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wHOPE Protocol Cover Page

Official Title: Implementation of a Pragmatic Trial of Whole Health Team vs. Primary Care Group Education to Promote Non-Pharmacological Strategies to Improve Pain, Functioning, and Quality of Life in Veterans

Acronym: wHOPE

Study Type: Interventional

Brief Title: Pragmatic Trial of WHT vs. PC-GE to Promote Non-Pharmacological Strategies to Treat Chronic Pain in Veterans

NCT Number: NCT04330365

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Implementation of a Pragmatic Trial of Whole Health Team vs. Primary Care Group Education to Promote Non-Pharmacological Strategies to Improve Pain, Functioning, and Quality of Life in Veterans

Grant Number: UH3AT009765

Supported by:
The National Center for Complementary and Integrative Health

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List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

AE – Adverse Event
CAVHS –Central Arkansas Veterans Healthcare System
CCDOR – Center for Chronic Disease Outcomes Research
CeMHOR – Center for Mental Healthcare & Outcomes Research
CHIO – Chief Health Information Officer
CIH – Complementary and Integrative Health
CIRB – Central Institutional Review Board
CR – Clinical Reminder
DMAP – Data Management and Access Plan
DSMB –Data and Safety Monitoring Board
DTA – Data Transfer Agreement
DUA – Data Use Agreement
EBQI – Evidence-Based Quality Improvement
EHR – Electronic Health Record
EMR – Electronic Medical Record
HBC – Health Behavior Coordinator
IMPACT – Integrated Medicine – Patient Aligned Care Team
LDS – Limited Data Set
MOI – Manual of Interventions
MVAHCS – Minneapolis VA Health Care System
OHSU – Oregon Health & Science University
OPCC – Office of Patient Centered Care
PC-GE – Primary Care Group Education
PCP – Primary Care Provider
PDSA – Plan-Do-Study-Act
PET – Pragmatic Effectiveness Trial
PI – Principal Investigator
POC – Point of Care
PTSD – Post Traumatic Stress Disorder
QE – Quick Ethnography
RCT – Randomized Control Trial
SAE – Serious Adverse Event
SDM – Shared Decision-Making
SFVAHCS – San Francisco VA Health Care System
TBI – Traumatic Brain Injury
UAMS – University of Arkansas for Medical Sciences
UCSF – University of California, San Francisco
VACHS – VA Connecticut Healthcare System
VASLHCS – VA St. Louis Health Care System
VAPORHCS – VA Portland Health Care System
WHT – Whole Health Team

Tool Revision History

Version Number: 1.1

Version Date: 02.27.20

Summary of Revisions Made:

- Updated References
- Corrected typos
- Adjusted formatting
- Updated assessments for study participants
- Clarified Implementation-Focused Process Evaluation
- Clarified Budget Impact Analysis process
- Clarified fidelity monitoring process

Version Number: 1.2

Version Date: 07.06.20

Summary of Revisions Made:

- Added the 'COVID-19 Impacts Questionnaire' to all telephone research assessment timepoints for veterans; specified implementation of a supplemental COVID-19 addendum for veteran & clinician SSIVs during the COVID-19 era
- Removed Patient Global Impression of Change (PGIC) questionnaire from baseline assessment; removed Anti-Inflammatory Diet Index, Sexual Dysfunction Questionnaire, and Menopausal Symptoms questionnaire from our list of assessments
- Added telephone as another option for WHT clinic visits & PC-GE sessions in addition to in-person, video telehealth formats (specifically mentioned VVC & Doximity for telehealth purposes)
- Requested EHR access to COVID-19 status and COVID-related healthcare utilization in VA and community (reimbursed by VA); specified that we plan to use the COVID-19 Shared Data Resource
- Added clarifying language on the Usual Primary Care arm
- Updated statistical analysis plan
- Changed process for collecting PEG/PHQ-4 data
- Clarified process for documenting adverse events
- Specified that full-length assessments will take 60-75 minutes
- Updated Protocol Appendices
- Added figures corresponding to the study timelines/visits for participants in the PC-GE and UPC arms
- Updated precis.

- Updated UPC section to reflect how usual care visits will be tracked and mode of care delivery will be determined.

Version Number: 1.3

Version Date: 2.1.21

Summary of Revisions Made:

- Requested Cisco WebEx as a telehealth platform
- Clarified that participants will be sent a copy of the Personalized Health Inventory (PHI) to review by mail or encrypted email prior to their first call with the Whole Health Coach
- Added Natural Products Survey details

Changed eligibility criteria and inclusion criteria- Change PEG cut off score to ≥4; changed 100-mile radius to 500-mile radius; NRS score of changed to ≥4 within last 2 years

Version Number: 1.4

Version Date: 04.05.21

Summary of Revisions Made:

- Added exclusion criteria - excluding individuals that are currently enrolled in a similar interdisciplinary pain service
- Changed time point for when veterans will be asked to conduct interview (~30-40 participants)

Added clarifying language for e-consent process with DocuSign.

Version Number: 1.5

Version Number 1.5

Version Date: 06.14.21

Summary of Revisions Made:

- Added clarifying language for e-consent process with DocuSign.

Version Number 1.6

Version Date: 08.30.21

Summary of Revisions Made:

- Added Natural Products Survey timeline, process, and procedures
    - NP survey and feedback form (N=50)
    - Semi-structured Interviews (N=20)
- Remove provider referral process with full name and last 4 SS through encrypted email or voicemail.
- Amended timepoint for when qualitative interviews are conducted for veterans

- Clarify language for timeline in regards to:
    - Fidelity monitoring
- WHT Coaching Sessions Clarify language for exclusion criteria

Version Number 1.7

Version Date: 11.12.21

Summary of Revisions Made:

- Added additional fidelity monitoring for Coaching sessions
- Clarifying language for which date study visits and assessments are anchored on
- Added language for PMC collaboration for COVID-19 data collection
- Clarifying time duration for Qualitative Interviews

Version Number 1.8

Version Date: 12.22.21

Summary of Revisions Made:

- Clarifying language for target sample of Natural Products Survey

Version Number 1.9

Version Date: 02.01.22

Summary of Revisions Made:

- Adjusting language for when PC-GE booster sessions will be offered
- Adjusting language for final assessment timeline

Version Number 1.10

Version Date: 03.14.22

Summary of Revisions Made:

- Adjusting total target sample from 745 to 765
- Recalculating screening and eligibility pools based on new target sample N=765
- Changing randomization block sizes to 24 and 48
- Adding language to control for race and ethnicity in the data analysis

Version Number 1.11

Version Date: 10.26.22

Summary of Revisions Made:

- Adjusting target sample for Natural Products N~465 with an initial pilot group of n~50
- Incorporate NP survey into the baseline and 6-month assessment
- Adding Bedford VA as another recruitment site
- Adding Co-investigators under key personnel
- Adding additional staff under Newington/West Haven
- Adding language about initial visit/orientation completion window

Version Number 2.0

Version Date: 01.20.23

Summary of Revisions Made:

- Adding an additional Aim 3

Version Number 2.1

Version Date: 10.19.23

Summary of Revisions Made:

- Changing Target Sample to 800

Version Number 2.2

Version Date: 11.1.24

Summary of Revisions Made:

- Changing qualitative interview target sample to approximately 50 for both stakeholders and veterans, subject to adjustment based on iterative assessment of thematic saturation.

Version Number 2.3

Version Date: 05.13.25

Summary of Revisions Made:

- Updated the “Other Study Staff – VACHS” section to clarify that the biostatisticians who will assist with data analysis are based at Yale University (a non-VA entity).
- Updated data sharing information to indicate that we will submit a DUA to gain permission to transfer a limited dataset to Dr. Denise Esserman and save this dataset on Yale University’s server (via a folder on Microsoft OneDrive).
- Information was added to section 14.0 Publication of Research Findings regarding dissemination of results to collaborators and veterans.
- Corrected numerous spelling and grammatical errors.

- Updated page numbers in Table of Contents.

Contents

PRECIS

Study Title: Implementation of a Pragmatic Trial of Whole Health Team vs. Primary Care Group Education to Promote Non-Pharmacological Strategies to Improve Pain, Functioning and Quality of Life in Veterans.

The overarching goal of this Pain Management Collaboratory Demonstration project, *w*HOPE (Whole Health Options for Pain Education) is to generate evidence for the VA Whole Health model in addressing chronic pain in a national sample of veterans across six geographically distinct VA healthcare systems. Specifically, we will evaluate a Whole Health Team (WHT), including a medical provider with training in integrative medicine, a CIH provider (e.g., yoga instructor, acupuncturist, nutritionist) and a Whole Health coach that collaborates with patients to develop a Personalized Health Plan, emphasizing non-pharmacological approaches to pain management. **Specific Aim 1** is to determine whether a Whole Health Team approach is superior to Primary Care Group Education (modified group Cognitive Behavioral Therapy for Chronic Pain), and whether both are superior to Usual VA Primary Care in decreasing pain interference in veterans with moderate to severe chronic pain (**primary outcome**). Secondary outcomes include changes in pain severity, quality of life, non-pharmacological therapies, use of pain medications (including opioids), and mental health symptoms in trial participants across the three study arms. To collect patient-reported outcomes, masked telephone assessments will be conducted at baseline, 3, 6, 9, and 12 months. Aim 2 is to conduct a process evaluation of the two active interventions (WHT and PC-GE) and a budget impact analysis that includes costs to implement and execute the two active interventions as well as the control condition (UPC) to inform the development of an implementation toolkit for scaling and dissemination. Eligible participants are veterans reporting moderate to severe chronic pain present every day or nearly every day for ≥ 6 months. The total sample size for the population is based on our main study aim/hypothesis and is N=765. This breaks down to n=341 in each of the active interventions (WHT and PC-GE) and N=83 in the Usual Primary Care arm (Control). Results of this UG3/UH3 Pain Management Collaboratory Demonstration project will contribute to the overall mission of the NIH/VA/DoD initiative to build national-level infrastructure that supports non-pharmacologic pain management in veterans and military service personnel. As the study is conducted during the COVID-19 pandemic, **Aim 3** will be using a nationwide cohort of veterans from the entire VA system, to investigate the differential impact of the COVID pandemic on racial/ethnic minority, women, and rural Veterans' use of Whole Health and CIH services for chronic pain management.

Study Personnel

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1.0 Introduction/Background and Rationale

Chronic pain is one of the most challenging public health issues in the U.S. today. Over 100 million Americans—nearly one-third of the U.S. population—suffer from chronic pain,[7,8] pain lasting longer than 3 months.[9] More Americans are affected by chronic pain than by heart disease, cancer or diabetes, with annual costs in medical care and lost productivity exceeding $600 billion.[8] Chronic pain, including back pain, neck pain, and other musculoskeletal disorders, is the second most common reason for outpatient primary care visits[10] and is among the leading causes of disability in the U.S. Patients with chronic pain report negative impacts on enjoyment of life, mood, concentration, energy levels and sleep, which in turn may result in psychosocial dysfunction including vocational, family and marital problems and overall poor quality of life.[11] In 2019, it remains challenging for patients with chronic pain to access effective pain care that not only improves pain symptoms, but also restores functioning and quality of life

Veterans suffer disproportionately high rates of chronic pain compared to the general population. As many as 50% of all Veterans report one or more chronic pain complaints.[12] It is concerning that the prevalence of chronic pain among young Veterans of the wars in Iraq and Afghanistan is similar to that of older Veterans. High rates of chronic pain in younger Veterans can be attributed to combat-related trauma, coupled with advances in protective gear and battlefield medicine allowing many to survive traumatic injuries that previously would have been fatal. The result is a generation of Veterans with a high prevalence of chronic pain and comorbid mental health conditions such as posttraumatic stress disorder (PTSD), depression and traumatic brain injury (TBI).[13,14]

In Veterans, chronic pain and prescription opioid use are strongly associated with mental health problems. Veterans with chronic pain and comorbid mental health conditions experience greater pain severity and more pain catastrophizing than those with chronic pain alone.[15,16] The

theory of “Mutual Maintenance” posits that anxiety and depression can amplify and perpetuate the experience of chronic pain in a vicious downward cycle culminating in disability.[17] Our own research demonstrates that among Iraq and Afghanistan War Veterans diagnosed with chronic pain, those with comorbid PTSD are significantly more likely to be prescribed opioids, exhibit prescription opioid misuse, and be at heightened risk for serious adverse clinical outcomes related to opioids.[18] Our research also demonstrates a strong positive correlation between an increasing number of co-occurring mental health conditions (e.g., TBI plus depression plus PTSD) and increasing risk for chronic pain and prescription opioid use. [4,62]

The higher prevalence of opioid use among patients with chronic pain and mental health problems may be driven, in part, by a desire to alleviate mental health symptoms. For instance, patients with PTSD report a reduction in intrusive and hyperarousal symptoms of PTSD with opioids.[19,20] These patients typically present to primary care providers (PCPs) who are not trained to manage complex chronic pain or deployment-related mental health problems, and who may default to prescribing opioids to mitigate their patients’ distress. Prescribing opioids in the context of chronic pain and mental health conditions can exacerbate both mental health and chronic pain conditions, worsen psychosocial functioning, increase risk for serious adverse medical events, and culminate in break-downs in patient and provider communication and trust.[21-23]

Currently, there is little evidence that opioids are effective in the long-term treatment of chronic pain; furthermore, they can result in poorer quality of life and serious adverse outcomes. Starting in the early 1990s, concern about pain under-treatment and aggressive and sometimes deceptive pharmaceutical marketing drove dramatic increases in opioid analgesic prescribing.[24,25] Although the use of opioids may be appropriate in acute, inpatient, and palliative care settings, there is no evidence to support a benefit from long-term use of opioids for chronic non-cancer pain.[26-28] Instead, most patients receiving long-term opioid therapy continue to experience severe pain, functional limitations and poorer quality of life.[29-31] Evidence suggests Veterans may be disproportionately affected by opioid-related harms; VA patients have nearly twice the rate of accidental poisoning deaths as U.S. adults overall and opioid analgesics are the drug class most commonly involved in these deaths.[32] In short, the expansion in opioid prescribing has triggered an epidemic of opioid-related deaths and addictive disorders, without reducing the burden of pain or improving patients’ functioning and quality of life.

Concurrently, the opioid crisis has led to a breakdown in primary care management of chronic pain that has negatively impacted both patients and providers. New national guidelines and policies intended to reduce harms from opioids have put pressure on health care systems to change their approach to pain management. The medical community has responded with attempts to rein in the use of opioids,[33] leaving many patients who have relied on them in need of effective alternatives. Patients continue to be dissatisfied with their chronic pain care and frustrated in their relationships with providers caring for them.[34-39] Indeed, only 28% of patients receiving VA pain treatment reported very good or excellent treatment effectiveness.[40,41] Similarly, PCPs experience job stress and burnout at high rates, with chronic pain care contributing to some of the most challenging patient-provider relationships.[42-44] The 2014 NIH Pathways to Prevention of Opioids for Chronic Pain panel recognized that individual clinicians “are often overburdened and have insufficient resources,” so “systems of care must facilitate implementation” of pain and opioid management guidelines.[45] Unfortunately, numerous barriers limit effective pain management in primary care, including ineffective communication, patient

and provider knowledge deficits, limited time, and insufficient access to information, assessment tools, and treatment pathways.[36,43,46,47] Healthcare systems lack guidance and resources for implementing effective systems of chronic pain care within primary care. This study specifically addresses these health services gaps.

As a result of the opioid epidemic, there is increasing recognition that pain care requires a more multi-modal, biopsychosocial approach.[48-50] The Biomedical Model has been the dominant paradigm for chronic pain care; it assumes a singular biological etiology for pain and focuses provider-patient interactions on the diagnosis and treatment of physical symptoms.[51] Furthermore, it posits that chronic pain often can be eliminated, a stance that has contributed to the overuse of surgery, procedures and medications—particularly opioids—for the treatment of chronic pain.

Newer research suggests that multi-modal and integrated pain care that incorporates non-pharmacological modalities such as exercise, physical therapy, behavioral health care, social supports, and self-care strategies can be more effective than medication-based therapies alone.[9,49] Because response to individual treatments is variable and individual therapies typically generate only partial improvement, combining a variety of non-pharmacologic therapies has been shown to be effective in improving chronic pain.[52-55] Moreover, the integration of such services into primary care could help more patients access safe, effective, multi-modal pain treatment. Indeed, the Institute of Medicine's consensus report (2011), Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain (2016) and the Department of Health and Human Services' National Pain Strategy (2016) have all called for a multi-modal, biopsychosocial approach in the treatment of chronic pain focused on improving the experience of individuals with chronic pain and enhancing functioning and quality of life.[8,33,56]

Despite high-level recommendations for biopsychosocial pain management, little to no evidence is available for specific strategies to taper or replace opioid therapy and to promote a primary care-based, multi-modal, non-pharmacological approach to chronic pain care.[57] The Chronic Care Model was developed as a guiding heuristic for the delivery of biopsychosocially-informed chronic disease management and has been adapted to pain care.[148] Self-management is at the core of this patient-centered model in which patients engage in shared decision-making with their providers to develop a multidisciplinary pain self-management approach. Despite numerous randomized controlled trials (RCTs) demonstrating the benefits of the Chronic Care Model for chronic disease, the model lacks clear implementation guidance and has had limited penetration in larger health care systems, like the VA. The Chronic Care Model also remains disease-focused rather than wellness-focused.

Thus, there is a critical need to develop new pragmatic, primary care-based healthcare delivery approaches for the management of chronic pain in Veterans, most of whom have co-morbid mental health problems and many of whom rely on opioid therapy. To be successful, such an approach must be patient-centered, yet prescriptive in terms of implementation; it should support care of the whole person, build self-awareness, and orient patients toward their underlying values and goals for health. In the case of chronic pain, a focus on decreasing underlying stress from mental health problems like depression is also crucial.

We posit that the VA's patient-centered Whole Health Model[5,6] can help guide the implementation of multi-modal pain care for Veterans in primary care. The Whole Health Model borrows elements of the evidence-based Chronic Care Model with its focus on activated patients practicing self-management with the support of their providers, ancillary care

managers/coaches, community/social support and use of health information technology infrastructure to enhance information-sharing among stakeholders. However, the Whole Health model adds a specific Whole Health clinical pathway, more practical guidance for implementation and a focus on evidence-based integrative treatment approaches.

Implementation of the Whole Health model or clinical pathway relies on three central components: (1) Personal Health Planning, (2) Personal Health Coaching, and (3) Referral to evidence-based Complementary and Integrative Health (CIH) modalities as well as other supportive resources.[5,6] The VA is implementing the Whole Health model and supporting expanded access to CIH resources at VA facilities and in the community. The VA's Whole Health model goes beyond the Chronic Care Model by operationalizing a specific approach to care that activates patients to achieve their own health goals. The Whole Health model also differs from the Chronic Care Model in its focus on active self-management activities that engage *both mind and body* to achieve overall health and wellness, and to improve functioning and quality of life.

CIH interventions may be reasonable alternatives to opioid therapy for chronic pain; the magnitude of pain reduction for CIH has been found to be comparable to opioids, but without the serious side effects. Although there is already high use of and willingness to try CIH modalities among Veterans with chronic pain,[59] studies show under-use of CIH specifically in patients with chronic pain prescribed opioids.[60,61] Thus, in Veterans who currently rely on opioids for the treatment of chronic pain, there may be an opportunity to gradually replace opioid therapy with at least as effective CIH modalities, which are also safer. The Whole Health model is specifically designed to facilitate patient engagement in self-care and CIH modalities that emphasize self-management. This model can be readily adapted to address chronic pain care in primary care, and through a grant from the VA Office of Patient-Centered Care, several VAs are currently piloting the use of this Whole Health Team (WHT) approach to develop personalized care plans with Veterans to improve pain and overall health, functioning and quality of life.

The comparator arm that we will be testing in this trial – Primary Care-Group Education (PC-GE), is an adapted version of Cognitive Behavioral Therapy for Chronic Pain (CBT-CP) delivered in a group format in primary care. CBT-CP is an evidenced-based treatment that follows the central tenet that individuals' thoughts and perceptions drive behaviors both in productive and life-sustaining ways, but in the pathological state, counterproductive ways. In the chronic pain state, maladaptive thoughts (e.g. catastrophizing) and distorted perceptions (e.g. disability) drive avoidance behavior that leads to further deconditioning and worsened pain. CBT-CP promotes patients' re-evaluation of distorted cognitions and empowers them to change cognitions and thus behaviors through a series of practical skill-building modules. The choice of group CBT-CP as the comparator arm is meant to be a less resource- and time-intensive, but not a markedly less potent intervention for chronic pain than the WHT approach. Effect sizes for CBT-CP are moderate in published research.

Since most patients with chronic pain present to primary care and primary care is the hub of patient care in integrated health systems, it is important in a pragmatic trial to test pain management approaches that can be readily implemented in primary care. To our knowledge, neither the WHT nor CBT-CP approach for chronic pain has been implemented in a primary care setting. Nevertheless, two of our prior studies and one ongoing study suggest that

biopsychosocial pain management approaches can be successfully implemented in primary care.[167]

2.0 Objectives

The goal of the 4-year UH3 implementation phase is to conduct a trial to compare two health care delivery approaches for chronic pain management (Whole Health Team and Primary Care Group Education) and both will be compared to Usual Primary Care in approximately 765 Veterans from 6 geographically diverse VA facilities in order to achieve the following study objectives:

UH3 Aim 1: Conduct a multi-site pragmatic trial of Whole Health Team (WHT) vs. Primary Care Group Education (PC-GE) and both compared to Usual Primary Care in veterans with moderate to severe chronic pain. **We hypothesize that WHT will be superior to PC-GE and both will be superior to Usual Primary Care (UPC) with respect to the following outcomes:**

***H1.*a.** Improved pain interference **(primary outcome)** and pain intensity, functioning and quality of life **(secondary outcomes).**

H1.b. Decreased use of higher-risk pain medications, including opioids or high-risk combinations of pain medications (i.e., co-prescription of opioids and benzodiazepines) **(secondary).**

H1.c. Engagement in a greater number of non-pharmacological pain management activities **(secondary).**

H1.d. Improvement in mental health-related symptoms, including sleep problems and suicidality **(secondary)**.

UH3 Aim 2: Conduct a process evaluation of the two active interventions (WHT and PC-GE) and budget impact analysis that includes costs to implement and execute the two active interventions as well as the control condition (UPC), to support the development of an implementation toolkit for scaling and dissemination.

UH3 Aim 3: Using a nationwide cohort of veterans, investigate the impact of the COVID pandemic on Veteran subgroups' utilization of non-drug, Whole Health, and CIH services for chronic pain management.

H3.a. Racial/ethnic minority veterans' utilization of pain management services may be differentially negatively impacted by the COVID pandemic.

H3.b. Women veterans' utilization of pain management services may be differentially negatively impacted by the COVID pandemic.

H3.c. Rural veterans' veterans' utilization of non-drug pain management services may be differentially negatively impacted by the COVID pandemic compared to urban-dwelling veterans.

3.0 Resources and Personnel

The main aim of this research is to conduct a multi-site pragmatic trial of WHT vs. PC-GE and both compared to Usual Primary Care in approximately 765 veterans with moderate to severe chronic pain, irrespective of the use of long-term opioid therapy across six geographically diverse VA facilities. The study will be based at the San Francisco VA Health Care System (SFVAHCS), the VA Connecticut Healthcare System (VACHS), the VA Portland Health Care System (VAPORHCS), the James A. Haley Veterans Hospital (Tampa VA), and the VA St. Louis Health Care System (VASLHCS). The Central Arkansas Veterans Healthcare System (CAVHS) will serve as a back-up site in the event that we are not meeting our enrollment targets.

San Francisco VA Health Care System (SFVAHCS)

Key Personnel

Karen H. Seal, MD, MPH, *Principal Investigator.* Dr. Seal is a primary care internist, Chief of the Integrative Health Service and Director of the Integrated Pain Team Clinic and Post-9/11 Integrated Care Clinic for Iraq and Afghanistan Veterans at the San Francisco VA Health Care System (SFVAHCS). Dr. Seal is a Professor in Residence in the Departments of Medicine and Psychiatry at the University of California, San Francisco and has a decade of data analysis and clinical trials research experience. Dr. Seal will be responsible for oversight of all trial implementation activities, including staff training and management, human subjects enrollment, safety and tracking, and an implementation-focused process evaluation and budget impact analysis. She will also oversee a data core based at the SFVAHCS which is responsible for data collection, quality control, validation and data analysis. Finally, Dr. Seal will ensure the development of the implementation toolkit, manuscript preparation and dissemination of project results. Dr. Seal is the corresponding PI of the overall study, will have primary oversight of the Whole Health team arm of the trial, and will serve as the site PI for the SFVAHCS. **Access to PHI: YES**

Natalie Purcell, Ph.D. *Co-Investigator.* Dr. Purcell is a sociologist who specializes in employing mixed qualitative methods drawn from the social sciences and humanities. Based at the San Francisco VA, she is the former Chief of the local Office of Patient Centered Care and is now the Program Director of the Integrative Health Service at the SFVAHCS. Dr. Purcell will be focused on assuring the implementation and fidelity to the Whole Health model during the UH3 phase and will lead an implementation-focused evaluation. She will also oversee the analysis of qualitative data collected in the UG3 portion of the study and will be the first author of a manuscript describing this formative evaluation in preparation for the study. Finally, Dr. Purcell is helping to oversee the development and implementation of the web/mobile Whole Health Resource Directory. **Access to PHI: YES**

Carolyn Gibson, Ph.D., *Co-Investigator.* Dr. Gibson is a Clinical Research Psychologist in the Women's Health program at the SFVAHCS and Dr. Seal is her primary mentor for her VA Career Development Award. Dr. Gibson brings expertise in women's health, specifically how reproductive transitions impact chronic pain. Her contributions to the research will be to guide

examination of needs related to women's health. She has broad experience conducting related research in the context of interdisciplinary collaborations, demonstrated productivity in the area of women's health, and clinical experience in the provision of integrated chronic pain care as a mental health provider in the VA setting. **Access to PHI: YES**

John Hixson, M.D, *Co-Investigator.* Dr. Hixson is a Neurologist and Clinical Informatics Specialist at the SFVAHCS. Additionally, he is a National Clinical Director for the Office of Connected Care based in the VHA Central Office in Washington DC. Through this role, he directs the development of patient-facing digital health technologies for the Veteran patient community. Dr. Hixson will be involved in developing Point-of-Care data collection instruments that will be used in the WHT and the PC-GE arms of the study. **Access to PHI: YES**

Shira Maguen, Ph.D., *Co-Investigator.* Dr. Maguen is a Staff Psychologist at the San Francisco VA Medical Center (SFVAMC) and an Associate Professor at the University of California, San Francisco. Dr. Maguen has particular experience in PTSD and PTSD-related sleep disorders, both of which commonly occur with chronic pain conditions. Drawing on her clinical and research experience, Dr. Maguen will assist Drs. Seal in evaluating comorbid mental health conditions in Veterans with chronic pain. **Access to PHI: YES**

Other Study Staff

Program Manager, holds a Master's degree in psychology and has worked closely with Dr. Seal for the past 10 years. She is a Master's-level experienced Program Manager who has served as the Project Coordinator for multiple prior VA, DoD and NIH funded studies. She will oversee all field operations of the proposed project, including the hiring and supervision of project staff, obtaining and maintaining Central IRB approval, including submission of modifications, and ensuring human subjects protections. She will maintain the project budget and will be responsible for all reporting requirements. **Access to PHI: YES**

Project Manager, an experienced project manager will oversee coordinating regular meetings of the co-investigators in setting the agenda for these meetings and posting meeting minutes to a study SharePoint site. She will also oversee coordinators at the other enrollment site in the finalizing of study materials for their site, subject recruitment, initial telephone pre-screening of subjects, verification of study eligibility, enrollment and informed consent procedures, randomization, and specific data collection activities, including conducting baseline phone assessments. She will also oversee the SFVAHCS Data Core, including supervising the data manager. As such, she will oversee the implementation of web-based applications for participant recruitment, enrollment, tracking and data collection. **Access to PHI: YES**

Qualitative Researcher, an experienced qualitative researcher with expertise in implementation methodology will assist with evidence-based quality improvement (EBQI) meetings, focus groups and semi-structured interviews. Specifically, she will assist Dr. Purcell in conducting all qualitative work required in the UH3 phase of the study. She will also be closely involved in working with Dr. Purcell in conducting the qualitative research analyses of data collected. **Access to PHI: YES**

Statistician will develop and oversee the statistical design, data quality assurance and analysis activities of the proposed study. He will also provide support for the data manager and programmer for the study data core and as such, will work closely with them to program software for centralized subject recruitment for the as well write code to regularly download participant outcomes from the VA administrative datasets. He will be primarily responsible for data analysis and interpretation and will be heavily involved with manuscript preparation activities and dissemination of results. **Access to PHI: YES**

Data Manager is a highly experienced data programmer and manager. He is familiar with VA data systems and peculiarities of accessing and analyzing VA national data. He will work alongside the statistician to develop study applications for recruitment, enrollment, randomization, tracking and data collection using a data management system. He will maintain the study sever and database in compliance with VA and UCSF standards for data security and will conduct data quality checks and back-ups regularly. He will also be responsible for data cleaning and validation in preparation for data analysis by the statistician, assuring data quality. **Access to PHI: YES**

Research Assistant (s) (TBD), An experienced research assistant (RA) will provide assistance to the PI, Program Manager and Project Coordinator. Specifically, this Research Assistant will be responsible for assisting with the submission of protocol changes to the VA Central IRB and for conducting some of the quantitative assessments (baseline and follow-up) during the RCT. He/she/they will also be responsible for scheduling and organizing meetings of the co-investigators, clinical interventionists and other stakeholder groups involved with the study. **Access to PHI: YES**

VA Connecticut Healthcare System (VACHS)

Key Personnel

William C. Becker, MD, ***Principal Investigator.*** Dr. Becker is an Associate Professor in the Department of Medicine at Yale University. He is also the Director of the Opioid Reassessment Clinic and Co-Director of the Integrated Pain Clinic at VACHS. Dr. Becker has extensive experience working with large multi-disciplinary groups of collaborators. For this project, Dr. Becker will serve as PI in the NIH multiple PI mechanism. He will be responsible for collaborating with Dr. Seal on administration of the proposed study, including assisting in overseeing the development of all study materials, staff training, quality control, human subjects, data collection, validation and analysis, manuscript preparation and dissemination of study results. In particular, he will oversee the development and implementation of the PC-GE arm across the 6 sites for this study. He will also be the site PI for the VACHS. **Access to PHI: YES**

Other Study Staff – VACHS

Statistician. A PhD level statistician, who will develop and oversee the statistical design, data quality assurance and analysis activities of the proposed study. She will take lead and work closely with the statistician at the SFVAHCS for various data monitoring reports required each quarter. She will also take lead on data analysis at the conclusion of the study. This statistician

is based at Yale University (a non-VA entity) but has a VA contract (WOC) that allows her to work with VA data. **Access to PHI: YES**

Biostatisticians: Two PhD level biostatisticians who have expertise in the use of the VA national-level database to investigate chronic pain management in veterans using complementary and integrative health therapies as well as disparities research. They will assist with the design and conduct of additional analyses using national-level VA administrative data related to the main study aims. They will also assist with the conduct and interpretation of these analyses and participate in manuscript preparation. These biostatisticians (Dr. Denise Esserman and Dr. Eugenia Buta) are based at Yale University (a non-VA entity) but have VA contracts (WOCs) that allow them to work with VA data. ***Access to PHI: YES***

Project Coordinator. An experienced Project Coordinator will oversee all field operations of the proposed study at VACHS. This includes assisting development of study materials, subject recruitment, verifying study eligibility, enrollment and informed consent procedures, randomization, and all data collection activities, including conducting baseline and follow-up masked phone assessments. The Coordinator will also be responsible for maintaining local site CIRB approval and ensuring human subject protections. The coordinator based at the VACHS will be supervised by Dr. William Becker. **Access to PHI: YES**

Central Arkansas Veterans Healthcare System (CAVHS)

Key Personnel

Jacob T. Painter, PharmD, MBA, PhD, ***Co-Investigator.*** Dr. Painter is an Associate Professor at the University of Arkansas for Medical Sciences (UAMS) in the Division of Pharmaceutical Evaluation and Policy; and an Investigator for the Center for Mental Healthcare & Outcomes Research (CeMHOR) at the CAVHS. Dr. Painter has experience with economic evaluations of clinical interventions including cost-effectiveness and budget impact. Dr. Painter will conduct the budget impact analysis, providing input on the design, data collection, and statistical analysis. He will be responsible for presentations and manuscript preparation on the BIA. The **CAVHS will serve as a back-up site in the event that the study is not on track to meet enrollment targets. Access to PHI: YES**

VA Portland Health Care System (VAPORHCS)

Key Personnel

Benjamin J. Morasco, Ph.D., *Co-Investigator*. Dr. Morasco is a Professor of Psychiatry at Oregon Health & Science University (OHSU) and a Staff Psychologist at the VAPORHCS. He will serve as the local site lead investigator for OHSU and oversee conduct of the trial at the VAPORHCS. He will collaborate closely with Dr. Seal and other study investigators. Dr. Morasco will provide oversight to the project coordinator for research activities and will work with local site clinicians to ensure the successful conduct of the study at the VAPORHCS. Dr. Morasco will participate in regular meetings with study investigators and contribute expertise in recruitment of the study population, strategies for implementing study interventions, and

collaboration with stakeholder groups. Dr. Morasco will also participate in manuscript writing and dissemination of study results. **Access to PHI: YES**

Lauren Denneson, PhD, *Co-Investigator*. Dr. Denneson is an Associate Professor of Psychiatry at OHSU and a Research Psychologist at the VAPORHCS. She is an expert in health-coaching, including the VHA's Whole Health Coaching approach, and will provide guidance on and evaluate coaching skills and procedures. She will collaborate closely with all investigators in the development, tailoring, and oversight of the Whole Health intervention. Dr. Denneson will also participate in manuscript writing and dissemination of study results. **Access to PHI: YES**

Other Study Staff – VAPORHCS

Project Coordinator An experienced Project Coordinator will oversee all field operations of the proposed study at VAPORHCS. This includes assisting with development of study materials, subject recruitment, verifying study eligibility, enrollment and informed consent procedures, randomization, and all data collection activities, including conducting baseline and follow-up masked phone assessments. The Coordinator will also be responsible for maintaining local site CIRB approval and ensuring human subject protections. The coordinator based at the VAPORHCS will be supervised by Dr. Benjamin Morasco. **Access to PHI: YES**

James A. Haley Veterans Hospital – Tampa, FL

Key Personnel

Jennifer L. Murphy, PhD, ***Co-Investigator*.** Dr. Murphy is a VA Supervisory Psychologist at the James A. Haley Veterans' Hospital in Tampa, Florida. She is an Assistant Professor in the Department of Neurology at University of South Florida College of Medicine. Dr. Murphy has served as the lead manual author, master trainer, and subject matter expert for the VA's Cognitive Behavioral Therapy for Chronic Pain (CBT-CP) evidence-based psychotherapy initiative since its advent in 2012. She also serves as a co-investigator on numerous funded grants focused on applications and outcomes of CBT-CP. For this project, Dr. Murphy will be responsible for developing the primary care-based cognitive behavioral therapy for chronic pain group education intervention (PC-GE) and will serve as the site PI at the Tampa VA where she will assist with administration of the proposed study, overseeing staff training, quality control, human subjects, data collection, manuscript preparation and dissemination of study results. She will collaborate with Co-PI's Drs. Seal and Becker on an ongoing basis. **Access to PHI: YES**

Aaron Martin, PhD, ***Co-Investigator*.** Dr. Martin is a clinical psychologist on staff at James A. Haley Veterans' Hospital in Tampa, Florida. He is CBT-CP (Cognitive Behavior Therapy for Chronic Pain) certified by VHA. In addition to working with Veterans with CP he also has extensive experience delivering behavioral interventions within primary care settings. He has experience adapting group interventions to suit clinical settings (primary care "friendly" including CBT for insomnia) and target co-occurring conditions (Pain, Activation and Sleep Skills; PASS to address insomnia in patients Veterans with CP). Dr. Martin will be responsible for assisting in the development of the primary care-based CBT-CP group education intervention (PC-GE) and will serve as a site coinvestigator at the Tampa VA. He will assist with administration and

coordination of the proposed study, including staff training, quality control, human subjects, data collection, manuscript preparation and dissemination of study results. He will collaborate with Co-PI's Drs. Seal and Becker on an ongoing basis. **Access to PHI: YES**

Other Study Staff – James A. Haley Veterans Hospital, Tampa, FL

Project Coordinator. An experienced Project Coordinator will oversee all field operations of the proposed study at James A Haley Veterans Hospital. This includes assisting with the development of study materials, subject recruitment, verifying study eligibility, enrollment and informed consent procedures, randomization, and all data collection activities, including conducting baseline and follow-up masked phone assessments. The Coordinator will also be responsible for maintaining local site CIRB approval and ensuring human subject protections. The coordinator based at this site will be supervised by Dr. Jennifer Murphy. **Access to PHI: YES**

VA St. Louis Health Care System (VASLHCS)

Key Personnel

Kavitha Reddy, MD, *Co-Investigator*. Dr. Kavitha Reddy is currently an emergency medicine physician at VA St. Louis Health Care System in Missouri. She has worked closely with the Office of Patient-Centered Care and Cultural Transformation as a Whole Health clinical champion since 2011, and currently is the National Lead Whole Health Champion for the Integrative Health Coordinating Center under this office. For this study she will be responsible for the administration of the study, including assisting in development of study materials related to the Whole Health Team intervention, as well as staff training, quality control, human subjects, data collection, validation and analysis, manuscript preparation and dissemination of study results. She will be overseeing the implementation of the study interventions at the St. Louis VA site. She will also be the site PI for VA St. Louis Health Care system during the UH3 phase of the project. **Access to PHI: YES**

Theresa Van Iseghem, *PhD, Co-Investigator*. Dr. Van Iseghem is a clinical psychologist with the St. Louis Veterans Healthcare Administration. She is part of the integrated medicine team within the whole health model of care. Dr. Van Iseghem specializes in the delivery of complementary and integrated health modalities; she is a qualified MBSR teacher, a registered yoga teacher, and soon to be certified biofeedback and clinical hypnosis practitioner. Dr. Van Iseghem is the recipient of innovative seed-grant funding. She spearheaded the implementation of the Shared Medical Appointments (SMAs) for the treatment of Type 2 Diabetes within the St. Louis VA and, more recently, worked within primary and specialty care clinics to develop and integrate whole health programming and that provides comprehensive mind-body interventions for patients living with chronic and complex medical conditions. For this study, she will serve as a site Co-Investigator along with Dr. Kavitha Reddy. She will assist with administration and coordination of the proposed study, including staff training, quality control, human subjects, data collection, manuscript preparation and dissemination of study results. **Access to PHI: YES**

Other Study Staff – VASLHCS

Project Coordinator. An experienced Project Coordinator will oversee all field operations of the proposed study at VASLHCS. This includes assisting with the development of study materials, subject recruitment, verifying study eligibility, enrollment and informed consent procedures, randomization, and all data collection activities, including conducting baseline and follow-up phone assessments. The Coordinator will also be responsible for maintaining local site CIRB approval and ensuring human subject protections. The coordinator based at this site will be supervised by Dr. Kavitha Reddy. **Access to PHI: YES**

Minneapolis VA Health Care System (MVAHCS)

Key Personnel

Erin E Krebs, MD, MPH, *Co-Investigator.* Dr. Krebs is an Associate Professor of Medicine at the University of Minnesota Medical School, core investigator in the Minneapolis VA Center for Chronic Disease Outcomes Research (CCDOR), and women's health medical director for the Minneapolis VA Health Care System. Dr. Krebs will collaborate with Dr. Seal, to ensure the success of this proposed multi-site trial, including finalizing study protocols in collaboration with co-investigators and study partners, and generating manuscripts, reports, and other products for dissemination of findings. Dr. Krebs will work closely with Dr Seal and her statistical team to ensure successful execution of tasks related to data management, study tracking, data quality assurance, and data analysis. **Access to PHI: YES**

Beth DeRonne, PharmD, *Co-Investigator*. Dr. DeRonne is an experienced clinical pharmacist. Although the present proposal focuses on non-pharmacological care, many participants are expected to be on complex analgesic regimens at the time of study enrollment. Dr. DeRonne will contribute her considerable experience with pain clinical trials to advise PI Dr. Seal and team in labor mapping effort for each of the active study arms, coordinating protocols related to medication safety, developing clinical electronic medical record templates, and assisting in analysis and dissemination of study results. **Access to PHI: YES**

Other Study Staff – MVAHCS

Data Analyst will provide assistance with data management support for this project, based on his experience in managing the Data Core for another similar VA multi-site study. The data analyst will provide technical advice to the San Francisco-based Data Core data manager regarding a VA-approved web-based study application to facilitate study implementation, including writing programs to identify eligible participants for study recruitment as well as enrollment, extracting administrative data, collecting participant self-report data, cleaning data, creating data files for analysis, reports and manuscripts. **Access to PHI: YES**

Memoranda of Understandings (MOUs):

SFVAHCS holds an MOU with the Northern California Institute for Research and Education (NCIRE), the non-profit affiliate that administers this grant.

4.0 Study Design

We aim to conduct a large-scale pragmatic randomized controlled trial in VA focused on non-pharmacological approaches to pain management and other comorbid conditions. This trial will compare two experimental health care delivery approaches for chronic pain management to each other and also to usual primary care in approximately 765 veterans from 6 geographically diverse VA facilities. ***Aim 1*** compares Whole Health Team (WHT) and Primary Care Group Education (PC-GE), two distinct patient-centered pain management approaches that differ in structure, comprehensiveness, and intensity. The *more* intensive WHT model employs a Whole Health multi-modal biopsychosocial approach delivered by an interdisciplinary pain team consisting of a primary care provider (PCP), integrative health clinician (e.g. mindfulness instructor) +/- a psychologist. The WHT will use the VA Whole Health Personalized Health Planning and Coaching model to promote wellness in veterans with chronic pain. The *less resource-intensive,* PC-GE adapts Cognitive Behavioral Therapy for Chronic Pain (CBT-CP) for a group format based in primary care. This model consists of psychologist-led weekly group sessions emphasizing pain self-management skill-building, coping techniques and multi-modal nonpharmacologic approaches to pain management. Elements common to both arms include point-of care data capture, and access to a web/mobile Whole Health Resource Directory. Both interventions will be compared to Usual Primary Care in which enrolled patients with chronic pain will be randomized to receive usual primary care. All subjects will be followed for 12 months to complete study assessments at baseline, 3, 6, 9 and 12 months.

We will allow for enrollment up to 800 veterans with moderate to severe chronic pain (irrespective of opioid therapy status), across 6 geographically distinct VA facilities including the medical centers and community-based outpatient clinics. Due to varying rates of recruitment at our six sites, we will continue to enroll until we achieve our target sample size of 765 veterans enrolled. As all our sites are actively recruiting it will be difficult to cut off exactly at 765. Thus, we plan to enroll any veteran who has received a recruitment call while attempting to reach our target sample size of 765 enrolled, allowing for up to 800 veterans. Participants will be randomly assigned at the individual level to either WHT, PC-GE or Usual Primary Care, stratified by site, sex, and use of prescribed opioids for chronic pain. The follow-up period for the three arms will be 12 months. The primary outcome is change in pain interference. Secondary outcomes include change in pain intensity, functioning, quality of life, changes in use of pain medications, including opioids (if applicable) and changes in nonpharmacological pain self-management activities. In addition, change in comorbid mental health-related symptoms (with a focus on sleep and suicidality), will be evaluated. To guide interpretation of trial findings and facilitate future implementation, ***Aim 2*** will consist of a process evaluation in which we will assess participants' and stakeholders' experiences of the implementation and execution of the two active interventions, as well as relative costs of all three study arms through a budget impact analysis. Aim 2 activities will inform the development of an implementation toolkit for scaling and dissemination.

As the study is during the COVID-19 pandemic, **Aim 3** will be using a nationwide cohort of veterans from the entire VA system, to investigate the differential impact of the COVID pandemic on racial/ethnic minority Veterans' use of Whole Health and CIH services from chronic pain management. (Specifics detailed in Section 15.0)

4.1 Implementation-Focused Process Evaluation:

During the 4-year trial, we will conduct a process evaluation of the implementation of the two active interventions (WHT and PC-GE), consisting of patient semi-structured interviews and EBQI meetings with study stakeholders. The overarching goal of the process evaluation is to understand patients', clinicians' and VA leadership's experiences with these interventions and identify strategies to enhance future implementation and dissemination of effective pain care interventions.[101] Specific goals of the process evaluation are fourfold: 1) to increase the relevance of the primary research findings to patients, clinicians and health care decision-makers; 2) to increase the likelihood of timely translation of research findings into diverse practice settings; 3) to generate information to guide interpretation of primary trial findings; and 4) to create an implementation toolkit to support future implementation of study interventions in diverse practice settings.

The process evaluation will start in the second half of the first year of the UH3 trial and conclude in the first half of the final year. Rapid analysis of process evaluation findings[171] will inform iterative improvements to the implementation strategy as the trial progresses. The goal of this rapid learning approach is to ensure that the intervention is aligned with everyday clinical care and the evolving needs for pain management within the VA healthcare system. This in turn will increase the likelihood that the approach is sustained in real-world clinical care settings after the trial has ended. The final trial year will be devoted to both quantitative and qualitative data analysis; dissemination of findings through reports, manuscript, abstracts and cyberseminars; and completion of an implementation toolkit including all study materials and software to support future scale and dissemination activities.

The **RE-AIM *(Reach, Effectiveness, Adoption, Implementation, Maintenance)* Framework** [172,173] will guide our process evaluation of the implementation strategy. The table below delineates the methods we will employ to assess each RE-AIM domain: ***Reach*** represents the proportion of eligible participants that enrolls in the study.[174] ***Effectiveness*** represents patient-level clinical outcomes of the interventions as pragmatically implemented in routine care settings at each of the sites.[172,175] Effectiveness will be evaluated through our pragmatic effectiveness trial using the pre-specified outcomes. ***Adoption*** represents the proportion of VA staff referring participants to the study, as well as adoption of the care delivery strategies (WHT and PC-GE) by the clinical teams based at each of the VA study sites at the end of the study.[174] A more in-depth qualitative understanding of both reach and adoption will be obtained at stakeholder EBQI meetings and through informal ethnographic observation of other key meetings/events associated with study implementation at each site. ***Implementation*** represents the fidelity with which the interventions are implemented in routine care.[174] Supervision and fidelity monitoring of staff conducting each of the interventions at the study sites will be used to evaluate adoption as well as implementation**.** In addition, the EBQI meetings with stakeholders will evaluate the acceptability and feasibility of the interventions (as implemented) and specific barriers to and facilitators of implementing the interventions. ***Maintenance*** represents the degree to which the pain management approach (WHT vs. PC-GE) is likely to be sustained.[174] This dimension will also be assessed during EBQI meetings at the end of the trial.

RE-AIM Implementation Evaluation: Quantitative & Qualitative Components

Reach (Years 1-2)	On a quarterly basis, we will monitor: • The number of potentially eligible participants contacted • The proportion of participants that enrolls • The percentage of enrolled participants that attends required study-related visits
Effectiveness (Years 1-3)	Effectiveness will be evaluated at the conclusion of this pragmatic trial using pre-specified outcomes. Primary and secondary outcomes to be measured include: • Pain interference score (primary) • Pain intensity, functioning and quality of life, decreased use of higher-risk pain medications, engagement in a greater number of non-pharmacological management activities, and improvement in mental health-related symptoms ***Outcomes ascertainment methods and specific measurement instruments are detailed in Section 7.2.4.***
Adoption & Implementation (Years 1-2)	A process evaluation will be conducted to assess acceptability, feasibility, satisfaction, barriers to, and facilitators of implementation, consisting of: • Semi-structured interviews with study stakeholders (n=~40-50). • Semi-structured interviews with veterans (n=~40-50) • EBQI meetings with study stakeholders (n=20-30 at each meeting) • Rapid qualitative analysis to identify interview and EBQI themes In addition, study staff fidelity to the interventions will be monitored via: • Monitoring staff attendance rates for monthly case conference calls with WHT & PC-GE providers • Conducting ethnographic observation during monthly WHT/PC-GE/Coach provider calls • Auditing clinic notes • Reviewing audio-recorded coaching sessions (5-10% across sites)

Maintenance (Years 3-4)	Through ethnographic observation and rapid analysis of stakeholder EBQI meetings conducted at the end of the trial, the likelihood that each pain management approach (WHT and. PC-GE) will be sustained will be assessed, and we will identify potential barriers to and facilitators of sustainment.

1. ***Qualitative data collection with study stakeholders and clinical interventionists:*** The RE-AIM framework will guide qualitative data collection during the process evaluation. We plan to interview a purposive sample of stakeholders and clinical interventionists across all sites, anticipating that we will reach thematic saturation through interviews with 4-6 participants at each site for a post-implementation timeframe (i.e., 18-24 months after intervention launch at each site; n=~40-50 interviews). These interviews will be rapidly analyzed, and salient themes will be distilled for the EBQI meetings that follow each round of interviews. We will potentially also collect ethnographic data from monthly national clinician meetings. During the COVID-19 era, semi-structured qualitative interviews with veterans and clinicians will also include a supplemental addendum addressing experiences with care during COVID-19.

   Following each round of VA staff and veteran participant interviews, we will conduct an EBQI meeting with study stakeholders, including study clinicians, VA leadership, non-study clinicians and veteran study participants. The EBQI meetings will be led by one of the study PIs, the site PI, a senior member of the qualitative team, and another qualitative investigator to observe and take detailed notes. The EBQI meetings will draw on information gleaned from completed stakeholder and veteran interviews to recap trial progress at the individual sites and pose several discussion questions related to the sites' unique implementation strategy, including acceptability and feasibility of recruitment and enrollment as well as delivery of the pain management interventions (WHT and PC-GE) within each site's clinical settings. The second EBQI meeting will also focus on the potential for long-term sustainability, including barriers and facilitators to widespread dissemination and scale-up at the study site and other VAs.[173,174,176-178]

2. ***Qualitative data collection with veterans:*** Veteran participants in both the WHT and PC-GE intervention arms will be interviewed by telephone at a single timepoint between study enrollment and the end of their study participation. We will purposively sample diverse participants to maximize participant diversity with respect to age, sex, race/ethnicity, study site, and level of participation in the intervention (defined by the number of intervention visits completed over the first 6 months). Semi-structured interview questions will address experiences with the WHT or PC-GE intervention, perceptions of the value and convenience of the intervention, what (if any) aspects of the intervention influenced their personal treatment outcomes, and any recommendations for improvements. We will continue to conduct interviews with patients until thematic saturation is reached. Based on recommendations for qualitative sampling,[179] we expect to conduct 15-20 interviews for each study arm, for a total of 40-50 participant interviews.

3. ***Qualitative data analysis:*** Data from all interview transcripts and EBQI meeting field notes will be analyzed by the qualitative research team using rapid analysis methods developed for health services research.[171,182] At least two trained analysts will independently listen to each interview, read each ethnographic note set, and prepare a written summary using a templated matrix organized by topical areas. The analysts will then collaborate with the investigators to review all matrices, identify recurring themes, and refine the description of each theme for each relevant RE-AIM domain. Identified themes will form the basis of qualitative summary reports and will inform the development of implementation toolkit.

4.2 Budget Impact Analysis (BIA)

BIA has become the standard for developing the business case for healthcare implementation decisions because it provides a straightforward economic comparison of different interventions. [65,66,80] In collaboration with the Coordinating Center, Dr. Painter will direct the BIA for this study. Results from this BIA will be included as part of the implementation toolkit and will inform future implementation and dissemination efforts.

Costs will be collected for each of the three arms of the study (WHT, PC-GE, Usual Primary Care). Relevant costs can broadly be classified as implementation costs, intervention costs, and other healthcare costs. Implementation costs will be zero for Usual Primary Care, but there will be implementation costs for the two active interventions (WHT and PC-GE), which include staff time for intervention development activities, qualitative assessments for implementation readiness, EBQI activities and training of clinical and intervention staff at each of the enrollment sites. The calculation of costs for implementation of the interventions will require primary data collection.

In addition to health services utilization costs associated with Usual Primary Care (UPC) for chronic pain, intervention costs in this arm will be minimal but will include training of UPC veteran participants and primary care staff on use of the Whole Health Resource Directory. For the WHT and PC-GE interventions, intervention costs will be calculated using a combination of VA administrative and clinical staff time devoted to each of the active interventions as well as costs associated with participant services utilization. Specifically, for the WHT intervention, visit costs will include team conferencing time and clinician time, including coach time (hourly rate for each team member) that will be ascertained using clinic visit notes in the electronic medical record (EMR) plus estimated administrative time for each clinical visit. PC-GE intervention costs will be estimated by accounting for the number of PC-GE modules for patient participants per site and the clinician and administrative time associated with each module. All other VA and non-VA community care healthcare costs will be collected using Decision Support Systems (DSS) National Data Extracts, the official cost managerial accounting system for VHA as well as new databases for computing costs for non-VA community care (after the Mission Act). These analyses will focus on VA and non-VA outpatient visits and outpatient pharmacy costs. Outpatient costs for the main analysis will be organized in the following groups by stop code field: integrative (CIH), primary care, emergency department, mental health, substance use disorder care, specialty pain care, ancillary, physical health specialty, and other. Outpatient VA medication costs will also be assessed using VA DSS data and will be divided by medication

class into opioid, non-opioid pain related, and other. We will also track inpatient admissions of all study participants during follow-up.

The BIA will be conducted in accordance with guidelines from the International Society for Pharmacoeconomics and Outcomes Research.[181] To estimate the budget impact of each intervention relative to UPC we will conduct two analyses, i.e. UPC versus WHT and UPC versus PC-GE. For each analysis, we will estimate the total 12-month cost that would be incurred by VA to implement and deliver the intervention to all patients eligible for the trial relative to UPC. The BIA covariates will be the same as those used in the primary analysis (including sociodemographic characteristics, enrollment site, use of long-term opioid therapy, other pain medication use, presence of comorbid mental health symptoms, baseline pain intensity and interference) plus one-year pre-intervention healthcare utilization costs to control for baseline cost differences. Because healthcare costs are likely to be non-normally distributed, we will use generalized linear models to estimate the effect of each intervention on total costs. To calculate the incremental treatment effect on costs, we will compute two predicted costs for each participant. The first cost prediction will be for costs as though the patient had been randomized to the relevant intervention arm and the second cost prediction will be for costs as if the participant had received UPC. The difference between these two cost predictions represents the potential additional cost of the intervention for the participant because all covariate effects will be identical. Individual cost differences will then be averaged to provide an estimate of the cost to provide the relevant intervention to an average patient at an average site relative to UPC.

4.3 Pragmatic Features

Pragmatic trials combine the strength of randomized treatment assignment with design elements intended to maximize applicability of findings to diverse patient populations and clinical practice settings.[131,132] With the goal of maximizing pragmatism, we applied the PRECIS-2 tool for trial design to assess the consistency of our design choices with our overall goals.[131] We adhere to a highly pragmatic approach to eligibility, setting, care delivery models, flexibility of intervention delivery, and flexibility of intervention adherence.[75] Our primary outcome, improvement in pain interference, is highly pragmatic because it is relevant to patients with chronic pain. Our care delivery models for the two active intervention arms are flexible. We will allow providers to conduct the active intervention visits in-person, through video platforms, or via telephone. To securely conduct video telehealth visits, providers are permitted VA Video Connect (VVC), Doximity, and/or Cisco WebEx. To securely conduct visits via telephone, providers may use: on-campus VA telephones, VA-issued cellular devices, soft lines, VANTS lines, and/or Doximity. These options for delivering the interventions are highly pragmatic and will enhance protocol adherence, especially in light of the COVID-19 pandemic and VHA's mandate to convert all elective healthcare to telehealth. We anticipate that veteran participants will be hesitant and/or unable to attend study visits in-person not only during the COVID-19 pandemic, but for an extended period thereafter. The variety of telehealth options offered for the active intervention arms are identical to the telehealth options that veterans are currently offered as part of usual primary care. Study clinicians will be trained in optimal use of all platforms offered at their respective sites and the use of any and all chosen platforms will be piloted by the clinical teams prior to use with enrolled participants.

The least pragmatic elements of our design are follow-up intensity and recruitment. Given the importance of patient-reported outcomes in pain research, we will have frequent follow-up contacts and telephone assessments by masked study staff members to reduce ascertainment bias, minimize missing outcome data, and reduce participant attrition. We will test the reliability of point of care and VA administrative data in comparison to patient-reported outcomes as another potential source of data that is more pragmatic. For recruitment, we are using a well-established centralized approach to achieve and retain the target sample size, while oversampling women (who are under-represented in the veteran population). We are also encouraging providers to refer patients to our study. Centralized and local recruitment efforts will attempt to address potential barriers to recruitment of patients with chronic pain, particularly those receiving opioids. One aspect that will make our recruitment more pragmatic in light of COVID-19 is to place participants on a secure call-back list if they are unable to participate due to COVID-19-related barriers at the time of recruitment but are interested in participating at a later date, not to exceed one year prior to study end.

The COVID-19 pandemic requires even greater pragmatism with respect to intervention delivery. Telehealth resources reflect an alternative way of delivering care when in-person care delivery may not be feasible or available, such as with the COVID-19 pandemic. [186]. Some participants may be less willing or able to use telehealth than others and thus with shelter-in-place orders or phased recovery plans, COVID-19 may impact subjects' ability to remain engaged in the study interventions and provide outcomes data. On the other hand, with more and more veterans learning to use telehealth and prohibitions on travel and relocation, more veterans may complete the study interventions and the follow-up assessments, providing outcomes data. Thus, given the unknown impact of COVID-19 pandemic on participants and study outcomes, we will need to plan for the possibility that a per-protocol analysis may be needed in addition to the planned intention-to-treat analysis (ITT). As opposed to the ITT analysis which includes all participants who were enrolled and randomized to one of the three study interventions, the per-protocol analysis includes only subjects who completed the protocol of the originally allocated treatment. This per-protocol effect is the maximum potential benefit of the active treatments[187] and is estimated without being affected by incomplete adherence; therefore, the per protocol analysis may be of more interest for patients who consider whether to use the intervention[188]. If using per-protocol analysis the effect size of a COVID-19 period is attenuated compared with that of a non-COVID period, we can infer that COVID-19 may have mitigated the effect of the intervention for a variety of reasons; e.g., telehealth vs. in-person intervention delivery; lack of available pain resources in VA or the community etc. On the other hand, if it is feasible to conduct both ITT and per-protocol analyses, and if the results agree, we can conclude that COVID-19 had limited influence on the treatment effects. In summary, we expect more pragmatic features in the "organization" and "primary analysis" domains of the PRECIS-2 Tool due to the impact of COVID-19.

5.0 Selection, Recruitment, and Enrollment of Participants

5.1 Inclusion Criteria

Participants must meet the following inclusion criteria to be enrolled in the study:

- Assigned to a VA PCP;

- Report pain present every day or nearly every day for ≥ 6 months using a phone eligibility screener; and
- PEG score of ≥ 4 (including at baseline assessment)

5.2 Exclusion Criteria

Candidates with any of the exclusion criteria at baseline will be excluded from study participation:

- Moderate or severe cognitive impairment as determined by a failed 6-item, validated cognitive screener on initial phone screening (see Appendix 1.0: Phone Eligibility Script/Screener);
- Active suicidality as determined by medical record review, standardized assessment (PHQ-9) and/or is unable to attend study visits because of an unstable or severe psychiatric or medical condition or is receiving palliative or hospice care; or
- Current involvement in any similar longitudinal interdisciplinary pain clinical service including local integrated/integrative pain management programs
- Any other factors that would interfere with study participation including inability to communicate by telephone; being a non-English speaker; plans to relocate within 12 months and concurrent participation in another pain-related study.

5.3 Recruitment

Recruitment of Clinician Participants:

Local site investigators will identify volunteer clinician participants by discussing the study with local clinical colleagues, pain champions, and primary care teams. Local site investigators will share contact information with the San Francisco research staff, who will provide study information to potential clinician participants and invite them to participate. Written informed consent for participation will be obtained by the local site investigator or study coordinator at the local site level prior to the local site trial launch or, for clinicians who join after the trial launch, prior to their participation in the intervention teams. If a clinician prefers to become a member of the study team (study collaborator) instead of a participant, appropriate training and qualifications will be required.

Sample Size

We plan to enroll up to 20 clinician participants at each site (including replacements over the course of the active intervention period), which we expect will be approximately evenly distributed across the 6 enrollment sites.

Recruitment of Study Participants:

The total sample size for the population based on our main study aim/hypothesis is

N=765. This breaks down to N=341 in each of the active interventions (WHT and PC-GE) and N=83 in the Usual Primary Care arm (Control). In other words, we hypothesize that the effect size differences will be smaller between the two active interventions than for each of the active interventions compared to Usual Primary Care. Therefore, we will require the larger sample size to detect differences between the two active interventions than each compared to Usual Primary Care. At each of the initial five enrollment sites, we will need to enroll, on average, 69 patients each in the WHT and PC-GE arms and 17 patients in the Usual Primary Care arm over the enrollment period. We will be adding a sixth enrollment site to help achieve our target sample. While this is an average projection, we expect that enrollment rates will differ across sites and, consistent with the pragmatic trial design, we will allow sites to go over and under projected averages. Based on prior similar studies, given the pragmatic eligibility criteria, we anticipate that at a minimum, 70% screened will be eligible to participate and of those eligible, roughly 20% will enroll. If we require approximately 765 patients for the trial to test the primary study hypothesis, anticipating a 20% drop-out rate, we would need to screen 5,464 to identify roughly 3,825 potentially eligible patients.

Table 1. Plan for recruitment of an adequate sample

Total number of patients expected to be screened	~ 5,464
Of those screened, total number expected to be eligible:	~ 3,825
Target sample size:	~ 765

Compared to the general U.S. population, women are underrepresented in veteran samples. Thus, to achieve better representation of women in the pragmatic trial, we will oversample women by inviting *all* preliminarily eligible women and only a proportion of preliminarily eligible men. If estimated enrollment rates are accurate, we would then enroll women at approximately twice the rate of their prevalence in the veteran population.[133] We will monitor enrollment of ethnic minority participants and if lower than that represented in the veteran population, we will prioritize recruitment of ethnic minorities. Historically, we have found it challenging to recruit veterans prescribed opioids for chronic pain into research studies of alternative management interventions. We will thus also over-sample veterans prescribed opioids.

Site-Based Recruitment and Enrollment Targets

To take maximum advantage of the study's geographic diversity, we will attempt to enroll similar numbers of participants at each site. Monitoring of eligibility, contact and enrollment rates will be performed for the study overall and by site on a monthly basis. The number of patients contacted each month will be adjusted to maintain overall target enrollment rates. If enrollment rates are lower than expected at an individual site, site-specific factors will be addressed as indicated. If needed, site-specific enrollment targets will be adjusted to achieve overall enrollment targets; for example, this could include increasing recruitment contacts at a successful high-volume site to make up for lower-than-expected enrollment at another site. If one site is consistently under-performing, this is the scenario in which we would stop enrollment at that site and activate our back-up enrollment site. As our target sample is 765, we will allow

for recruitment of up to 800 veterans to hit our target sample. Due to varying recruitment speeds at our six sites, we will continue to enroll until our target sample of 765 is met.

Specific Recruitment Strategies for Veterans

Determining Eligibility: VA administrative data will be used to identify eligible patients at all 6 enrollment sites. The following are the broad eligibility criteria used to search VA administrative databases for potentially eligible participants, consistent with the recommendations of the Pain Management Collaboratory Coordinating Center:

- ≥1 clinic visit at an enrollment facility within the past year and resides within 500 miles of an enrollment site (including VA community-based outpatient clinics); and
- Has received at least 2 diagnoses within the same pain category, at least 90 days apart, within the past 2 years (Goulet ICD-9/10-CM classification); and
- Has reported a pain numerical rating scale (NRS) score of ≥ 4 on at least 2 occasions, within two years with at least 30 days between scores

Veteran eligibility data will be entered into our SQL database by the study team's data manger, to which each site's study coordinator will have access. The SFVAHCS will serve as the study's Data Coordinating Center. The SFVAHCS Coordinating Center's study coordinator and data manager will train enrolling site coordinators on how to use the database for recruitment and enrollment.

Recruitment method:

1. Administrative Database: Potentially eligible veterans (identified through VA administrative databases using a HIPAA waiver for recruitment) will be mailed recruitment materials: patient letters, study information sheets, recruitment brochure, and opt-out letters (including a return envelope addressed to the local study site). We will wait 10 days for opt-out letters to be returned or for patients to call the study staff. If subjects do not opt out or call the study staff first, we will contact them via phone. No cold calls will take place. The coordinator will make up to 5 attempts to reach potential participants and leave up to 3 discrete voicemails. On reaching potential participants, the study coordinator will attempt to determine interest in participating and assess eligibility using a phone eligibility screener (see Appendix 1.0 Phone Eligibility Script/Screener). This screener will assess:

    - Presence of chronic pain for at least the past 6 months
    - Overall pain severity in the last 30 days from 0-10 of at least a '4'
    - Plans to relocate in the next 12 months
    - ≥ 2 errors on Callahan, et al., "six-item screener" to assess for moderate to severe impairment
    - Current enrollment in another pain-related study

2. Provider Referral: Providers will be able to refer veterans with moderate to severe chronic pain to be assessed for study enrollment. Providers may identify patients whom they believe would meet study inclusion criteria and provide the study flyer and informational brochure to the patient. The potential participant (with or without the assistance of the provider) can call

the study staff to receive more information about the study. The veteran can opt to receive more information about the study in the mail or they can be phone screened for eligibility (see telephone eligibility screener and script) at that point. If the patient requests additional information, a recruitment letter, recruitment brochure, and information sheet will be sent in the mail and study staff will call 10 days later to conduct the phone eligibility if they are still interested.

3. Self-Referral: Veterans can respond to flyers posted in VA clinics at the enrollment sites by calling the number of the site coordinator to receive more information about the study. If veterans call the study staff directly for self-referral, they can have the option to receive more information about the study in the mail or they can be screened for eligibility (see telephone eligibility screener and script) at that point. If the patient requests additional information, a recruitment letter, recruitment brochure, and information sheet will be sent in the mail and study staff will call 10 days later to conduct the phone eligibility if they are still interested.

Once a potential participant who appears to be eligible wants to participate, we will also conduct an EMR chart review to check for the following exclusion criteria: a life-threatening condition in which death is imminent, active suicidality or enrollment in another pain-related research study, as evidenced by another study enrollment note or active research flag.

5.4 Participant Payment

To encourage participation and retention and to compensate veterans for their time and effort, in the research portion of the study (i.e. the assessments), Veteran participants will receive compensation after completion of each masked assessment. Veteran participants will be compensated $50 for completion of each full-length telephone assessment (baseline, 6, and 12 months) and $25 for each brief assessment (3 and 9 months).

We will allow for recruitment of up to 800 subjects over the enrollment period across all 6 enrollment sites, once all sites have been activated. The subject timepoints and reimbursement schedule for participation in the trial are as follows:

Study Assessment Reimbursement Schedule per Subject (N= 160)	
Baseline	$50
3-month	$25
6-month	$50
9-month	$25
12-month	$50
TOTAL compensation	***$200***

Of the subjects enrolled in the trial at each site, n=~8 participating in one of the two active interventions will be randomly selected to participate in a one-time Qualitative Interview

during their participation in the one-year trial. The Qualitative Interview will last 30-60 minutes, and each subject will be compensated an additional $50 for their time and effort.

Qualitative Interviews N~8	
30-60minute interview	**$50**

Subjects who complete all time points of the trial will be compensated $200 for their participation over the one-year enrollment period. Subjects who complete all time points of the trial and, in addition, complete the 30–60-minute Qualitative Interview, will be compensated $250 for their participation.

Subjects that endorse natural product use during their baseline assessment will be invited to complete a separate survey on natural products use and qualitative interview.

Natural Products Survey completion:

Subjects (n~50) will be paid $50 after receipt of their completed NP survey.

Natural Products Survey Semi-Structured Interview:

Subjects will be paid $25 for completing the brief semi-structured interview.

5.5 Study Enrollment Procedures

Prior to the start of enrollment, the study team at each individual site will conduct a brief study information session with PCPs at that enrollment site to describe, introduce, and orient them to: (1) the purpose of the trial, (2) the three study arms, (3) principles of multi-modal pain self-management with an emphasis on non-pharmacologic modalities, and (4) the web-based/mobile Whole Health Resource Directory that lists CIH pain-related services at their VA sites and in their communities, which they can use with all patients with chronic pain irrespective of study enrollment. An email with the same content will also be sent to all PCPs in the enrolling primary care clinics because it is expected that not all PCPs will be able to attend the in-person briefing about the study. We will repeat the study information session several times at each of the enrolling sites throughout the enrollment period.

Once patients are contacted by the local site coordinator following the recruitment mail-out (described above), if they are interested, they will be asked to undergo a telephone eligibility screening (see recruitment section). If participants indicate that they are experiencing technology-related barriers preventing them from participating at this time (such as lack of a smart device or computer and/or internet access), but that they may be able to participate in the future, they will be placed on a secure list for future follow-up. If they are determined to be eligible and are interested in participating in the study, they will be scheduled for an appointment with the local site coordinator to be enrolled in the study and complete the baseline assessment.

Eligible patients unsure about participation will be encouraged to discuss the study with their PCP and will be provided the option of a future follow-up recruitment call.

At the appointed date/time, eligible participants will be recontacted for enrollment and telephone baseline assessment. At the beginning of the call, the study coordinator will email the potential participant a link to the electronic Informed Consent form to be completed via VA-approved DocuSign. DocuSign will require a two key digital signature from the participant. In the case where a participant does not have an email address or access to email, the study coordinator will mail out a paper copy of the informed consent document prior to contacting the participant for their telephone baseline assessment. Whether the participant receives the informed consent over email while on the phone or previously via mail, the study coordinator will carefully review the informed consent (IC) document and answer any questions about the study with patients. Study coordinators will ask patients to follow along using the IC document that was e-mailed to them via the link or using the physical copy that was mailed. For patients that were e-mailed the link, we will ask them to electronically sign the form on DocuSign after completing the IC process. For patients who do not have email and received a physical copy of the IC in the mail, we will ask them to review, sign and mail back the document using a pre-addressed envelope provided. The local site coordinator will then complete the baseline assessment which determines final eligibility for the trial. For subjects without email/internet, the baseline passement will not be conducted until the participant returns their signed consent form to the research staff. The baseline assessment will further ensure the absence of any exclusion criteria including:

- Severe untreated mental health or substance use disorder, active suicidal ideation that was not identified in the EMR or disclosed during phone eligibility screening, obvious intoxication, delirium or other cognitive impairment.

Once the study coordinator verifies the electronic signature of the IC form or receives a copy of the signed informed consent form via mail, and the baseline assessment is completed, participants who remain eligible (i.e., no active suicidal ideation etc.) will be randomized to one of the three study arms. During this call or a subsequent phone call in the near future, the study team member will provide the individual with an orientation to their specific study arm, schedule of study assessments, and to the web/mobile Whole Health Resource Directory (see Appendix 2.0 Orientation Scripts). The study team member will assist the participant in accessing the Whole Health Resource Directory through either their personal computer or mobile phone or give them ideas for where they can access it. After the baseline assessment, the participant will be scheduled for their 3-month outcome assessment.

6.0 Study Interventions

6.1 Interventions, Administration, and Duration

Whole Health Team Arm

Rationale: We selected the Whole Health Team (WHT) as our more intensive pain management approach because it expands on the evidence-based VA Integrated Pain Team[2-4] model in its structured patient-centered approach to supporting the health and wellness of the whole person and its emphasis on self-management skill-building and the use of non-pharmacological and CIH modalities. The VHA has already implemented the Whole Health model to support veterans in preventing and better managing chronic disease, including chronic pain.[5,6] Yet, while RCTs provided evidence for interdisciplinary chronic pain management programs using cognitive behavioral therapy[142, 143] and exercise,[144,145] there has been no trial to date that tests the VA Whole Health model for chronic pain management. This trial will compare a WHT approach, with other more established models such as cognitive behavioral therapy for chronic pain (CBT-CP) as well as usual primary care.

WHT intervention elements: The WHT intervention arm includes four core elements: 1) An interdisciplinary WHT collaborating with primary care; 2) Personalized Health Planning with prioritization of multi-modal non-pharmacological and CIH pain management approaches; 3) Whole Health Coaching sessions to assist patients in developing and implementing a Personalized Health Plan for chronic pain care; and 4) the web/mobile Whole Health Resource Directory provided to patient participants (in addition to their providers) to support non-pharmacologic/CIH chronic pain care.[5,6] Due to variation in local site resources and constraints, WHTs will be configured somewhat differently at the different enrollment sites. Given this heterogeneity and our pragmatic research framework, we define WHT elements in terms of ***"core"*** and ***"optional"*** components.

(a) Interdisciplinary Whole Health team: Two types of clinicians are core to most interdisciplinary pain clinic models described in the literature or implemented within VA[2-4] and will also be core providers for the WHT model in this study. These are a PCP (physician, nurse practitioner, or PA) and an integrative health clinician (e.g. mindfulness instructor, yoga instructor, chiropractor or acupuncturist etc.) +/- a mental health provider (i.e., psychologist or mental health social worker). At a minimum, all WHT providers will have participated in VA's Whole Health in Your Practice training—a 2.5-day clinical education program offered by the VHA Office of Patient Centered Care and Cultural Transformation (OPCC-CT)—or an equivalent alternative training that emphasizes an integrative Whole Health non-pharmacological approach to chronic pain management (i.e., Whole Health Pain and Suffering Course).[146,147] A Whole Health coach is also a core member of the WHT. Whole Health coaches will be certified veteran peer support specialists or another type of VA employee with the requisite OPCC-CT training in Whole Health coaching. Other core elements of WH team-based care are collaboration in the development and monitoring of patients' Personalized Health Plans (PHPs) and regular communication among team members about patient's care; WHTs will meet at least weekly as a team for case review. Optional elements include: (1) inclusion of a mental health provider; (2) co-located vs. sequential visits with WHT members; (3) embedding the WHT in primary care (preferred) vs. use another location if space in primary care is limited. We will monitor fidelity of the WHT clinicians by auditing their clinic notes (see below) to determine the completed elements of the WHT clinic visit. The site PI will attend WHT visits (at least 1 visit a month in the first 6 months of the first trial year) to monitor that key elements are being covered. Additionally, there will be a

monthly all-site WHT call lead by the SFVAHCS site to calibrate and standardize the WHT intervention across sites.

(b) Multi-modal pain management: The WHT arm will use a multi-modal approach emphasizing evidence-based non-pharmacological/CIH therapies that target biopsychosocial contributors to pain and disability. In a pragmatic trial of a health care delivery approach emphasizing non-pharmacological pain management, we recognize that most trial participants will be using medications for pain, some of which they may find effective. The provider(s) in the WHT may make changes to the participant's medication or work with the participant's PCP to make these changes. However, the use of medications is more of a passive activity that does not require the same degree of patient activation and proactive self-management that predicts improved functioning and quality of life in the Chronic Care and Whole Health models.[5,6,148] One primary goal of the WHT will be to help patients shift from solely relying on medications to adopting multiple strategies for chronic pain management. The WHT model uses the analogy of a "**car with four flat tires."** Filling only one of the tires with medication will not result in the car functioning; instead, all four tires must be filled for the car to function. The four modalities of non-opioid chronic pain management include: (1) Procedural and Manual modalities such as acupuncture[110] and massage;[119,120] (2) Behavioral Health including cognitive behavioral therapy,[50] and mindfulness;[116-118] (3) Physical modalities such as yoga,[149] and stretching and strengthening programs;[150] and (4) Medication, preferably non-opioid analgesics. Treatment options with strong evidence will be emphasized. Personalized Health Plans may also contain patient-directed activities like gardening, wood-working, etc. that encompass multiple modalities and are consistent with patients' personal values and goals (see below).

(c) Whole Health Coaching sessions: WHT clinicians, particularly the psychologists and coaches will use a mix of communication techniques, including Motivational Interviewing (MI), to engage patients in shared decision-making, starting with eliciting core personal values and functional goals at the initial visit. MI techniques will be used to develop Personalized Health Plans and to guide follow-up coaching sessions throughout the intervention period. These Whole Health coaching sessions will be unscripted and guided by Whole Health and MI principles:[133,151] expressing empathy, developing discrepancy between values and current behavior, rolling with resistance, and supporting self-efficacy.[152] Fidelity of WHT coaching sessions will be assessed by experts in Whole Health coaching and MI. For this purpose, the majority of coaching sessions will be audio-recorded. Fidelity monitors will then randomly select 10% of all audio-recorded coaching sessions/quarter to monitor for fidelity to the Whole Health coaching model and MI principles. The WH coach supervisor may also listen in to coaching sessions in lieu of recordings for coaches who are unable to produce audio recordings. They will provide global feedback to the WHT coaches during supervision sessions. After WHT coaches demonstrate competency (as determined by the supervisors), fidelity will be monitored in 5% of randomly selected visits/quarter.

(d) Whole Health (WH) technology: Patients in both active intervention study arms (WHT and PC-GE) will receive an initial orientation about use of the web/mobile Whole Health Resource Directory (WHRD) website. The difference between arms is that WHT staff will actively check with patients during WHT clinical visits and coaching sessions to monitor participants' use of the

WHRD and troubleshoot any technical difficulties, so as to optimize use and benefit. Participants randomized to the PC-GE will be oriented on the WHRD and may ask the group facilitator or the study coordinator at their site for assistance. PCPs of participants in the Usual Primary Care arm will be introduced to and oriented on the WHRD and can use it to make referrals for their patients.

WHT approach to pain management: All clinical encounters in the WHT intervention will be guided by and captured in standardized templated notes, with some elements programmed using VA Clinical Reminder software. Therefore, any elements in the templated notes programmed as Clinical Reminders will be captured by the back-end VA Health Factors file which is obtainable by permission, like other VA administrative data files. This will allow the study team to retrieve data collected at the point-of-care (see below). Additionally, key elements of the WHT clinic notes will be programmed as Clinical Reminders (retrievable in CDW for subsequent audits and feedback) for fidelity monitoring purposes to ensure adherence to study protocol. After randomization, the study coordinator will send a copy of the **Personalized Health Inventory (PHI)** to the participant by mail or encrypted email. Then, Whole Health coach will call the participant to conduct the PHI (approximately 1 hour) prior to the first visit with the WHT. The clinical objective of the PHI is to increase self-awareness among study participants re: current vs. desired progress across 8 dimensions of health, e.g., physical health, spiritual health etc. (see Appendix 3A. PHI Note Template). The coach concludes the PHI by asking participants what they value most in life, what they want their health for, and their overall (functional) goals. This information is then communicated to the WHT both through the EMR and during the weekly team meeting. The first WHT initial visit with the entire team present will be a one-hour visit [in-person, by video telehealth, or telephone which will occur within 45 days of randomization. In the case that initial visit does not happen in the first 45 days, study coordinators will call monthly with 5 calls and 3 voicemails, up until the 6-month mark to try to schedule the initial visit. At this visit, the participant will meet with the WHT PCP, other CIH provider and/or MH provider that constitute the interprofessional WHT. The following core tasks will be completed (see Appendix 3B. Personalized Health Plan (PHP) Note and Appendix 3D. WHT Initial Visit – PCP Note).

(V) The WHT PCP will **Validate** the patient's pain by asking about pain and pain interference (using the PEG),[86] obtain a history of opioid and non-opioid pain medication and probe for non-pharmacological self-management techniques and response/adverse effects with each.

(E) The WHT will **Educate** patients on: (1) lack of evidence for superiority of opioids (vs. other non-opioid medication) for chronic pain weighed against potential harms and decreased quality of life with opioids[31] (if relevant), and the observation that all pain medications combined typically only alleviate about 30% of chronic pain, and benefit often wanes over time while many side effects do not; (2) the biopsychosocial model of chronic pain and the rationale for use of multi-modal treatment approaches, including specific non-pharmacological/CIH and self-management options (other than medications); and (3) reframing treatment goals from eliminating pain to improving functioning and quality of life.

(M) To **Motivate** patients to make changes in pain management, the WHT will review patients' core values and functional goals (obtained during the PHI). Then, patients and providers will

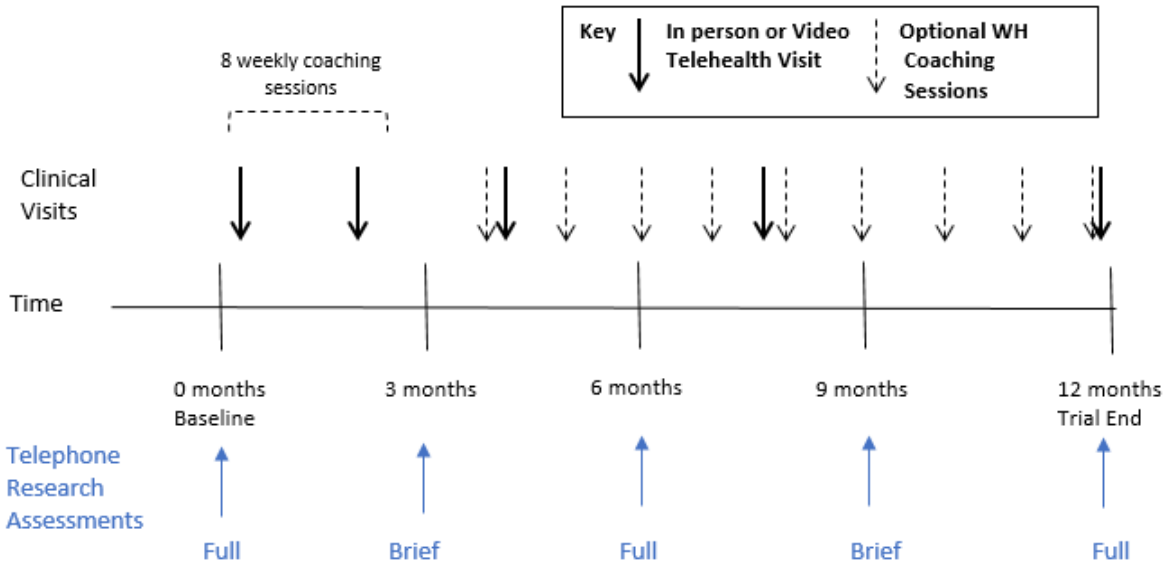
collaborate to develop a Personalized Health Plan aligned with these values and goals. Specifically, the Personalized Health Plan will include at least one new nonpharmacologic/CIH pain management approach articulated as a "SMART" (Specific, Measurable, Action-oriented, Realistic and Time-bound) Goal.[155,156] Personalized Health Plans will be documented in the templated EMR note.

(A) To **Activate** patients, the WHT will utilize communication techniques like Motivational Interviewing (including the Readiness Ruler and Decisional Balance exercise) to resolve ambivalence about carrying out the Personalized Health Plan.[58]

Following the initial baseline visit, subsequent face-to-face WHT visits will be scheduled with all or individual WHT clinicians, with at least 3 visits (in-person, through video telehealth, or telephone) visits in the subsequent 12-month period plus a final WHT visit. If follow-up visits are missed, the study coordinators will attempt to reschedule monthly with 5 calls and 3 voicemails. The PCP's presence will be required at each of these required follow-up visits because they are the prescriber and thus needed should the patient wish to make changes to their pain medications or add a supplement, e.g. fish oil etc., included in the VA formulary. Specifically, there will be at least two follow-up visits after the initial baseline visit within the first 6 months and at least one follow-up visit in the second six-month period with the final visit occurring around 12 months.

Within 24 hours of the WHT visit, the study coordinator will call the participant to collect PEG and PHQ-4 data and will email the WHT this information via encrypted email. The WHT PCP will enter this information into the standard clinic note template in the EMR as health factors retrievable in VA administrative databases. In keeping with our pragmatic trial design, participants will be able to attend WHT visits in- person, by video telehealth, or telephone. The mode of intervention delivery for each participant will be captured through the clinic note templates as health factors retrievable through VA administrative databases.

WHT motivational coaching protocol: WH coaches will aim to conduct eight WH coaching sessions (following the initial session to complete the PHI) roughly weekly for the first few months and then provide participants the option of additional 'booster' coaching sessions which will be offered monthly for the remainder of the 12 months. WH coaches will provide patients support in pursuing, refining and tracking SMART goals and using communication techniques like MI, and examine barriers and ambivalence where appropriate. Coaching sessions will be guided by a structured EMR template (see Appendix 3C. Whole Health Coaching Note), and will be conducted by telephone or video telehealth, and last approximately 20-30 minutes.



Primary Care Group Education (PC-GE) Arm

Rationale: We selected Primary Care Group Education (PC-GE) as the comparator arm, which is an abbreviated form of Cognitive Behavioral Therapy for Chronic Pain (CBT-CP) adapted for group use in primary care. This adapted form of CBT-CP represents best practice in how high-performing VA facilities are shifting away from an opioid-centric chronic pain treatment approach to a more behaviorally-based approach in keeping with the VA's Opioid Safety Initiative (OSI) (2014).[1]

As technology is increasingly leveraged to enhance patient care, in addition to primary care-based group education, we will provide the online/mobile WHRD focused on pain self-management innovations to patients in the PC-GE arm just as we will to patients in the WHT arm. Providing PC-GE participants equal access to the WHRD will facilitate equipoise, make the comparator condition more attractive, and will ensure a condition that meets the current standard of pain care.

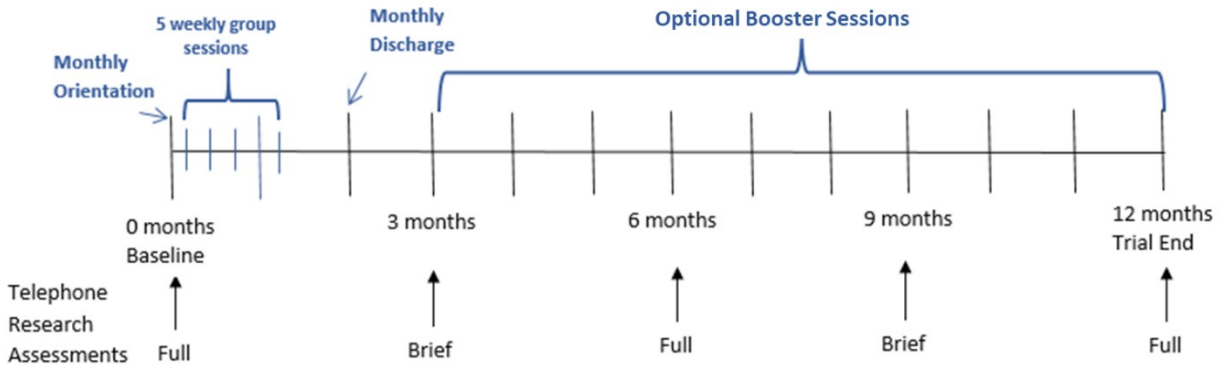
PC-GE intervention elements:

(a) PC-GE Group Sessions: In addition to continuing to receive usual primary care from their regular providers throughout the study, patients randomized to this arm will be asked to participate in an initial 90-minute PC-GE orientation session within 45 days of randomization. In the case that orientation does not happen in the first 45 days, study coordinators will call monthly with 5 calls and 3 voicemails, up until the 6-month mark to try to schedule the orientation. Orientation sessions will be offered at least once a month. This session will serve to orient new study participants to the PC-GE model. The psychologist or other mental health provider leading the group will also check in and ensure that all participants know how to access and use the online/mobile WHRD. There will be five 90-minute PC-GE MH provider-led weekly group sessions that participants will join following completion of the orientation session. The

topics of the 5 weekly modular sessions are: 1) Activation and Pacing, 2) Relaxation Training, 3) Pleasant Activities, 4) Reframing Thinking, and 5) Sleep. These group sessions will run weekly throughout the intervention period and because there will be rolling admission, (with participants joining the groups after they have completed orientation), there will be a mix of new and established participants. If scheduled group sessions are missed, the study coordinators will attempt to reschedule the session with the participant monthly, with 5 calls and 3 voicemails. The ideal size for groups will range from 4-10 veteran participants. However, in keeping with our pragmatic trial design, we will not cancel group sessions with fewer than 4 participants. Following completion of five different PC-GE modular sessions, participants will be required to attend a 90-minute discharge session held each month that will cover anticipated obstacles and weekly activities scheduling. Also available to participants for the reminder of the one-year enrollment period will be a 90-minute booster session, occurring several times throughout the year for all participants who have completed orientation, and at least four core sessions. Booster sessions will be offered approximately every month, depending on the number of participants available to meet group size constraints.

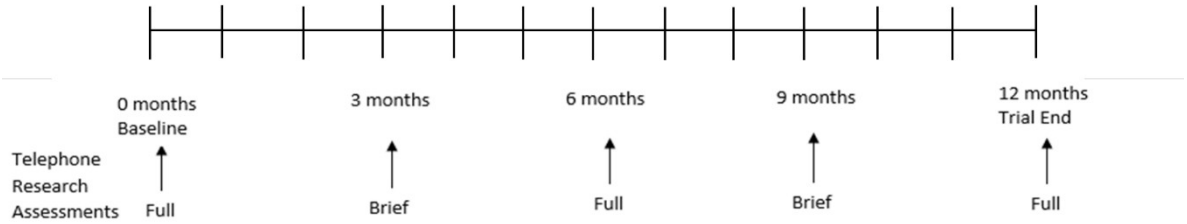
Within 24 hours of each PC-GE session, the study coordinator will call the participant to collect PEG and PHQ-4 data and will email the PC-GE provider this information via encrypted email. This data will then be entered by the MH provider in the clinic note template embedded in the VA EMR (see Appendix 4.0 PC-GE Clinic Note Templates). In keeping with our pragmatic trial design, participants will be able to attend group education sessions in-person, by video telehealth, or telephone, so groups may be mixed by intervention delivery mode. The mode of intervention delivery for each participant will be captured through the clinic note templates as health factors retrievable through VA administrative databases.

Psychologists or MH providers leading the group PC-GE sessions will be trained on the adapted protocol created for this treatment arm. The therapists will receive the VA's CBT-CP Therapist Manual (Murphy, Co-I) as a reference and additional resources to complement the adapted group therapy manual. As a part of training, clinician leads will also be provided with videos of patient-therapist vignettes demonstrating role-plays of common scenarios featuring a master trainer as the therapist and an actor as the patient). Dr. Jennifer Murphy will provide these trainings and will be available directly via email or telephone as needed for PC-GE consultation. Fidelity will be monitored by having all trained therapists document the intervention they deliver on a treatment fidelity checklist as a portion of the PC-GE group note template documentation. There will also be a monthly national case conference call where PC-GE providers will have a chance to review cases from the previous month.



Usual Primary Care

In VA, patient-aligned care teams (PACTs) or primary care is step 1 of VA's Stepped Care Model in the treatment of chronic pain. PCPs are expected to possess the requisite skill set for management of common chronic pain-causing conditions, which includes biopsychosocial assessment, multi-modal treatment, and coordination of specialty pain care after shared-decision making that incorporates patient preferences and values. Participants randomized to this arm will continue to have their PCP and PACT serve in this role. All participating PCPs/PACT members will have been oriented to the web-based/mobile WHRD and can use this to identify CIH pain-related resource at VA and in the community for their patients who are enrolled as study participants. Study visits will be captured through use of VA administrative data as each of the clinics will be mapped to clinic stop codes denoting the research study as well as the mode of care delivery (in-person, video telehealth, or telephone).



6.2 Handling of Study Interventions

The two active study interventions described above, the WHT and the PC-GE interventions, will be described in depth in a Manual of Interventions (MOI). Specifically, the content of the WHT in-person (or video) visits as well as Whole Health coaching sessions will be described in depth in the MOI. In addition, each of the PC-GE sessions in the PC-GE

intervention will be delineated in modular form. All clinician and patient forms and hand-outs used for each active intervention will be included in the Appendix of the study MOI. We will include telephone scripts for study coordinators and study staff conducting the study assessments to use before and after study procedures and assessment timepoints. We will also include study emails and flyers advertising the study for recruitment purposes as well as safety protocols around suicidality/disruptive behavior.

6.3 Concomitant Interventions

6.3.1 Allowed Interventions

Medications used to treat depression, PTSD or other anxiety disorders will be allowed. Also allowed are opioid and other non-opioid pain medications the patient is already on, or other medications used to treat other medical and physical problems in primary care patients (e.g., hypertension and diabetes).

6.3.2 Required Interventions

N/A

6.3.3 Prohibited Interventions

- Participation in another pain-related intervention study.

6.4 Adherence Assessment

Adherence will be used to define how engaged the veterans are in the intervention component of the study. This will be determined by the number of scheduled study visits (intervention sessions) that are completed by veterans in each arm. Adherence to the study intervention will be recorded in our study database by the study team after each study visit and by review of the EMR at the conclusion of the study. Recording adherence to study interventions in two locations will serve to validate the adherence assessment procedure. Separately, we will record adherence to the study assessments at the study timepoints of baseline, 3, 6, 9, and 12 months. Participants will be permitted to drop out of the intervention, if they so desire, but will be encouraged to continue to adhere to the study assessment schedule. Study staff will call participants 5 times and leave up to 3 discrete voicemails for each missed timepoint, and subjects will not be discontinued unless they actively withdraw.

Intervention Discontinuation

Criteria for discontinuing intervention are as follows:

- Participants will be discontinued for safety reasons if, during the study period, there is evidence that they develop prohibited criteria.
- Participant refuses to participate in the intervention and the study assessments. Note that participants may drop out of the study interventions but continue to participate in the research study assessments.

Possible Reasons for Discontinuation

- Self-withdrawal
- PI-initiated withdrawal (based on consultation with the clinical intervention team or other study staff)
- Endorses suicidal or homicidal ideation or becomes medically or psychiatrically unstable

We will notify PCPS of participants who discontinue the study intervention for any of the above reasons so that the PCP can resume care as they see fit.

7.0 Study Procedures

7.1 Schedule of Evaluations

Assessment	Telephone Eligibility Screening	Baseline (Day 0)	3-month Assessment	6-month assessment	9-month Assessment	12-month Assessment
Inclusion/Exclusion Criteria	X					
Informed Consent/ Randomization		X				
Demographics/Full Baseline Assessment N~50 Subset Natural Products Survey		X				
Full Masked Assessment				X		X
Brief Masked Assessment			X		X	
Adverse Events			X	X	X	X

7.2 Description of Evaluations

The telephone eligibility screen and baseline assessment will be administered by the local site study coordinator. The subsequent 3, 6, 9 and 12-month telephone assessments will be administered by a masked evaluator at one or more of the study sites.

7.2.1 Screening Evaluation

For recruitment, we are requesting a HIPAA waiver to access roughly 60,000 veteran records in the VA Corporate Data Warehouse (CDW). We will follow the recruitment procedures outlined in section 5.2 of this protocol. When telephone contact is made with potential subjects, we will introduce the study and conduct the initial telephone eligibility screen (see Appendix 1.0 Phone Eligibility Script/Screener). We will ask the minimum number of required screening questions to gauge potential interest and study eligibility. If the individual is interested in participating and study eligibility criteria are met, we will schedule a telephone appointment to review the IC, followed by administration of the baseline assessment. We will allow no more than 45 days from the date of the initial telephone eligibility screen to the first baseline assessment.

7.2.2 Enrollment, Baseline, and Randomization

On reaching the potential subject on the phone for the IC process and baseline assessment, study staff will send an email to the potential participant with the link to the IC form on VA-approved DocuSign. DocuSign will require two key digital signatures from the participant. This will allow the participant to then proceed to the IC form. In the case where a participant does not have an email address or access to email, the study coordinator will mail out the IC document prior to contacting the participant for their telephone baseline assessment. The study staff will read through the IC document describing the purpose of the study, the study procedures and the risks and benefits of participating. After each major section of the script, the interviewer will pause and ask whether the participant understood what was read and whether they have any questions. Study staff will use clear, declarative statements when answering these questions. At the conclusion of reviewing sections of the IC, study staff will ask the subject questions to see if they understood basic aspects of the trial as well as relevant human subjects issues. At the script's conclusion, if the individual is interested in participating, they will be asked to electronically sign the informed consent document or physically sign the copy that was mailed. Study staff will then be able to begin the baseline assessment over the phone immediately after obtaining for those using e-consent. For subjects without email/internet, the study staff will have the subject mail back their signed IC document. Once received, a telephone baseline assessment will be scheduled.

All study-related contact with potential subjects will be recorded in our SQL database. This includes their consent decision and, if they agree to participate, the date and version of the consent document. Prospective study participants will be given as much time as they need to consider study participation, limited only by the length of the study period; those wishing to consider study participation further will be invited to call study staff back if and when they are ready to participate. In these circumstances a later date will be scheduled for the baseline assessment.

After electronic signature of the IC has been verified or study staff receive a copy of the signed informed consent via mail, and after completion of the baseline assessment, participants who remain study-eligible will be officially enrolled and randomized to one of the three study arms. The study staff will then provide a comprehensive orientation to the study arm to which they were assigned either at the end of the baseline call or at another scheduled telephone appointment, depending on patient preference.

We will perform stratified random allocation with a blocked randomization scheme that includes varying block sizes of 24 and 48. We plan to stratify by site, gender and current opioid therapy, which will yield 24 strata (=6 sites x 2 genders x 2 levels of current opioid therapy). Randomization will be carried out within the strata, ensuring that the main covariates are balanced across treatments. The blocking technique helps ensure a constant ratio of treatment allocations maintained throughout the randomization period. To assist concealing the pattern of blocks, we will randomly order the blocks of different sizes. We will use a Stata Module called "RALLOC" (Ryan, 1997) to perform the random allocation. This program saves the allocation sequence into user-defined Stata files and helps ensure that a record is kept of the randomization protocol.[182]

Finally, the study staff will then provide a comprehensive orientation to the study arm the patient was assigned to either at the end of the baseline call or at another scheduled telephone appointment, depending on patient preference. Participants randomized to the WHT and PC-GE arms will also receive a patient binder (electronically through encrypted email or hard copy) containing intervention-related documents to help reinforce topics covered.

Audio Consent

Participants randomized to the WHT arm will have their Whole Health coaching sessions audio-recorded for fidelity purposes. The audio consent will be included in the informed consent document they will sign prior to enrollment. If participants choose not to be audio-recorded, they may still participate in the trial. The consent document will have a check box for "agree to be audio-recorded" or "do not agree to be audio-recorded."

7.2.3 Masking

Evaluators conducting the 3, 6, 9, and 12-month telephone assessments and the study statistician will be masked. The masking will be retained using a password-protected randomization list. The Study Coordinators and Data Manager will be the only study team members to have access to this password. Only the PIs are authorized to break the masking in the event that emergency care is necessary. The Study Coordinator will notify the PI if emergency unmasking is necessary.

7.2.4 Follow-Up Visits

Overall description of outcomes measures: Outcome measures are from the following sources/modalities: (1) point-of-care (POC) data collected as part of clinical encounters; (2) EMR/administrative data; and (3) patient-reported assessments collected outside clinical encounters by assessors masked to treatment assignment. The latter, despite being the least pragmatic, has been the gold standard for pain research to date. We will evaluate the reliability of pragmatic forms of data collection by comparing and contrasting results across modalities. For example, we will compare the PEG collected at the point of care with the same items contained within the Brief Pain Inventory (BPI) collected as part of our patient report instrument. In addition, we will compare the pain *intensity* rating contained in the PEG and BPI with the NRS pain score (contained in VA administrative data) collected in the course of usual VA care within

1 year of the PEG and BPI. We will also survey the clinicians in the WHT and PC-GE arms as part of our Process Evaluation as to their experiences conducting POC data collection.

1. Point-of-Care (POC) Measures: For this study, we will collect POC data using VA Clinical Reminder (CR) programming because this allows data entry at the point of care and back-end data capture through the VA Health Factors file, available for analysis. For this study, we propose to use the recently programmed VA "Pain Clinical Reminder" consisting of the validated 3-item PEG[86] as it is administered in routine clinical practice in VA. The Pain Clinical Reminder is required at least once a year, so we will compare the PEG done as part of the Pain Clinical Reminder at the point of care with the PEG that is administered by masked assessment closest in time as part of the study.

Given the strong relationship between mood and persistent pain, we will also measure anxiety and depression using the PHQ-4[125] which already exists as a VA Clinical Reminder. To be consistent across the two active arms, local study coordinators will call their site participants within 24 hours of scheduled WHT visits and PC-GE sessions to remind them of upcoming visits and collect PEG and PHQ-4 data over the phone. Local study coordinators will then send providers this information via encrypted email so that it can be recorded into templated notes in the VA EMR after the clinic visits/sessions. Because these are programmed as Clinical Reminders, these data (from the PEG and PHQ4) will be retrievable for analytic purposes through the VA "Health Factor" file. Finally, the WHT intervention also involves the use of templated notes adapted from the VA Office of Patient Centered Care. There are currently several templated notes that support the WHT intervention: (1) Personalized Health Inventory (PHI) template, (2) Personalized Health Plan (PHP) template, and (3) Personalized Health Coaching (PHC) template, as well as initial, follow-up, and final WHT visit note templates adapted from one of our ongoing clinical programs for pain (see Appendix 3.0 WHT Clinic Note Templates). Further, elements of the WHT clinical notes and the PC-GE templated notes will be programmed as health factors for fidelity monitoring to ensure that clinical teams in each arm at each of the study sites are adhering to the required elements of the protocol.

2. VA Administrative (EMR) Data: We will use the EMR not only for recruitment as described above, but also for select outcome measures for participants across both arms. The following data elements are available upon request (with IRB permission) through CDW or other national VA administrative databases: gender, date of birth, race/ethnicity, and dates veteran entered and left VA care (in some cases due to death). At most clinical encounters (both study visits and other non-study clinical visits), vital sign information is entered into the EMR including weight, height, BMI, blood pressure, pulse and a pain NRS score with these data retrievable through CDW (Vital Signs file). We will use these biomarkers if collected via clinical care in a window of 3 months before or three months after study assessment timepoints at baseline (time 0), 3, 6, 9 and 12 months. The following VA administrative data will also be used:

- ICD-9/ICD-10 diagnostic codes and laboratory values associated with stress, inflammation, and morbidity (e.g., Albumin, A1C, ALT, AST, creatinine, hemoglobin, platelets, white blood cell count, HCV status, COVID-19 status, lipid panel, blood glucose, ESR and C-Reactive Protein etc.) as associated with individual VA clinic/inpatient visits by date. As above, we will use these biomarkers if collected via

clinical care either 3 months before or 3 months after study assessment timepoints at baseline, 3, 6, 9 and 12 months.

- All VA health services utilization: outpatient (ambulatory and urgent care), inpatient care (including emergency services) and non-VA community care reimbursed by VA identified through primary and secondary stop codes. This will also include COVID-related health care utilization. Study visits will also be captured through use of VA administrative data as each of the clinics will be mapped to clinic stop codes denoting the research study. Receipt of pain-related services outside of intervention visits will be estimated by capturing primary care and non-VA care visits with pain-related ICD-CM codes as well as pain-related specialty visits. The use of clinic stop codes (e.g., 139 and 159 etc.) and CHAR4 codes for capture of VA CIH clinical and wellness services is expanding and will be captured as well. We will also search Current Procedural Terminology (CPT codes), Note Titles from the Text Integration Utility, and Health Factors to ensure we capture all CIH utilization. To maximize capture of VA CIH service delivery and ensure validity of these data across sites, study coordinators at each site will inventory local CIH offerings and clinical coding practices on an annual basis; these inventories will be reviewed by the SFVAHCS data core and the PMC Coordinating Center, harmonized, and considered in administrative data extraction and cleaning protocols. In addition, we will utilize the following VA administrative data/databases in our planned analyses:
  - Prescription medications, including generic name, dispensing information, dose, and instructions. Opioid daily dose will be calculated as the mean dose in morphine equivalents (MEs).[159]
  - VA Health Factors file
  - National Opioid Dashboard: Detailed information about opioid prescribing for chronic pain, opioid safety information, e.g.., urine drug tests, dispensing of naloxone kits, opioid informed consent, plus common adverse events associated with opioids—suicide, overdose, accidents and injuries.
  - Managerial Cost Accounting (MCA) (Decision Support System, DSS) National Data Extracts and the Health Economics Resource center (HERC) Average Cost Datasets (for the planned Budget Impact Analysis, see below).
  - COVID-19 Shared Data Resource.

Because some CIH care (e.g. acupuncture and chiropractic care) is by referral to community care providers through the Mission Act, we will also obtain the relevant VA administrative databases that capture care delivered by community providers (Purchased Care, Payment Integrity Tool (PIT) and the Fee Basis Claim System). Of note, because this is an evolving area for VHA, new databases are being added to capture care purchased in the community and we request permission to use these newer databases as they come online.

3. Description of Patient-Reported Measures: Patient-reported outcome measures will be collected at baseline, 3, 6, 9, and 12 months. All outcome assessments will be conducted as telephone interviews by research staff masked to treatment arm assignment. *Full-length* outcome assessments will be conducted at baseline, 6, and 12 months. *Abbreviated* assessments will be conducted at 3 and 9 months. Participant responses will be recorded by study staff entering responses directly into REDCap, data collection and management software

approved by VA. A participant stipend ($50 for each of the full-length assessments and $25 for the brief assessments) will be provided. We have used outcome assessment protocols of similar or greater duration in multiple trials involving patients with mental health conditions, pain and opioid use and have found them to be well-tolerated and associated with minimal missing data and attrition**.** If assessment burden becomes a problem at any point during the study, participants will be given the option of completing a minimum assessment composed of core outcome measures. We will use standard validated instruments to ascertain our primary and secondary outcomes.

If wHOPE study participants endorse using natural products during their baseline assessment, they will be asked to complete a more in-depth survey related to their use of natural products (target N~465). We will aim to invite a sample with sociodemographic representation of approximately 30% women, 30% non-white, and 30% under the age of 50. A subset of (n=20) natural product survey completers will be asked to participate in a 30-min telephone interview to better understand their experience using NPs. We will aim for a similar sociodemographic representation as in our sample for NP surveys.

a. Natural Products (NP) Survey Administration among veterans participating in the wHOPE study: For the first 50 surveys, the *w*HOPE study coordinator will mail out NP surveys to a minimum of 50 participants (but not more than 300 participants) who endorse NP use on the baseline assessment until adequate representation of typically under-represented sociodemographic subgroups (women, ethnic minorities, and younger veterans) is achieved. The coordinator will initially mail out surveys to up to 250 Veterans to allow for the possibility of a lower-than-expected response rate and the need to over-sample under-represented subgroups.

Participants will receive an NP survey, cover letter, and a brief feedback form evaluating their experience in completing the survey. This packet will be sent to participants via U.S. mail. Veterans will be instructed to gather their NPs prior to completing the survey. They will be given two weeks to complete the NP survey and feedback form, then return it via U.S. mail (using a pre-stamped, pre-addressed envelope).

For these initial 50 surveys, participants who require assistance completing the NP survey may contact the study coordinator, and the coordinator will record the type of assistance needed and the length of the call. If the NP survey is not returned within 2 weeks, the coordinator will call participants and remind them to complete it as well as offer assistance in doing so. Surveys and feedback forms that are coordinator-administered may be recorded in Redcap, and thus the paper copies would not need to be mailed back. Veterans will receive up to three reminder calls after which time the NP survey will be considered missing. Veterans, in the initial pilot group (n~50), who return the NP survey will be compensated $50.

Once the first 50 paper surveys have been received, with both follow-up semi-structured interviews (n=20), and double data entry completed; the coordinator will proceed to include the NP survey as part of the baseline and 6-month assessment for the remainder of the target sample (N~465) for any wHOPE participants that endorse natural products.

b. Follow-Up Semi-Structured Interview: A sub-sample of veterans (target N=20) who return the survey will be purposively selected and scheduled for a one-time 30-minute semi-

structured qualitative interview. Purposive selection will be guided by participant demographics in an effort to maximize diversity among those providing qualitative feedback; recruitment for the semi-structured interview will continue until thematic saturation is achieved. This interview will be audio-recorded with the participant's informed verbal consent. The NP study coordinator (or other study staff), trained in qualitative semi-structured interviewing, will start the 30-minute interview with brief open-ended questions about their experience in completing the NP survey using the "Think Aloud" approach. Next, the study coordinator will review participants' individual responses to the descriptive questions on the NP survey and feedback form and invite participants to elaborate on each of their responses using a variety of probes. The subset up to 20 veterans that participates in the brief follow-up semi-structured interview will be compensated $25.

c. Data Collection and Management: The first 50 quantitative NP surveys and feedback form data that has been completed by participants on a paper form and returned will require manual data entry into a study database. The study coordinator (masked to the participant's wHOPE study arm) will manually enter these data into a VA-approved REDCap database that is encrypted and behind the VA firewall. Each data field will be automated to flag outliers, redundancies, and missing data etc. For quality control, the first 20 paper surveys received back will undergo double-data entry by two separate staff members, compared, and discrepancies resolved based on the original paper survey. Because full sentences will be transcribed as well as the names and contents of various natural products, we will allow for some spelling and grammatical errors. Thus, for the purposes of this study, we will define an error as a discrepancy in the reporting of a quantitative item (e.g., one entry is "less than once per week" and the other is "every day"). If the error rate among the first 20 paper surveys is equal to or exceeds 1%, then the remainder of the returned paper surveys (n~50) will undergo double-data entry. When surveys are completed electronically, data will be automatically entered in REDCap and automatically checked for quality and transmitted to the study SQL database. The semi-structured interviews described above will be audio-recorded (with participant's informed verbal consent) and transcribed for analysis.

Patient-reported outcome assessment schedule

Measures	Baseline Full Assessment	Follow-up Full Assessment (6 months and 12 months)	Follow-up Brief Assessment (3 months and 9 months)
Demographics	X		
Brief Pain Inventory	X	X	X
THE VETERANS RAND 12-ITEM HEALTH SURVEY (VR-12)	X	X	X
Use of Nonpharmacological and Self-Care Approaches from PMC (NSCAP)	X	X	X
Pain Catastrophizing Scale (PCS: 4-item)	X	X	

Pain Self-Efficacy Questionnaire (PSEQ: 4-item)	X	X	
Patient Global Impression of Change Scale		X	X
Pain Medications Used (including non-VA, OTC medication, natural products)	X	X	X
Godin Leisure-Time Exercise Questionnaire	X	X	X
PROMIS - Sleep Disturbance	X	X	X
Perceived Stress Scale (PSS: 4-item)	X	X	
COVID-19 Impacts Questionnaire	X	X	X
Patient Health Questionnaire (for depression, PHQ-9)	X	X	X
Generalized Anxiety Disorder 7-item Scale (GAD-7)	X	X	X
Primary Care PTSD Screen (PC-PTSD-5)	X	X	
AUDIT-C (Brief Alcohol Screen)	X	X	X
The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool – Part 2 (TAPS-2)	X	X	
EPOCH - Pain Treatment Satisfaction	X	X	X
CDC High Impact Chronic Pain Measure	X	X	
Natural Products Use Survey	X		

Timing and Duration of Assessment Interviews

Full-length assessment interviews will be conducted at baseline, 6, and 12 months. The duration of assessment interviews will be approximately 60-75 minutes. Abbreviated assessment interviews addressing core outcome measures will be conducted at 3 and 9 months. The duration of these abbreviated interviews will be approximately 30-45 minutes. Timing of follow-up assessment interviews will be anchored to the date of randomization. Follow-up assessments may be completed up to 30 days early when extenuating circumstances (e.g., planned travel or move) suggest that data may be otherwise unable to be collected. 3- and 9-month assessments may be completed up to 45 days late. 6- and 12-month assessments may be completed up to 45 days late. Data from assessments completed outside of these time windows will not be included in primary analyses.

7.2.5 Completion/Final Evaluation

The final evaluation will be the 12-month full length assessment. This evaluation may be completed up to 45 days past the 12-month date. This will be conducted around the 12-month timepoint regardless of whether study-related visits have been completed.

8.0 Statistical Considerations

8.1 General Design Issues

We hypothesize that WHT will be superior to PC-GE and both will be superior to Usual Primary Care in improving pain interference (primary hypothesis), pain intensity, functioning and quality of life, decreasing use of high-risk pain medications, promoting engagement of non-pharmacological pain management activities, and improving mental health symptoms (secondary hypotheses).

Our trial design is individual randomization because the interventions are delivered at the individual level, although the PC-GE intervention is performed in a group format. Even in this group-format intervention, therapists may rotate over time, so there is no consistent cluster effect measured by the intra-class correlation coefficient. Furthermore, we are interested in outcomes measured at the patient-level rather than the aggregate group level.

Before randomizing individual patients into 3 arms, we will construct strata based on prognostic variables including site, sex, and opioid use. This stratified randomization approach helps ensure balance of the treatment groups with respect to the combinations of the prognostic variables. We will use permuted blocks of sizes 3, 6, or 9 within each stratum to achieve balance.

The total Brief Pain Inventory (BPI) interference sub-scale score is our primary outcome measure. The BPI interference subscale includes seven numeric ratings of pain interference with general activity, mood, walking, work, relations with other people, sleep, and enjoyment of life and is scored as the average of the individual item scores.[158,160] We will also report scores of the total BPI and BPI intensity. The BPI is a multidimensional measure that has been validated for use in numerous populations, including primary care patients with chronic pain,[85,158,160,161] and is responsive to change.[67,68]

Past-year use of complementary therapies and self-management practices will be measured using the Nonpharmacological and Self-Care Approaches from PMC (NSCAP)[185]. The inventory assesses use of several CIH modalities such as yoga, etc. We will also probe for other self-directed pain management activities.

Because mental health symptoms are important comorbidities in chronic pain and represent secondary outcomes in this study, we will include a battery of validated brief measures: The Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorders questionnaire (GAD-7) are widely-used screening measures for depression and anxiety, respectively.[167] The Primary Care PTSD screen assesses symptoms associated with past trauma.[168] To assess alcohol and substance use and smoking, we will use the Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool,[183] and the Brief Alcohol Screen (AUDIT-C),[184] both validated screening instruments to detect presence/absence and severity of

alcohol and illicit drug abuse and dependence, and smoking. We will assess sleep and fatigue symptoms as these are important to patients with chronic pain using the PROMIS – Sleep Disturbance.[166] We will be screening for suicidality using the PHQ-9.[167]

8.2 Sample Size and Randomization

Sample Size

The sample size calculation was based on the BPI interference sub-scale (primary outcome), which is calculated by summing 7 item scores and dividing by the number of items without missing values. Based on repeated-measures ANOVA, using the F test, we focused on 2 types of pair-wise comparisons:

1. Two active interventions compared with each other: WHT vs. PC-GE.
2. Two active interventions respectively compared with Usual Primary Care (UPC): WHT vs. UPC and PC-GE vs. UPC.

For the 1st pair-wise comparison, we used an alpha of 0.03 and effect size (between-group) of 0.15. For the 2nd pair-wise comparison, we used an alpha of 0.01 and effect size of 0.30. The final family-wise error rate is 0.05 (0.03+0.01+0.01). We assumed a power of 0.9 and two-repeated measures, and an equal allocation (ratio 1:1) for the first pair-wise comparison. Given the sample sizes for the 2 active arms calculated in the first step, we assumed an unequal allocation ratio when computing sample size for the UPC arm in the 2nd pair-wise comparison. We used our prior OPTI study data for this computation: the correlation between repeated measures is 0.66 and the variance is 5.90 (assuming stays constant over time). Using these prior data, we determined a sample size of 273 per arm for the 1st pair-wise comparison, and 50 for the UPC arm in the 2nd pair-wise comparison. Allowing for a 20% attrition rate, the final sample size is 765 (83 in the UPC arm, 341 in the PC-GE arm and 341 in the WH arm). Based on prior similar studies, we anticipate that at a minimum, 70% screened will be eligible to participate and of those eligible, roughly 20% will enroll. If we require approximately 765 patients to complete to test the primary study hypothesis, we would therefore need roughly 3,825 eligible patients, and would need to screen 5,464 patients.

Randomization

After obtaining written consent and completing the baseline interview, the local site coordinator will initiate randomization using the study application randomization form. For those who sign the IC document and mail back the forms, the study coordinator will wait until the written consent form is received before randomizing the patient to a study arms. The randomization code will not be visible to personnel conducting randomization and can be completed only once per study ID, preventing study personnel from influencing treatment allocation. This process will simultaneously inform the coordinator and participant of the primary study arm assignment.

- The unit of randomization is the patient. After eligible and interested patients complete a written informed consent, each site will randomize enrolled patients to WHT, PC-GE, or

Usual Primary Care in permuted blocks of 24 and 48, stratified by site, prescription opioid use (yes/no) and sex. We will oversample women veterans, aiming for roughly 20% at each site. Because the sample size computation was based on 2 types of pair-wise comparisons with different pre-specified effect sizes and alpha levels, the numbers of patients are different across intervention arms. The enrollment period is approximately 24-30 months: The target enrollment for each site is 17 patients in the UPC arm, 69 in the WHT arm and 69 in the PC-GE arm over the duration of the enrollment period.

8.3 Definition of Populations

The intention-to-treat (ITT) population includes all randomized subjects regardless of their noncompliance, protocol deviations, withdrawal, or anything after randomization. The per protocol population is a subset of randomized subjects who completed the study without major protocol violations. In the per protocol analyses, we will include any subject who completely complied with treatment assignment indicated by the protocol, but will exclude the protocol violators who did not meet the following threshold criteria:

- WHT arm participants: attended at least 6 coaching sessions, the WHT initial visit, and at least 2 follow-up WHT visits;
- PC-GE arm participants: attended the orientation and at least 4 core modules.

In addition, participants will be excluded from the per-protocol analysis if they received prohibited concomitant interventions or if they missed all outcome measurements. Since we plan to collect time-dependent data (especially those on COVID-19), we will utilize these data to account for incomplete adherence and post-randomization confounding.

8.4 Interim Analyses and Stopping Rules

Subjects in the UH3 Phase will be withdrawn if it is determined that they are actively suicidal or otherwise seriously unstable medically or psychiatrically (requiring hospitalization). In this case, withdrawal may occur without their consent. We will follow the procedure outlined in the “Reporting” section of this protocol and appropriate mental health referrals will be made. Also, if at any time during the study the subject wishes to withdraw, they may do so via phone call or written correspondence to a study staff member. They will have contact information with staff phone numbers and mailing addresses to reference in case they need to contact the team. We use our SQL database to track subjects and can record if a subject withdraws, so that no future contact will be made. Subjects will be made aware that there will be no negative consequences should they elect to withdraw. In particular, they will be advised that they can continue to receive all VA health care benefits and services. The Data and Safety Monitoring Board (DSMB) will review aggregate and individual participant data related to safety, data integrity, and overall conduct of the trial and will provide recommendations to continue, modify, or terminate the trial. Termination or modification may be recommended on the basis of serious safety concerns, non-compliance with human safety regulations, or serious protocol violations. The DSMB will not review interim analyses of effectiveness. This study has no pre-specified endpoints that would trigger immediate suspension of research. If termination or suspension is

triggered by unexpected events (e.g., SAE, serious noncompliance, major information security violations, loss of funding), the PIs will email notification to local site facility directors and to local site approving bodies (including local site IRB and R&D committees), along with Central IRB and PCORI, within 5 business days. Additionally, the PIs will provide local sites with detailed information about procedures to ensure continuation of appropriate clinical care for research participants.

8.5 Outcomes

8.5.1 Primary Outcome

The primary outcome is change in pain interference score of the BPI from baseline to the final study outcome assessment at 12 months. We selected this outcome based on its fundamental importance to patients with chronic pain as well as clinical relevance. The BPI will be administered at baseline, 3, 6, 9 and 12-month assessments.

8.5.2 Secondary Outcomes

Our secondary outcomes are:

- Pain intensity
- Functioning and quality of life (VR-12)
- Decreased use of higher-risk pain medications, including opioids or high-risk combinations of pain medications (i.e., co-prescription of opioids and benzodiazepines)
- Engagement in a greater number of non-pharmacological pain management activities
- Improvement in mental health-related symptoms, including sleep problems and suicidality

8.6 Data Analyses

For the primary analysis, we aim to follow the intention-to-treat (ITT) principle. We will conduct two types of pair-wise comparisons with different alpha levels:

- Two active interventions respectively compared with Usual Primary Care: WHT vs. UPC (alpha=0.01) and PC-GE vs. UPC (alpha=0.01);
- Two active interventions compared with each other: WHT vs. PC-GE (alpha=0.03).

We will use a mixed-effects linear regression using BPI interference score (averaged by the number of items with non-missing values provided that at least 4 of the 7 items were answered, per guidelines) as the outcome for each of the three pair-wise comparisons. We will include intervention, time (6 months and 12 months) and their interaction term, and will report the treatment effect at 12 months. In terms of covariance structure for repeated measures, we mainly consider the unstructured and compound symmetry (or exchangeable), given that we have a relatively large sample size and equally spaced repeated measures. In practice, we will use the Akaike Information Criterion (AIC) to assess model fit and determine the best

covariance structure for the repeated measures. We will adjust for baseline BPI interference score, stratification variables including site, gender and prescription opioid use. We will relegate *post hoc* identified covariates that are imbalanced between groups for sensitivity analysis. For the first type of pairwise comparison (WHT vs. UPC and PC-GE vs. UPC), we will consider tests with $p<0.01$ to be significant. For the second type of pairwise comparison (WHT vs. PC-GE), we will consider tests with $p<0.03$ to be significant.

With the COVID-19 pandemic, treatment implementation may vary during the study period, and there may be incomplete adherence to the interventions and outcome assessments. We will collect additional time-dependent data to attempt to capture these fluctuations. The following is a list of variables we aim to collect:
System-level variables: sites' degree of openness (fully closed/partially open/fully open (categorical), mode of treatment delivery (in-person, tele-health, phone, categorical), availability of non-pharmacologic pain management services (Yes/Partially yes/No, categorical);
Individual-level variables: COVID infection status (categorical: yes, no, unknown), self-reported socio-economic outcomes such as lack of access to transportation, food, prescription refills, and community resources (categorical), health outcomes such as mental health and pain (categorical), number of missed intervention sessions. (numerical).

For the issues of fluctuations in mode of treatment delivery and temporal variations, our strategies are to: (1) adjust for time-dependent variables that reflect changes in the implementation of treatments, and (2) perform an exploratory analysis stratified by time periods sites, and site characteristics such as degree of openness. The exploratory analysis has an inherent limitation of inadequate power, because the analytical sample will be partitioned by time periods and sites.

We will also consider a per-protocol analysis to supplement the ITT analysis. This analysis includes only patients who minimally or completely adhered to treatment assignment indicated by the protocol, but will exclude the protocol violators who did not meet the following minimal threshold criteria: if randomized to the WHT arm, participants attended at least 6/8 coaching sessions, the WHT initial visit, and at least 2 of 3 follow-up WHT visits; if randomized to the PC-GE arm, participants attended the orientation and at least 4 of 5 core modules. In addition, participants will be excluded from the per-protocol analysis if they received prohibited concomitant interventions or if they missed all outcome measurements. We will follow recommendations by Hernan and Robins[188] and adjust for both pre-randomization (baseline) and post-randomization prognostic factors. We will examine if the post-randomization prognostic factors are affected by prior treatment. If so, we will use the inverse-probability weighting method. This entails estimating a sequential propensity score based on post-randomization time-dependent factors and reweighting subjects using the propensity score estimated earlier. This method helps us minimize post-randomization confounding and selection bias.

In summary, while adhering to our pre-specified ITT analysis plan, we will perform real-time, ongoing monitoring of the impact of COVID-19 on intervention delivery and availability of pain resources and collect relevant time-dependent data. This will enable us to conduct a per-protocol analysis if necessary, in addition to an ITT analysis.

All analyses will be done by the study's biostatistical team. We will be using R (R Foundation for Statistical Computing, Vienna, Austria), SAS (from SAS Institute, Cary, N.C.) and SQL Service Management Server (SSMS)provided by VA for data analysis.

Missing Data

First, we will assess the amount of missing data and its impact on the statistical power. Second, we will examine the patterns of missing data and specify plans for various sensitivity analyses based on different assumptions of the missing data mechanisms.

Our sample size, 765, was computed based on an assumption of 20% loss-to-follow-up. This means that if we have 612 subjects with outcomes data, we will have sufficient power (90%) to detect pre-specified effect sizes (which vary by different pair-wise comparisons). We place emphasis on preventing and minimizing missing data in study design and execution. One of the strategies is to continue collecting outcomes data even if a participant withdraws or deviates from the assigned treatment. As long as the patient has not withdrawn consent, we will continue to collect outcomes data from surveys and VA administrative data sources (which supplement data other than the primary outcome). We anticipate that this strategy will help minimize missing outcomes data and preserve statistical power.

Before conducting the analyses, we will examine the patterns of missing data with a focus on intervention arms, enrollment sites, time periods, and potential prognostic factors such as severity of comorbidities and post-randomization time-dependent variables. This examination will help us make assumptions about missing data mechanisms.

In the main analysis, we consider it plausible to hold the “missing at random” (MAR) assumption. With this assumption, there is no systematic difference between subjects who are and are not lost to follow-up, and the probability of missingness only depends on observed data[189]. This is supported by our effort to collect a range of information that could explain the missingness. Under this assumption, our planned analytical strategies are unbiased. These will include a mixed-effects linear regression, inverse probability weighting and multiple imputation (MI).

In sensitivity analyses, we will test if results from the main analysis are robust with a departure from the MAR assumption. We assume a “missing not at random” (MNAR) mechanism, in which the probability of missingness depends on unobserved data[189], and there are systematically worse outcomes in those who are lost to follow-up than those who adhere to assigned treatment. With the multiple imputation (MI) procedure (“PROC MI” with “MNAR” statement using SAS), we can build a model by adding a clinically plausible amount to the imputed data (either in units of points or percentages), because a higher pain interference score indicates a worse outcome. By trying various imputation models, we can test how large an amount should be added to the imputed data without changing the clinical interpretation of the trial. This method applies to missing data of other continuous variables as well.

In summary, our strategies to minimize missing data will help maintain the statistical power. We will conduct a main analysis based on the MAR assumption. We will also consider a MNAR assumption and use a sensitivity analysis to test the robustness of the main analysis.

Note: See Data Analysis Plan for full statistical analysis protocol.

9.0 Safety Assessments

9.1 Specification of Safety Parameters

- Endorsement of mental health-related issues (e.g., suicidal ideation) during telephone assessments, visits with PCP, or intervention related visits
- Regular assessment of pain and functioning during the telephone sessions

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

The proposed study confers a **minimal** level of risk, posing no more risk than expected in daily life for patients who are undergoing treatment for chronic pain. Safety will be assessed at various times throughout the study.

Changes in pain management regimens and any resulting symptoms will be monitored closely by the study team. Patients will be closely monitored and will be referred for mental health or substance use disorder treatment, if appropriate. Participants in active interventions will remain in their usual primary care, mental health and specialty care clinical treatment relationships throughout their participation in the study. If study clinicians identify a concerning clinical finding, they will communicate with the participant's other treating clinicians, as is the standard in VHA care. Based on this level of risk, the PIs will monitor and record the safety issues in accordance with IRB guidelines.

9.3 Adverse Events and Serious Adverse Events

Adverse Events. An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease that either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention. AEs that do not meet criteria for reporting within five days in accordance with VHA Handbook 1058.01 will be reported to the IRB of Record at Continuing Review.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

9.4 Reporting Procedures

Site PIs will be notified by the site project coordinator(s) immediately of any possible event that poses a risk to a subject. In addition, at least one of the PIs (Seal or Becker) or both will also be notified. The PI(s) will promptly respond to the problem and mitigate any negative consequences for the participant(s) involved. The PI and/or study coordinator will report the event to the IRB of Record within the timeline as follows:

a. **Unanticipated Problems Involving Risks to Subjects or Others.** Members of the VA research community are required to ensure that unanticipated problems involving risks to subjects or others in research are reported promptly to the IRB within five business days.

b. **Serious Unanticipated Problems Involving Risks to Subjects or Others.** Within five business days of becoming aware of any serious unanticipated problem involving risks to subjects or others in VA research, members of the VA research community are required to ensure that the problem has been reported in writing to the IRB.

c. **Local Unanticipated SAEs**. Within five business days of becoming aware of any local (i.e., occurring in the reporting individual's own facility) unanticipated SAE in VA research, members of the VA research community are required to ensure that the SAE has been reported in writing to the IRB.

If an AE/SAE is reported by a veteran directly to the local study coordinator at their participating site, the local study coordinator will complete an AE form on the study database within 24 hours of notification. If this event also meets the criteria for an SAE, the local study coordinator will indicate this on the AE form in the study database within 24 hours. For SAEs, the local study coordinator will download a pdf of the completed SAE form and send this as an attachment via encrypted email (see draft email A below) to the Project Manager, LSI, and Co-Principal Investigators Drs. Seal and Becker. The LSI and PIs will confer via email to determine the severity and relatedness of the event to the study intervention within 48 hours of notification. The Coordinating Center will follow VA Central IRB reporting guidelines as appropriate.

If an AE/SAE is reported by a veteran during a telephone research assessment to a masked coordinator located at another site, the masked coordinator will immediately send an encrypted email (see draft email B below) to the local study coordinator to notify them of the event. The local study coordinator at the veteran's participating site will call the veteran participant to learn details of the event and complete the AE form on the study database, within 24-48 hours of event notification. If this event also meets the criteria for an SAE, regardless of whether related to the study or not, the local study coordinator will indicate this on the AE form in the study database within 24 hours. For SAEs, the local study coordinator will download a pdf of the completed SAE form and send this as an attachment via encrypted email (see draft email A below) to the Project Manager, LSI, and Principal Investigators Drs. Seal and Becker. The LSI and Co-PIs will confer via email to determine the severity and relatedness of the event to the study intervention within 48 hours of notification. The Coordinating Center will follow VA Central IRB reporting guidelines as appropriate.

The PIs have developed a suicide and homicide ideation safety protocol for other studies with Veterans that will also be used for this study in the event of active suicidal or homicidal ideation.

If we are unsure whether a document requires submission or reporting, we will contact the VA Central IRB @ the toll-free number 877-254-3130 or va.central.irb@va.gov.

9.5 Follow-up for Adverse Events

If a patient is deemed passively suicidal during the course of the study, appropriate referrals to mental health services will be made. If a patient becomes actively suicidal after enrollment in the study, the study team will activate the study's suicide protocol (see Appendix 5.0. Suicide Protocol), which includes notifying the site PI or designated study clinician of the situation so that they can assess the patient and obtain the proper assistance, if needed. Thus, if the site PI or designated clinician is sick or on vacation, they will need to designate a covering clinician to handle such emergencies. Once the urgent situation is addressed, the site PI or other member of the study team will notify the participant's PCP either over the phone, encrypted email or through a CPRS clinic note.

9.6 Data and Safety Monitoring Board (DSMB)

The DSMB will act in an advisory capacity to NCCIH to monitor patient safety for wHOPE. Dr. Janna Friedly of the University of Washington has been selected by the NCCIH to serve as the DSMB Chair. Dr. Catherine M. Meyers will serve as the NCCIH DSMB Executive Secretary (ES). The DSMB will meet annually at the call of the Chair, with advance approval of the DSMB ES. On a scheduled basis (as agreed upon by the DSMB), an Interim Study Report will be developed by the Data Coordinating Center; and will be developed every 4 months following a scheduled DSMB meeting, or at another time as required by the DSMB. The DSMB Roster for wHOPE is as follows:

wHOPE DSMB ROSTER

Chair:
Janna Friedly, MD
Medical Director, Amputation Service
University of Washington

Trials of Mind/Body Interventions
Julie Wetherell, PhD
Professor, Psychiatry
University of California, San Diego

Trials of Manual Therapy
Paul Dougherty, DC, PhD
Canandaigua VA Medical Center

Linda Resnik, PT, PhD, FAPTA
Professor, Department of Health Services, Policy and Practice
Director, Center on Health Services Training and Research
Brown University

Health Systems Data & Analytics
Andrea J. Cook, PhD
Senior Investigator,
Kaiser Permanente Washington Health Research Institute

Ryan E. Ferguson, ScD, MPH
Director, Cooperative Studies Program Coordinating Center
US Department of Veterans Affairs

10.0 Data Collection and Quality Assurance

10.1 Data Collection

Data collected from the baseline and follow-up assessments will be entered electronically into REDCap, a secure SFVAMC approved web-based tool for building surveys. Additionally, AEs/SAEs will be collected through REDCap. A secure SQL database will also be used to track recruitment and enrollment. The SQL database will also be used to store VA administrative data for study outcomes. This will also include any data collected at the Point of Care as health factors.

10.2 Data Management

The following software will be used:

In addition to the Microsoft Suite (Microsoft Word and Microsoft Excel), the project will use SAS (from SAS Institute, Cary, N.C.), Stata (StataCorp LC, College Station, TX), R (https://Cran.R-Project.org), SQL Server Management Studio (SSMS), Visual Studio, and other applications for data management and analysis.

The following web application will be used:

VA REDCap will be used for completing questionnaires. VA REDCap is a VA Intranet Web application that is only accessible within the VA intranet to authorized users. Security features include data redundancies, intrusion detection, access control, application software, testing environment, authorizations, demographics/server load, load/stress/penetration testing, and anti-malware. It supports compliance with 21 CFR Part 11, Federal Information Management Security Act (FISMA), and HIPAA.

The Whole Health Resource Directory, which contains location-specific information on CIH resources, will be hosted by InMotion Hosting, an independent web hosting service, and housed on shared Linux-based servers located in Los Angeles, CA and Ashburn, VA. This directory is a responsive website (accessible on computer or mobile device) and does not require installation. The directory content is displayed based on the VA site location embedded in the URL link. User actions are performed exclusively on the client's browser/mobile phone and this information will not be posted back to the server in any way or form.

Data will be stored as follows:

Data will be stored on a VA-approved server or locked file cabinet. Survey data collected via REDCap survey are transmitted from behind the VA firewall (on the VA intranet) to our SQL database. REDCap servers are housed at the VA Informatics and Computing Infrastructure

(VINCI). VINCI servers are physically located at the VA Austin Information Technology Center, located in Austin, Texas.

A limited dataset copy will be housed on the Yale University server so that our biostatisticians can easily access and analyze the data.

Data will be transmitted and/or shipped as follows:

Data will be transmitted via encrypted email, password-protected documents, or by granting access to the study servers for our enrolling sites. Study sites will login to the VA server using VA-approved protocols.

For data analysis purposes, our biostatisticians will grant our study team access to a folder housed on the Yale University server (through Microsoft OneDrive), and a limited dataset copy will be saved there.

Data will be shared as follows:

A function of the Pain Management Collaboratory (PMC) is to support analyses of data pooled from the different participating pragmatic trials. One of the PMC research teams (Dr. Sellinger) will obtain de-identified demographic and clinical data from other PMC research studies for analyses. Data will be transferred to the PMC electronically using email and PKI encryption. The data obtained will only be identified by a unique identifier that each research study maintains securely but does not share with the PMC or Dr. Sellinger's group. Dr. Sellinger's team will then combine data from the participating PMC studies to create a combined dataset for analysis. Data will be stored, managed, and analyzed in the VA environment (investigator folder and VINCI environment). The data sharing agreement will specify that: (1) the data/information will only be used for research purposes and not to identify any individual participant; (2) the information will be secured using appropriate computer technology; and (3) the data will be destroyed or returned after analyses are completed.

Specifically, under this data sharing agreement, wHOPE study investigators will collaborate with Dr. Sellinger's team and other participating PMC investigators to identify clinical and demographic variables associated with COVID-19-related impacts among PMC pragmatic trial participants. Specifically, the pooled de-identified dataset (all 18 HIPAA identifiers removed) will include clinical variables (e.g., pain scores, depression scores, suicidal ideation), demographic variables (e.g., age, military branch, race, ethnicity, sex), and the COVID-19 impact variables from several PMC pragmatic trials. Pooled data will be analyzed, and the aggregate de-identified results will used to prepare a manuscript and/or report.

In addition, a Data Use Agreement (DUA) for LDS with Non-Federal Entities will be completed to gain permission to save a copy of our limited dataset in a folder on the Yale University server. This will allow our biostatisticians (Dr. Denise Esserman, Dr. Eugenia Buta, and their associates) to easily access and analyze our study data.

Participant and research data will be stored as follows:

Data will be stored on encrypted VA servers. Servers at the SFVAMC, Bldg. 207, server room: R01SFCHSM02, VHASFCTMSSEAL, VHASFCWEBHOPE and the VASQL Server: OITSFCSQL001.r01.med.va.gov. No data will be transferred outside of the VA environment until a DUA/DTA is set up and approved by the IRB.

During the data analysis phase, a DUA (for LDS with Non-Federal Entities) will be completed to request permission to save a limited dataset copy in a Microsoft OneDrive folder on the Yale University server. This will allow our biostatisticians (Dr. Denise Esserman, Dr. Eugenia Buta, and their associates) to easily access and analyze our study data.

With the exception of the limited dataset saved on the Yale University server (following DUA and IRB approval), all study-related data is either stored in a locked filing cabinet in a locked office or on a VA secure server. Once a team member resigns, they no longer have access to the server and are required to turn in their keys to the building and office suit, including all filing cabinets, along with their VA Personal Identity Verification (PIV) ID badge, which ends their VA computer access.

10.3 Quality Assurance

10.3.1 Training

All study staff will be trained in the importance of maintaining confidentiality and privacy and will undergo mandatory NIH and VA education and training in research methods and data protection procedures. The PIs will also train project staff on the latest governmental requirements on the protection of participant confidentiality and privacy.

In addition to the clinical interventionist training, we will hire and train research study staff at all of the enrolling sites on all study procedures. Dr. Seal's research team, as well as teams at the enrolling sites, already have experience with many of these procedures, including fidelity monitoring.

10.3.2 Quality Control Committee

N/A

10.3.3 Metrics

Quality control metrics for outcome measures:

- Monitoring to ensure compliance with regulatory requirements
- Number of complaints (i.e., investigator, participants)
- Quality and completeness of IRB communications
- Feedback from NCCIH, the Pain Management Collaboratory and other study investigators
- Interval data analysis (if needed) to monitor progress, explain unusual observations, justify or explain outliers, gather additional data to resolve problem areas in data collection.
- Supervision meetings with Whole Health coaches and mental health providers

delivering PC-GE to monitor fidelity.

- Programming of core elements of active intervention note templates as health factors for fidelity monitoring tracking.
- REDCap has quality control processes in place to ensure data validity and integrity

10.3.4 Protocol Deviations

Members of the VA research community are required to ensure that unanticipated problems involving risks to subjects or others in research are reported promptly, in writing, to the VA CIRB within five business days. Protocol deviations will be reported to the PIs and study coordinator. Deviations will be documented in an IRB modification form and submitted to the VA CIRB for review.

10.3.5 Monitoring

This study is subject to be audited by the Central Office of Research Oversight and each study site is subject to regular monitoring by their local Research and Development Office. The DSMB will also monitor subject safety.

11.0 Participants Rights and Confidentiality

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the VA Central IRB and local VA Research & Development Committees responsible for oversight of the study.

11.2 Study Discontinuation

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

11.3 Participant Confidentiality

At the conclusion of the study, we will maintain all research data, including subject identifiers and the key linking the unique study identification code to subjects' personal information, in accordance with the VA Records Control Schedule 10-1. Prior to data transfer to Yale, study participants will be assigned a new arbitrary Data Link ID to connect their data with the information while further protecting participant anonymity. Therein, the destruction policy is 6 years after the cutoff (i.e., the end of the fiscal year after completion of the research project). The Information Security Officer will be contacted for guidance/assistance with best practices in destroying the data once the maximum retention period is reached.

There are some risks to participating in this study. First, for veterans, some of the questions asked (such as questions about mental health symptoms, including drug use) concern sensitive issues and possibly illegal activities. Similarly, some of the questions asked of

veterans may evoke memories of combat experiences. Being asked some of these questions may make participants feel uncomfortable; however, the questions asked do not fall outside what would normally be asked during a clinical mental health appointment. While the researchers will keep information as confidential as possible, complete confidentiality cannot be guaranteed.

Research data will be identified using study ID numbers only and will be kept separate from personally identifying information. Participants' personally identifying information, such as names, addresses, and phone numbers used to contact study participants will be secured on an approved VA server behind the VA firewall. This is accessed through use of a two-factor authentication system consisting of federally issued Personal Identity Verification (PIV) cards and PIN codes. Data will be reported only in aggregate form in any reports or publications; no names of study participants will be used in any reports or publications resulting from this study. NIH-funded projects are automatically issued a Certificate of Confidentiality. This certificate will provide additional protection for research participants. The Certificate of Confidentiality will allow Dr. Seal and Dr. Becker and the research team to refuse to release identifying information about participants in any civil, criminal, administrative, legislative or other proceeding at the Federal, State or local level. A Certificate of Confidentiality does not prevent researchers from disclosing information about participants that involves child abuse, elder abuse, and participants' intent to harm themselves or others. If a member of the research staff learns that a participant intends to harm him/herself or others, study staff will be obligated to report this information to the authorities and activate the study's safety protocols. Potential participants will be apprised of this possibility during the informed consent procedure.

The SFVAHCS data core will be responsible for maintaining the privacy and confidentiality of a linking list that associates unique study ID numbers to the identities of the participants. These will be maintained by the overall SFVAHCS-based Study Coordinator on an approved SFVAHCS server behind the VA firewall that is accessed through use of a password-protected computer terminal in a locked room. Access to the linking list will be limited to the Coordinator and Data Manager affiliated with the SFVAHCS data core and shared with Site Coordinators at the enrollment sites as needed for the enrollment and retention of study participants at their sites. Site Coordinators will, in turn, maintain the same levels of privacy and confidentiality through use of secure password-protected computers behind the VA firewall. PHI will be obtained from existing sources, such as medical records, clinical databases, or research records. We will use national and regional databases, such as CDW and VISTA to identify potential participants. Medical Records and Clinical databases are maintained by SFVAHCS.

12.0 Communication Plan

Participating sites will communicate to the overall study PIs (Dr. Seal and Dr. Becker) and project manager via encrypted email, Skype for business, or through a secure VA project SharePoint site.

The SFVAHCS coordinating center will maintain files of all IRB documentation for all 6 study sites, including consent forms, HIPAA forms and supporting documents. The research staff at SFVAHCS will have a minimum of bi-weekly telephone check-ins with other sites. At these meetings, the following will be addressed:

- Ensuring all required local site approvals are obtained.

- Keeping all engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization
- Informing each site of any Serious Adverse Events, Unanticipated Problems, or interim results that may impact conduct of the study.
- Ensuring the study is conducted according to the IRB-approved protocol.
- Notifying local facility investigators when the study reaches the point that it no longer requires engagement of the local facility.

All points above are considered time sensitive and will be communicated among study staff at the sites immediately. All sensitive materials will be shared among study staff at all sites via our VA server or using a VA-approved SharePoint site. Other study-related issues will also be addressed at the bi-weekly meetings (recruitment, challenges, issues and needed any changes) with the Coordinating Center and PIs to discuss and troubleshoot concerns. The PIs and co-investigators will also have quarterly telephone check-ins to discuss the progress/challenges of the study.

13.0 Committees

As part of the NCCIH Pain Management Collaboratory, this study is participating in the following committees:

PMC – Steering Committee
PMC – Implementation Science Workgroup

PMC – Stakeholder Engagement Workgroup
PMC – Electronic Health Record Workgroup
PMC – Biostatistics and Study Design Workgroup
PMC – Data Sharing Workgroup
PMC – Phenotypes and Outcomes Workgroup
PMC – Ethics and Regulatory Workgroup

14.0 Publication of Research Findings

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor.

At the conclusion of analysis, our research team will also disseminate results of the study to collaborators and veteran participants. Veterans will be mailed results in the form of a report, infographic, info sheet, or similar. Participants may reach out to research staff to request copies of future publications.

15.0 Aim 3

Background/Rationale/Study Aim: During the wHOPE trial, which has coincided with the COVID-19 pandemic, we have been enrolling and randomizing patients with chronic pain to one of three pain management approaches. Each of the three approaches- the Whole Health Team, Primary Care Group Education, and VA Usual Care, is intended to improve pain interference and secondarily, decrease reliance on pain medications, especially opioids, while encouraging greater use of Whole Health/complementary and integrative health (CIH) approaches. Veteran participants for the wHOPE trial are recruited from a geographically diverse set of five VA primary care clinics from across the country and include an over-representation of veterans from ethnic minority groups and women. We also facilitate rural veterans' participation in the trial as the study interventions are virtual. The differential impact of the pandemic on these subgroups' use of Whole Health and CIH pain services across VHA is an important contextual issue that will impact our trial findings and remains unknown. To better understand how equity and social determinants may impact our trial findings, we propose to add the following third specific aim to the trial:

Aim 3: In a national cohort of veterans derived from the VA electronic health record (EHR), investigate the impact of the COVID-19 pandemic on veterans' utilization of Whole Health and CIH services for chronic pain management.

- *H3.a. Racial/ethnic minority veterans' utilization of non-drug pain management services may be differentially negatively impacted by the pandemic compared to White veterans.*
- *H3.b. Women veterans' utilization of non-drug pain management services may be differentially negatively impacted by the COVID pandemic compared to male veterans.*
- *H3.c. Rural veterans' veterans' utilization of non-drug pain management services may be differentially negatively impacted by the COVID pandemic compared to urban-dwelling veterans.*

Methods: We will create a national retrospective cohort of up to 8 million VA-enrolled veterans with chronic moderate to severe pain enrolled in VA primary care, the same criteria used to identify and recruit potential participants for the wHOPE study. Among the subgroups of interest-racial/ethnic minorities, women, and rural veterans, we will compare utilization of the nine VA-endorsed CIH modalities (e.g., acupuncture, yoga, tai chi, mindfulness, chiropractic care) one year before the start of the global pandemic (March 23, 2020) and one and two years into the pandemic ending March 23, 2022. We will conduct descriptive comparative analyses as well as time-varying analyses examining person-level (e.g., age, income, COVID-related hospitalization) and site-level covariates (e.g., level of Whole Health implementation, level of COVID impact). Specifically, we will explore proportions of the patient population by site and across sites that accessed CIH modalities each month in the 12 months prior to and following the onset of COVID, stratifying by sex, race, ethnicity, and rural residence. Based on descriptive analyses of trends in use over time, we may aggregate time and time-varying factors across larger intervals. Then, using logistic regression modeling with random effects, accounting for patients nested within sites, we will estimate the probability of CIH use by time (with respect to COVID onset), sex, race, ethnicity, and rural residence, controlling for person- and site-level covariates and the potential interaction of site-by-person factors. In addition, we will also examine any negative impacts of lower utilization of non-drug therapies for pain management,

i.e., increased emergency department visits for pain, increased use of opioids or other pain medications etc.

Human Subjects Considerations: This is an ad hoc low-risk secondary data analysis; there will be no contact with subjects, and these analyses will not impact the conduct of the wHOPE trial. We will be recruiting upwards of over 8 million veterans (from the VA EHR), and it is not practicable to consent and enroll all of them in this low-risk secondary data analysis. This aim poses minimal risk because we will only be accessing pertinent information from CDW/VINCI that is required to collect information on the impact of COVID-19 on Veterans' utilization of non-drug, Whole Health, and CIH services for chronic pain management. We will also access race, ethnicity, sex/gender, and rural/urban identifiers for comparative analyses as well as other demographic, clinical and health services utilization variables to adjust for potential confounding. To do this, we will need access to PHI specified in the 103 form. The large number of records required makes it impracticable to contact all potential subjects and the attempt to contact subjects poses a greater risk than this secondary data analysis study. We will not record names or addresses and other contact information and are only interested in the information related to Veterans' utilization of non-drug, Whole Health, and CIH services, along with descriptive demographic, clinical, and health services information.

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