randomized Clinical Trial.

Our power calculation uses the Brief Pain Inventory (BPI) interference score over the follow-up period as the primary outcome measure. For our primary analysis we estimate up to 20% attrition, so at least 500 people will need to be randomized to obtain a sample of 400 people with complete data. 200 participants in each arm will yield 90% power, with an alpha of 0.05, to reject the null hypothesis of equal means over the repeated follow-up time points (i.e., 3 and 6 months) if the arms differ by an effect size of 0.3 or greater. This includes a conservative estimate that the repeated outcome measures are highly correlated (r=0.7) and even with only 1 time point there is power to detect effect sizes of 0.32. Analyses that are stratified by subgroups as small as 70 people per arm (i.e., equivalent to restricting to only women or minority Veterans) would have approximately 90% power to detect differences of 0.50. However, these would only be exploratory in nature and not adjusted for multiple comparisons.

7.3 Designation of a Monitoring Committee

The composition of the Data and Safety Monitoring Board (DSMB) for this study is detailed in Table 4. DSMB members are not associated with this research project and work independently of the MPIs. They are not part of the key personnel involved in this grant. No member of the DSMB has collaborated or co-published with the Co-PIs within the past three years. They are qualified to review the patient safety data generated by this study because of their unique expertise and have been approved by NINR.

Table 4. DSMB Membership

Name, Credentials	Institution	Expertise	DSMB Role
Linda Hanson, DC, MS	Assistant Research Professor and Assistant Director in the Integrative Health and Wellbeing Research Program, University of Minnesota	Implementation and management of multi-site, federally-funded clinical trials	Executive Secretary, non-voting member

Matthew Bair, MD, MS, FACP	Professor of Medicine, Indiana University School of Medicine; Core Investigator, VA HSR&D Center for Health Information and Communication and Staff Physician, Roudebush VA Medical Center; Research Scientist, Regenstrief Institute	Clinical trials, clinical aspects of the condition being studied, population being studied	Voting member
Beth Darnall, PhD	Professor of Anesthesiology, Perioperative and Pain Medicine; Director of the Stanford Pain Relief Innovations Lab, Stanford University School of Medicine	Ethics of clinical trials, clinical aspects of the condition being studied, work of DSMBs/IMCs, clinical trials	Voting member
Lynn DeBar, PhD, MPH	Distinguished Investigator, Kaiser Permanente Washington Health Research Institute; Affiliate Professor at the Department of Psychiatry, University of Washington	Clinical aspects of the condition being studied, work of DSMBs/IMCs, clinical trials	Voting member
Birgit Grund, PhD	Professor, School of Statistics, University of Minnesota	Biostatistician, work of DSMBs/IMCs	Voting Member
Sarah Krein, PhD, RN	Research Career Scientist, VA Ann Arbor Center for Clinical Management Research (CCMR); Rensis Likert Collegiate Research Professor and Research Professor of Internal Medicine, University of Michigan; Adjunct Professor, School of Nursing, University of Michigan	Clinical trials, clinical aspects of the condition being studied, population being studied	Voting member
Cynthia Long, PhD, PStat	Dean of Research, Professor, Director, Office of Data Management & Biostatistics, Palmer Center for Chiropractic Research, Palmer College of Chiropractic	Biostatistician, clinical aspects of the condition being studied, population being studied, work of DSMBs/IMCs	Chair, Voting member

7.4 Safety Review Plan

One virtual review meeting with the DSMB will occur during Phase 1/UG3, and two virtual meetings per year will occur during Phase 2/UH3. Progress reports, including patient recruitment, retention/attrition, adverse events, and unexpected events will be provided to the DSMB and NINR annually during the UG3 phase and semi-annually during the UH3 phase. DSMB meeting summaries will include the progress reports and meeting minutes. Additional check-ins via email or virtual meetings will occur as needed at the direction of the DSMB.

Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the DSMB semi-annually. An Annual Report will the items detailed in Section 7.5. The Annual Report will be sent to the DSMB and will be forwarded to the IRB and NINR, per each entities' respective reporting guidelines. The IRB and other applicable recipients will review progress of this study on an annual basis.

7.5 Study Report Outline for the Data and Safety Monitoring Board (Interim or Annual Reports)

The project team will generate Study Reports for the Data and Safety Monitoring Board and will provide information on the study parameters listed below. The Open Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population. The Closed Study Report tables will be presented by group (all reports including SAEs).

<u>Executive Summary</u>

- *General Comments*: Summary of the study status, enrollment, and any important developments since the last Data Safety & Monitoring Report.
- *Protocol Summary*: Brief description of primary aims, primary hypothesis, inclusion/exclusion criteria, interventions, sample size, and primary statistical analysis.
- *Protocol Amendments*: Description of protocol amendments since the last Data Safety & Monitoring Report.
- *Notes on Tables and Figures*: Presentation of notable findings in the report and any limitations or other contextual information that may impact the interpretation of the tables and figures.

<u>Enrollment</u>

- *Figure of cumulative enrollment over study time:* plot with the projected enrollment set forth in the Study Accrual and Retention Plan (SARP).
- *Table(s) of screening and enrollment:* Counts of screened, ineligible, eligible, and enrolled subjects. Reasons for ineligibility and reasons for not enrolling eligible subjects are also enumerated.
- *Table of baseline characteristics*: Baseline characteristics including demographics and pain severity measures.

<u>Study Retention</u>

- *Table(s) of subject retention:* Counts and rates of subject dropout. Timing relative to enrollment and reasons for dropout are also tabulated.

Intervention Attendance

- *Table(s) of attendance*: Rates of subject intervention attendance.

Intervention Fidelity

- *Table(s) of quantitative and qualitative measures of intervention fidelity*. Include total number of sessions completed, # observed, # of fidelity violations, etc.

Data Quality and Timeliness

- *Table(s). Follow-up rates.* The follow-up rate for a study survey instrument is defined as the number completed within a specified time window divided by the number expected to be completed at the time of the report generation. Follow-up rates are presented for each data collection time point.

Safety Summary

- *Table(s) of Serious Adverse Events and Unanticipated Problems.* Includes counts and rates of adverse events, serious adverse events, and unanticipated problems.

Protocol Deviations

- Summary or listing of protocol deviations that have occurred since the previous DSMB report and over the course of the study.

Quality Management

- Summary or listing of quality management activities and findings completed since the last DSMB review, including frequency and any corrective actions taken to address the findings or issues.

8 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

8.1 Data Management Responsibilities

Data collection and management will be overseen at the Minneapolis VA HSR&D Center of Innovation (COIN) by Dr. Brent Taylor. Data collection and accurate documentation are the responsibility of the project staff under the supervision of the investigators. All source documents will be reviewed by the project team and data entry staff, who will ensure that they are accurate and complete.

A history of CRFs and all fielded versions will be maintained. CRFs will be implemented as web-based eCRFs including checks for valid entry and incomplete responses.

8.2 Database Protection

Data will be collected using Qualtrics FedRAMP, VA REDCap, paper surveys, telephone, virtual or in-person meetings, and EHRs. Survey data will be collected using electronic data capture through Qualtrics FedRAMP or VA REDCap, secure web applications for building and managing online surveys.

Qualtrics FedRAMP is VA-approved to collect data from VA patients and store data on VA cloud servers. Qualtrics is accredited by FedRAMP, a government-wide initiative to protect sensitive data in federal agencies, ensuring gold standard security for data collected through Qualtrics. It features data isolation, differentiated user roles and privileges, audit login, multi-factor authentication, single-sign-on and SSL encryption. VA REDCap has an authority to operate (ATO) from VA Office of Information and Technology (OI&T) and is hosted on the VA Enterprise Cloud (VAEC). Login requires a VA Network ID and is accessible only on the VA network, data is backed-up nightly, and audit trails and logging is captured using individualized user rights management. Surveys will contain a study ID, time of data entry and limited individually identifiable information. Paper surveys are anticipated to be minimal in number and will be carefully entered into the VA REDCap or Qualtrics FedRAMP system by project staff. All access, processing, and analyses of VA EHR study data will be done within the Minneapolis VA analytical servers or the national secure VA Informatics and Computing Infrastructure (VINCI) by the CCDOR Statistical & Data Group (CCDOR/SDG). Patient and provider identifiers will be used only within these secure VA servers within the VA firewall when necessary to link records obtained from different files.

The entire study database (information retrieved from EHR data, recruitment outcomes) will be fully contained on secure VHA servers, behind the VA firewall (local CCDOR servers and National VA VINCI servers). Within the VA firewall, the project team at the VA will create a custom-built tracking app that will track each participant's enrollment and study status. Data will be routinely extracted from Qualtrics FedRAMP and VA REDCap in the VA cloud and stored on secure VINCI, VA Box, and Minneapolis VA CCDOR servers, using SQL database connections. Qualtrics FedRAMP and VA REDCap will contain the minimal identifying information needed to successfully conduct the study. This will include information that is self-reported by the participants (e.g., phone, email, which is best method of contact). No sensitive data will be stored outside of the VA protected environment. Once data are transferred for data analysis, data will be maintained on encrypted and password-protected VA computers in the VA environment and on secure VA servers.

To prevent improper use of any data collected for research projects conducted at the Minneapolis COIN we will use a combination of local Minneapolis VA secure servers as well as VINCI, VA Box, and the secure Qualtrics FedRAMP system in the VA cloud. The local VA secure servers facilitate data collection and provide a platform for the

customized research tracking application, while the VINCI platform provides a robust environment for pooling the primary research collected data with direct connections to daily or weekly updated mirrors of nearly the entire VHA EHR. VINCI also provides access to extensive storage area networks, drives, file shares, databases, SharePoint for collaboration and correspondence sites, SAS/Grid, and servers containing virtual machines with an extensive collection of software called the VINCI Workspace. We requested and were provided access to the Joint Legacy Viewer (JLV) in order to capture the highest follow-up response rate that is feasible. It is very important that we reach the participants in a timely manner; being able to access current address and phone numbers will help in tracking hard to reach participants. A secure link between local VA secure servers Qualtrics FedRAMP will be created. Limited study specific data will be collected on Qualtrics FedRAMP and will contain a study specific participant ID code. VINCI allows individual researchers and their staff the means to securely conduct their research projects within a secure and well controlled technical environment. All of these VA systems undergo backups of the servers nightly and servers are updated when new security patches become available.

CCDOR maintains strong protections for coded analysis datasets that will be stored on local VA server space. CCDOR provides protections for research data at least equal to that provided by the Minneapolis VA Health Care System for patients' private health information (PHI). Access to data is on a "need to know" basis. For example, data analysts will not have access to project data unless they can demonstrate that they are somehow needed for a particular analysis. Access to project data is obtained through Windows authentication (i.e., PIV card and password to the network). It is virtually impossible for any person without a login name, PIV card and password to the Minneapolis VA hospital's domain network to access data on the Center's servers. Thus, all data housed on the CCDOR Server is extremely secure. Access by unauthorized persons is highly unlikely. CCDOR maintains several secure servers that are located in the Minneapolis VA OIT server room. Physical access to the server room is limited to VA Office of Information and Technology staff. All individuals with administrative access privileges to the Center's servers, including VA OIT personnel and CCDOR programmers, have been screened and assigned a security clearance putting them in trusted positions of the hospital with authorization to work with patient-level data. VA OIT's access to the data is strictly limited to maintaining the server and backing up server data, which prevents catastrophic loss of data. Backups are written to tapes that are stored in a secure location accessible only to OIT personnel. Only individuals with a need to access the data, as vetted by the project's MPIs are granted access. Even then, only the absolute minimum number of data elements is released. This protects the integrity of the data as well as its confidentiality.

8.3 Source Document Protection

Electronic source documents will be stored on password protected VA computers. Participant IDs will be used to protect participants' confidentiality. Hard copy assessments and notes will be kept in locked cabinets in locked offices in locked buildings which are only accessible to authorized study personnel.

8.4 Schedule and Content of Reports

Real-time reports of study conduct and progress will be available to the study steering committee and will detail subject accrual, enrolled subject demographics, current status of enrolled subjects, compliance with the intervention protocols, data collection, and adverse event rates. The DSMB will review reports outlined in sections 7.6-7.7 following the UG3 phase and semi-annually during the UH3 phase of the project.

8.4.1 Interim Analyses

There are no planned interim analyses of primary or secondary outcomes data (including futility analyses) before the study is complete. However, in the context of evaluating the safety outcomes, if the DSMB requests interim effectiveness estimates they will be provided. In the event this is required, a statistician independent of the project team will be assigned.

The original unaltered data will be preserved in the electronic data capture system. All data alterations, recoding of variables, scoring of outcome measures, or data corrections will be clearly documented in a separate data file from the final, cleaned analysis-ready data set. For the purposes of preparing an analysis-ready data set, a csv file or statistical package format file will be exported from the original unaltered data provided directly from the electronic data collection and management system, with the result being an analysis ready data set. The analysis ready data set file will document and reproduce all analyses and study-monitoring reports and will employ detailed comments and time stamped output files. The analysis-ready data set will contain a coded variable for group allocation which will not be unmasked until after data analysis by the study statistician is complete.

8.5 Data Privacy and Data Breaches

The Minneapolis VA has policies regarding data privacy (MCP IM-02M). Any data breaches need to be reported immediately to the VA Investigator's facility's OI&T Information Systems Security Officer (ISSO) and VHA's Privacy Officer (PO), the investigator's supervisor, and others as stipulated in VA, VHA, and local facility's requirements. We will follow OHRP's guidance for 'prompt' incident reporting, outlined here: https://www.hhs.gov/ohrp/compliance-and-reporting/guidance-on-reporting-incident/index.html.

9 Informed Consent

9.1 Feasibility/Pilot Study and RCT Participants

The IRB has approved our request for a waiver of HIPAA authorization for the initial recruitment search of electronic health records (EHR) for potential participants. A signed HIPAA Authorization form will be obtained in order to 1) disclose the minimum necessary information to the Minneapolis VA Non-Profit Corporation, the Center for Veteran Education and Research (CVRE) and Greenphire, for payment to participants for completing surveys, and 2) share data with all approved project team members; and 3) share required and approved data with study sponsor, Data and Safety Monitoring Board (DSMB), IRB, and other federal agencies to monitor or oversee research via approved methods. Signature on the HIPAA Authorization forms will be obtained via electronic signature using DocuSign or mailed a physical HIPAA Authorization form and a pre-paid return envelope.

The IRB has also approved the use of verbal informed consent over the phone and a waiver of written informed consent. The rationale is that the research meets all of the criteria for requesting a waiver of documentation of informed consent process, including: involving no more than minimal tangible or intangible risk to the participants; the waiver will not adversely affect the rights and welfare of the participants; the research could not practicably be carried out without the waiver; and when possible participants will be provided with additional pertinent information after participation.

The following outlines the informed consent process for Research Participants:

1. The informed consent process begins at the point of first contact. Potentially eligible patients will be mailed a postcard describing the study and informing them that the study is voluntary. The postcard will provide instructions for opting out. Participants are provided the study website which includes an IRB approved Information Sheet (containing information that is typically including in an informed consent document including the activity is research, participation is voluntary, permission to participate can be withdrawn, permission for use of data can be withdrawn for exempt research activities involving the collection and use of identifiable data and contact information for the VA Investigator).
2. Trained project staff will contact participants who have not opted out by telephone to secure verbal informed consent over the phone and waiver of written informed consent. This will be documented in the research record.
3. A hard copy of the Information Sheet will be mailed when a participant is enrolled/randomized into the study.
4. To complete the informed consent process at the end of study participation, project staff will inform the participant when their participation has come to an end and will document the notification in the study record.

10 Reporting Changes in Study Status

During the funding of this study, any action by the IRB, DSMB, or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NINR Program Official within 14 business days of notification.