Cooperative Pain Education and Self-management: Expanding Treatment for Real-world Access
(COPES ExTRA)

A pragmatic superiority trial to examine the strengths and weaknesses of an IVR-based form of Cognitive Behavioral Therapy for Chronic Pain (CT-CP) called COPES versus synchronous CBT-CP provided by clinicians previously trained through VHA's evidence based psychotherapy program.

Study Chairman or Principal Investigators:

Alicia Heapy, PhD

Associate Director
Pain Research, Informatics, Multimorbidities, and Education (PRIME) Center
VA Connecticut Healthcare System (11ACSLG)
And
Associate Professor
Yale University School of Medicine
Department of Psychiatry

Diana Higgins, PhD

Associate Professor of Psychiatry
Boston University Aram V. Chobanian & Edward Avedisian School of Medicine
And
Research Pain Psychologist
Durham VA Healthcare System

Supported by:

The National Center for Complementary and Integrative Health (NCCIH)

National Institute of Alcohol Abuse and Alcoholism (NIAAA)

National Institute of Nursing Research (NINR)

Grant number: UH3 AT009767

NCT03469505

Version 0.10

Tool Revision History

Version Number:0.2
Version Date: 3/25/19
Summary of Revisions Made: Revisions made in response to NCCIH feedback including clarifying details of the interventions, adding DSMP language, clarifying the difference between VA CIRB engaged and non-engaged sites, changing the primary outcome to 4 months from 3 months post-treatment.

Version Number:0.4
Version Date: 4/26/19
Summary of Revisions Made: Final revisions in response to review. Added a blinded statistician and addressed a question about the number of sites on page 31.

Version Number:0.5
Version Date: 6/24/19
Summary of Revisions Made: Final sites included.

Version Number:0.6
Version Date:8/20/19
Summary of Revisions Made: Revisions made after PRC suggested comments including changing the primary outcome from total BPI to the interference subscale of the BPI, adding qualitative interviews for the VACHS coordinating center clinicians, correcting the description of the procedure of clinicians logging time spent in intervention-related activities, confirming electronic health record demographics with telephone screening questions, adding a per protocol analysis to compliment the intent-to-treat analysis described, and correcting various administrative typos.

Version Number 0.71
Version Date: 6/29/20
Summary of Revisions Made: Update of protocol to reflect COVID-19-related changes, plan for monitoring separation between treatment arms identified, email contact for study website and assessment reminders per patient request has been added, updated appendices and minor edits and corrections.

Version Number 0.8
Version Date: 2/1/21
Summary of Revisions Made: Updates include adding the sensitivity analyses to heterogeneity in therapist specific time trends and a propensity-score based exploratory analysis that takes into account the type of treatment received in the synchronous CBT-CP group (video/telephone vs in-person) as well as staff changes and minor edits and corrections.

Version Number 0.9
Version Date: 1/3/2023
Summary of Revisions Made: Updates include 1) adding the analysis plan for comparison between participants recruited from referral versus self-referral via letter outreach approaches, 2) addition of new transcription method for qualitative interviews, and 3) staff changes.

Version Number 0.10
Version Date: 4/17/2025
Summary of Revisions Made: Changes to secondary outcomes includes 1) removal of two secondary outcomes that are redundant with other secondary outcomes of equivalent or superior psychometric properties, 2) reclassification of some secondary outcomes to tertiary outcomes to improve power for the analysis of treatment related outcomes and allow for a separate tertiary analysis (paper) focusing on engagement, and 3) removal of two secondary outcomes that are not treatment outcomes.

TABLE OF CONTENTS

Page

STUDY TEAM ROSTER

Principal Investigator:

Alicia Heapy, PhD	VACHS/Yale University	*Alicia.Heapy@va.gov*
Diana Higgins, PhD	Durham VA/Boston University	*Diana.Higgins2@va.gov*

Co-Investigators:

Steve Martino, PhD	VACHS/Yale University	*Steve.martino@yale.edu*
Todd Kawecki, DC	VACHS/Yale University	*Todd.Kawecki@va.gov*
Christopher Ruser, MD	VACHS/Yale University	*Christopher.ruser@va.gov*
Mary Driscoll, PhD	VACHS/Yale University	*Mary.Driscoll3@va.gov*
Eugenia Buta, PhD	VACHS/Yale University,	*Eugenia.buta@yale.edu*
Sara Edmond, PhD	VACHS/Yale University	*Sara.edmond@yale.edu*
Todd Wagner, PhD	Palo Alto VA/Stanford University	*Todd.wagner@va.gov*
Kristin Mattocks, PhD, MPH	VACWM/University of Mass	*Kristin.Mattocks@va.gov*
Sarah Krein, PhD, RN	VA Ann Arbor/ University of Michigan	*Skrein@med.umich.edu*
John Piette, PhD	VA Ann Arbor/ University of Michigan	*Jpiette@med.umich.edu*
Jennifer Murphy, PhD	VA Central Office	*Jennifer.Murphy2@va.gov*
Lynn DeBar, PhD	Kaiser Permanente	*lynn.debar@kp.org*

Collaborators:

Kathryn LaChappelle MPH	VACHS, Project Coordinator	*Kathryn.lachappelle@va.gov*
Nicolle Marinec, MPH	VA Ann Arbor/ University of Michigan	*Stecn@med.umich.edu*
Caroline Quon, BS	VACHS, Study staff	*Caroline.quon@va.gov*
Allison Halat, BA	Boston University, Study staff	*allison.halat@va.gov*
Kim Selander, MA	VACHS, Study staff	*kimberly.selander@va.gov*
Kevin Payne, MA	VACHS, Study staff	*kevin.payne@va.gov*
Brett Ankawi, PhD	VACHS, interventionist	*brett.ankawi@va.gov*
Dana Cervone, APRN	VACHS, interventionist	*dana.cervone@va.gov*
Marianna Maly, MA	University of Michigan, interventionist	*marianna.maly@umich.edu*
Lisa Frantsve-Little	VACHS, interventionist	*lisa.frantsve-little@va.gov*
R. Ross MacLean, PhD	VACHS, interventionist	*ross.maclean@yale.edu*
Kathryn Min, PhD	VACHS, interventionist	kathryn.min@va.gov
Forrest Levin	VACHS, data manager	*woody.levin@va.gov*
Elizabeth Galliford	VACHS, study staff	*elizabeth.galliford@va.gov*
Denise Esserman, PhD	Yale University, statistician	*denise.esserman@yale.edu*

PARTICIPATING STUDY SITES

Table 1: Overview of participating sites

Location of staff	Role	Engaged in Research
VACHS	Consenting participants & centrally delivering COPES treatment via phone. Serves as the coordinating center.	Yes
VASLC, Palo Alto VA, VACWM, VA Ann Arbor, Boston University., Kaiser Permanente (details in Table 2)	Investigators (Co-Is) receiving funds for various study tasks including performing cost analysis, conducting qualitative interviews, transcribing interviews, and overseeing the IVR vendor in the build and maintenance of the IVR system	Yes
9 VA WH-PBRN site leads (details in Table 3)	Site champions, liaisons, educating local colleagues about the trial and the electronic health record referral alert	No
WH-PBRN VA sites that are also engaged	VACWM, VA Ann Arbor	Yes

Table 2: Sites engaged in research

VA Salt Lake City no longer engaged since 2022 due to new transcription methods.

Local Site Investigator: Steve Martino, PhD; Todd Kawecki, DC; Christopher Ruser, MD; Mary Driscoll, PhD; Eugenia Buta, PhD; Sara Edmond, PhD;	Facility: VA Connecticut Healthcare System
Telephone:203-932-5711 Email: Steve.martino@yale.edu; Todd.Kawecki@va.gov; Christopher.ruser@va.gov; Mary.Driscoll3@va.gov; Eugenia.buta@yale.edu; Sara.edmond@yale.edu	Facility Address: 950 Campbell Ave. West Haven, CT 06516
Local Site Investigator: Todd Wagner, PhD	Facility: Palo Alto VA Health Care System

Telephone: (650.493.5000 x22048 Email: Todd.wagner@va.gov	Facility Address: 795 Willow Road Menlo Park, CA 94025
Local Site Investigator: Susan Zickmund, PhD	Facility: VA Salt Lake City Health Care System
Telephone: (801) 582-1565 X5114 Email: Susan.Zickmund@va.gov	Facility Address: 550 Foothill Dr. Salt Lake City, UT 84113
Local Site Investigator: John Piette, PhD & Sarah Krein, PhD, RN	Facility: VA Ann Arbor
Telephone: (734) 845-3621 Email: jpiette@med.umich.edu; Sarah.Krein@va.gov	Facility Address: 2215 Fuller Rd Ann Arbor, MI 48105
Local Site Investigator: Kristin Mattocks, PhD, MPH	Facility: VA Central Western Massachusetts Healthcare System
Telephone: 413-584-4040 x2060 Email: Kristin.Mattocks@va.gov	Facility Address: 421 N Main St Leeds, MA 01053
Local Site Investigator: Diana Higgins, PhD	Facility: Boston University
Telephone: (857) 364-2221 Email: Diana.Higgins2@va.gov	Facility Address: 72 E Concord St, Boston, MA 02118
Local Site Investigator: Jennifer Murphy, PhD	Facility: VA Central Office
Telephone: (800) 827-1000 Email: jennifer.murphy2@va.gov	Facility Address: 810 Vermont Ave NW, Washington, DC 20420
Local Site Investigator: Lynn DeBar, PhD	Facility: Kaiser Permanente
Telephone: 206-287-2942 Email: lynn.debar@kp.org	Facility Address: 1730 Minor Avenue, Suite 1600 Seattle, WA 98101

Table 3: WH-PBRN participant recruiting sites (9 final sites)

Station	Description	Location
506	VA Ann Arbor Healthcare System	Ann Arbor, MI
534	Ralph H. Johnson VA Medical Center	Charleston, SC

549	Dallas VA Medical Center	Dallas, TX
537	Jesse Brown VA Medical Center (backup)	Chicago, IL
586	G.V. (Sonny) Montgomery VA Medical Center	Jackson, MS
631	VA Central Western Massachusetts Healthcare System	Leeds, MA
635	Oklahoma City VA Health Care System	Oklahoma City, OK
674	Central Texas Veterans Health Care System	Temple, TX
663	VA Puget Sound Healthcare System	Seattle, WA
578	Edward Hines Jr. VA Hospital	Hines, IL

PRÉCIS

Study Title

Cooperative Pain Education and Self-management: Expanding Treatment for Real-world Access (COPES ExTRA)

Objectives

Cognitive behavioral therapy for chronic pain (CBT-CP) is an evidence-based psychological intervention that is effective for reducing pain and improving function for patients with chronic pain. Numerous barriers exist to face-to-face delivery of this treatment, including patient travel limitations, the need for frequent in-person sessions, and the scarcity of trained therapists. Leveraging technology-based interventions, like interactive voice response (IVR), which allow patients to engage in treatment from their home with less patient and clinician burden, may improve access to CBT-CP. The overall goal of this project is to conduct a pragmatic superiority trial to examine the strengths and weaknesses of an IVR-based form of CBT-CP called Co-Operative Pain Education and Self-management (COPES) (asynchronous treatment) relative to synchronous CBT-CP provided by clinicians previously trained through VHA's evidence-based psychotherapy program, employment in the role of a "pain psychologist" or prior CBT-CP training in graduate school or in a clinical setting (synchronous treatment). Synchronous treatment will include individual or group in-person treatment and virtual treatment provided by VA video connect (VVC), Zoom, Skype, telephone, or other similar platforms that allow the patient and clinician to have real-time interaction, The control arm, formally called in-person CBT-CP will now be called synchronous CBT-CP because all the modalities used to deliver the treatment (in-person, telephone, and videoconferencing) allow for real-time interaction between the therapist and participant. IVR CBT-CP does not allow for real-time interaction, only asynchronous communication between the therapist and participant. This will give us information to guide both policy decisions and treatment recommendations for individual patients.

We will conduct a randomized hybrid type 1 pragmatic trial comparing a technology-based form of CBT-CP that patients can do from their homes (COPES IVR-CBT_CP) versus synchronous CBT-CP delivered by a VA clinician.

Our primary hypothesis is that asynchronous COPES (IVR-CBT-CP) will be superior to synchronous CBT-CP in terms of self-reported pain impact as measured by the interference subscale of the Brief Pain Inventory (BPI) scale at 4 months post-baseline. Our secondary hypotheses are that asynchronous IVR-based CBT-CP will be superior to synchronous CBT-CP in terms of secondary outcomes such as: interference subscale BPI score at 6 and 12-month post-baseline, , PEG-3 pain scale, depressive symptom severity, pain catastrophizing, Insomnia severity index, Pain Self-Efficacy scale, , Patient Global Impression of Change, dose, , treatment satisfaction, . Tertiary outcomes include patient engagement (a patient attending at least one session of CBT-CP or completing at least one treatment week of COPES), time to first treatment session, number of participants who complete all 10 treatment sessions (completion=yes/no), time to completion.

As a secondary aim, we will evaluate the intervention delivery costs of COPES (IVR-CBT-CP).

As a tertiary aim, we will conduct a process evaluation to explore providers' experience with COPES (IVR-CBT-CP) and synchronous CBT-CP.

Design and Outcomes

This is a pragmatic superiority trial to examine the strengths and weaknesses of COPES asynchronous (IVR-CBT-CP) versus synchronous CBT-CP using three aims. Aim 1: Using a randomized pragmatic trial design in 764 VHA patients, we will determine whether COPES+UC is superior to synchronous CBT-CP+UC at 4 (primary endpoint), 6 and 12 months post-enrollment on: 1) A measure of pain functioning (the interference subscale of the Brief Pain Inventory (BPI)-primary outcome), 2) NRS pain intensity, catastrophizing, insomnia, depression, pain self-efficacy, and treatment satisfaction, treatment dose, and Patient Global Impression of Change (4 months only). Tertiary outcomes include patient engagement (a patient attending at least one session of CBT-CP or completing at least one treatment week of COPES), time to first treatment session, time to complete treatment, number of participants who complete all 10 treatment sessions (completion=yes/no). . and 3) health care use including emergency and urgent care, and pharmacological and non-pharmacological pain care.

Evaluate uptake, engagement, and variation in outcomes across groups where treatment disparities are possible (e.g., gender, race/ethnicity) and among patients with co-morbid alcohol and substance use disorders that have traditionally been excluded from trials of non-pharmacological interventions.

Aim 2: Evaluate the intervention delivery costs of COPES and conduct a budget impact analysis.

Aim 3: Conduct a process evaluation using the Consolidated Framework for Implementation Research (CFIR) and RE-AIM to guide our evaluation. We will:

> 3a. Conduct CFIR-guided interviews with the coordinating site's clinicians (VACHS) and study site clinicians and administrators to assess their experience with and views regarding the COPES and CBT-CP interventions

3b. Communicate ongoing implementation findings with participating sites and stakeholders.

The study will occur in approximately 10 Women's Health-Practice Based Research Network (WH-PRBN) sites selected on the basis of site quantitative metrics and a diagnostic process evaluation. The study sample will be drawn from patients with an electronic health record (EHR) derived a) musculoskeletal diagnosis and b) 2 or more reports of pain of ≥4 on the pain numeric rating scale (NRS) occurring within the past 12 months. Musculoskeletal pain conditions will include the 29 most commonly diagnosed M codes used in VHA settings including (M54.5, M54.2, M25.561, M25.562, M25.511, M25.569, M25.512, M19.90, M17.0, M17.9, M54.16, M25.551, M51.36, M25.519, M25.552, M06.9, M79.673, M72.2, M19.91, M17.11, M79.671, M79.672, M17.12, M48.02, MS4.9, M79.7, M54.12, G89.4, F45.42). Broadly speaking these codes represent spine conditions, osteoarthritis, joint pain, fibromyalgia, and rheumatoid arthritis. Also included will be chronic pain syndrome and pain disorder with related psychological factors. After receiving a referral from a site clinician or patient self-referral, study staff will contact patients by telephone, and assess patient interest and consent eligible patients. All randomized patients will be asked to complete an automated telephone assessment prior to beginning treatment and 1, 4, 6, and 12 months after beginning, through the study IVR system.

Patients randomized to COPES (IVR-CBT-CP) will be enrolled in the daily IVR monitoring system and participate in 10 weeks of learning pain self-management skills as well as completing the assessments over 12 months. Patients who are randomized to synchronous CBT-CP will be referred to a site CBT-CP clinician by study staff and will also participate in completing assessments on the IVR system for a duration of 12 months at the time points specified above.

Interventions and Duration

COPES (IVR-CBT-CP)

Overview. COPES (IVR-CBT-CP is a 10-week, IVR-facilitated program of CBT for chronic pain. The primary components of the intervention include: 1) a self-help handbook containing the rationale and instructions for using eight pain self-management skills, and their corresponding weekly skill practice goals; 2) a pedometer-facilitated walking program; 3) daily, automated IVR calls to collect patient-reported pain intensity and pain interference, sleep quality, pedometer-measured step count, and adherence to the pain coping skill practice ratings; and 4) weekly, two to four minute pre-recorded, personalized therapist messages based on participant IVR-reported data. The COPES IVR system provides participants the ability to automatically connect to the Veteran Crisis Line during any call. In this study, COPES will be centrally delivered from the VA Connecticut site. Participants will be given up to 14 weeks to complete treatment to allow for missed sessions (vacations, illness).

Intake and materials. Each weekly IVR module will feature a single self-management skill (e.g., paced physical activity, stretching, or relaxation) reinforced via a companion chapter in the patient handbook. The handbook, developed for the initial COPES efficacy trial and refined prior to the ongoing COPES implementation trial, is written at the 6th grade reading level and features design strategies to enhance engagement and readability. The manual will assign a specific goal each week that promotes practice of the module's coping skill (e.g., practice deep breathing for 5 minutes each day this week). The participant will be instructed to practice that week's skill each day of the week and report via daily IVR assessment their daily skill practice completion (0=not at all completed to 10=totally completed). Participants will have access to a patient handbook through the COPES website. If patients do not have Internet access the handbook will be mailed to them. Participants will also be mailed an Omron Go Smart Model HJ-112 pocket pedometer to facilitate their participation in the walking portion of the treatment.

Daily IVR assessment calls. Prior to treatment and after the study baseline evaluation, participants will undergo daily IVR assessment of pain intensity, pain interference, pedometer-measured step counts, sleep quality, and sleep duration for seven days to establish a baseline of function. After the baseline period, participants will continue to receive daily calls for the duration of the 10-week treatment. During the treatment period two additional questions regarding pain skill practice and progress toward the weekly meaningful activity goal will be included. Patient-reported data collected on the IVR assessment calls will form the basis for therapist feedback. Calls will continue through an immediate one-week post-treatment assessment period. COPES participants will receive automated calls each evening between 6pm and 10pm at a time pre-selected by the patient to ensure that each call captures the full 24-hour reporting period. On evenings when participants miss their scheduled call, the IVR system will call again 2 additional times. Alternatively, participants may initiate a call into the system themselves. Study staff automatically receive alerts when participants do not respond to their first call or do not respond to two consecutive daily calls. During the IVR call, participants may directly access the VHA suicide crisis line by pressing 777# from the main menu or they may leave a message for their COPES therapist.

Pedometer-Assisted Graduated Walking Program. The COPES intervention includes a graduated walking component supported by daily reporting of pedometer-measured step counts.[37] Participants will report their daily step count during the daily IVR assessment. Each week, a new daily step target will be calculated by adding 10% to the prior week's average daily step count and that target will be communicated to participants during the weekly personalized, asynchronous therapist feedback.

Meaningful Activity Goal. Participants will learn the basics of goal setting using the SMART (specific, measurable, achievable, relevant, and timely) framework in the introductory handbook module. They will be asked to generate a weekly meaningful activity goal using this format.

These goals will focus primarily on increasing productive, pleasant, or social activities with others. This goal will be reported to the therapist during an automated IVR daily call, and participants will be asked to report on the degree to which they made progress toward this goal via the IVR system later in the week. If a participant misses that call, the therapist will not have the piece of information for the therapist feedback that week. Additional attempts to collect this data will not be made.

Asynchronous therapist feedback. Therapists will use data collected from daily IVR assessment calls to inform a 2-4 minute *personalized* feedback message for each participant. The message will be pre-recorded and left on the final day of each week. Procedures for developing feedback scripts, feedback script examples, and suggestions for common patient circumstances have been developed in prior trials and are included in a COPES therapist manual. Participants will be alerted to the feedback when they receive their nightly automated call and they may access or replay these messages as often as they like. Should they miss their scheduled call, they will be alerted to the waiting message during their next interaction with the IVR system. The IVR system is also designed to allow participant and therapist to leave messages at any time to seek clarification from therapists and to minimize any frustrations or confusion that may lead to attrition.

Centralized intervention delivery. COPES will be delivered from VACHS to all study sites. No additional clinicians will be placed in the study sites. Drs. Higgins, Driscoll, and Edmond all have experience delivering COPES in one of our current or previously funded trials and will train new COPES therapists. Because COPES can be delivered centrally, by a core group of therapists who receive consistent training and use therapist manuals and feedback scripts to further standardize treatment provision, COPES can be provided with a high degree of fidelity to the original treatment and is less subject to drift than synchronous treatments. After therapists complete the training period, we will monitor treatment fidelity and provide specific feedback to therapists regarding their delivery of the intervention in 30% of treatment sessions.[71] We will track participant participation (number of weeks engaged) and treatment completion (yes/no), time to first treatment session, dose, time to treatment completion, and treatment fidelity.

Synchronous CBT-CP. VHA Evidence-Based Psychotherapy CBT-CP[18] (referred to as in person CBT-CP) is a 10-session intervention containing skills similar to those contained in COPES (IVR- CBT-CP). In general, patients attend weekly, individual, 50-minute treatment sessions with a previously trained CBT-CP therapist. We anticipate that given the COVID-19 pandemic local adaptation of CBT-CP will be common. We will not attempt to influence how synchronous CBT-CP is provided and will accept a number of common treatment provision methods including individual and group in-person, telephone, VVC, Zoom, Skype and other platforms accept by VA. We will carefully track through electronic record review treatment type, fidelity, and treatment engagement. A fidelity checklist is in the process of being developed. A detailed therapist manual[18] provides pain education, case examples, and session by session guidance on treatment delivery. Following an initial assessment session, patients learn one pain coping skill

per week. Patients set goals with their therapists and are asked to regularly practice the pain coping skills they are learning in treatment at home. Therapists give feedback regarding goal accomplishment. Although all CBT-CP therapists have undergone training and demonstrated CBT-CP specific competencies, it is anticipated that they will still display a range of experience and skill in delivering the intervention and maintaining fidelity to the treatment manual. In the spirit of pragmatic trials, we will not attempt to impose fidelity to the treatment manual, or provide specific training or feedback, but we will monitor basic measures of treatment fidelity based on items from the checklist that will be developed. Using electronic health record clinical notes we will track participant dose (number of weeks engaged), time to first treatment session, time to completion, and treatment completion (yes/no). Thus, synchronous-CBT-CP will be delivered as it would in usual clinical practice.

Sample Size and Population

A sample size of 610 subjects (305 per group) would provide 80% power to detect a mean difference in the interference subscale of the BPI of 0.55 between COPES and CBT-CP at 4 months using a two-sided t-test at significance level alpha=0.05. To account for an expected attrition rate of 20%, we will enroll a total of 764 participants (382 per group) with a target of half of the participants being female.

1. STUDY OBJECTIVES

This is a randomized hybrid type 1 pragmatic trial comparing a technology-based form of CBT-CP that patients can do from their homes (COPES IVR-CBT_CP) versus synchronous CBT-CP delivered by a VA clinician.

1.1 Primary Objective

We hypothesize that COPES (IVR-CBT-CP) will be superior to synchronous CBT-CP in terms of self-reported pain intention-to-treat outcome as measured by the interference subscale of the Brief Pain Inventory (BPI) score at 4 months post-baseline.

1.2 Secondary Objectives

We hypothesize that IVR-based CBT-CP will be superior to synchronous CBT-CP in terms of secondary and tertiary intention-to-treat outcomes. Secondary outcomes include: interference subscale of the BPI score at 6 and 12-month post-baseline, , PEG-3 pain scale, depressive symptom severity, pain catastrophizing, Insomnia severity index, Pain Self-Efficacy scale, , Patient Global Impression of Change, treatment dosetreatment satisfaction. Tertiary outcomes include: patient engagement

(a patient attending at least one session of CBT-CP or completing at least one treatment week of COPES, number of participants who complete all 10 treatment sessions (completion=yes/no), time to treatment, and time to complete treatment),

To evaluate the intervention delivery costs of COPES and conduct a budget impact analysis.

To conduct a process evaluation using the Consolidated Framework for Implementation Research (CFIR) and RE-AIM to guide the evaluation. We will conduct CFIR-guided interviews with coordinating site clinicians and study site clinicians and administrators to assess their experience with and views regarding the COPES (IVR-CBT-CP) and synchronous CBT-CP interventions. Communicate ongoing implementation findings with participating sites and stakeholders.

2. BACKGROUND AND RATIONALE

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

Efficacy of CBT-CP. Cognitive Behavioral Therapy (CBT) is the most widely-accepted, evidence-based, non-pharmacologic treatment for chronic pain.[1,17] CBT is informed by a theory recognizing that patients' beliefs, attitudes, and coping styles play central roles in determining their experiences of pain.[18] CBT for chronic pain (CBT-CP) is an attractive adjunct or alternative to pharmacological treatments because its effects can persist after treatment is discontinued, without the negative side effects and potential harms of pharmacological treatments such as opioids. The goal of CBT-CP is for patients to develop skills to manage pain, and its associated disability and emotional distress as a means to improve functioning and quality of life. CBT-CP programs typically entail 8-12 weekly, 50 minute, in-person sessions focusing on teaching pain management skills and promoting productive activities and exercise. Sessions educate patients about chronic pain, teach and encourage the practice of pain self-management skills, and promote productive and pleasurable activities and exercise. Skills address both cognitive processes (e.g., catastrophizing) and behaviors (e.g., relaxation). A meta-analysis and Cochrane review both concluded that CBT-CP can have moderate to large effects on pain-related outcomes.[2,3]

Evidence-Based Psychotherapy Program (EBP) for CBT-CP. The Veterans Health Administration’s (VHA) Evidence-Based Psychotherapy Program (EBP) has endorsed CBT-CP as an evidence-based psychotherapy[4] and has trained over 400

VHA mental health clinicians to deliver this care to VHA patients. The EBP version of CBT-CP was developed by an expert panel of VHA clinicians and pain researchers.[18] Training is provided to VHA mental health clinicians in a 3-day participatory workshop followed by 6 months of weekly telephone supervision with an expert CBT-CP trainer. Trainers review session audiotapes, rate therapist performance with a standardized scale and provide feedback. In order to be certified, therapists must meet pre-specified criteria regarding the number of Veterans treated, the number of audiotapes reviewed by the trainer, and attainment of rating scores demonstrating specific CBT-CP competencies. Program evaluation conducted by the VHA EBP Program on the initial sample of 71 CBT-CP trainees found 85% completed training and reached trainer-rated competence scores; treated patients reported significant improvements in pain-related interference, pain catastrophizing and quality of life.[4] A subsequent evaluation of 586 Veterans treated in the initial 10 training classes found that patients demonstrated significant pre- post improvements in average pain intensity, pain-related interference, pain catastrophizing, and depressive symptoms.[19]

Barriers to wider CBT-CP use. Although there has been national dissemination of VHA EBP CBT-CP, trained therapists continue to be unavailable in some locations, especially in rural areas or smaller facilities such as community-based outpatient clinics.[20,21] Clinicians often have duties that go beyond EBP CBT-CP, limiting their ability to provide CBT-CP to patients.[20] Despite standardized training methods, CBT-CP services may vary in quality and continuing fidelity to best treatment practices is not assessed and cannot be assured.[23] Patient burden associated with attending multiple in-person visits is high and associated with patient attrition and lower than optimal dose.[24] The treatment schedule of 10 weekly sessions may put treatment out of reach for patients with limited time, transportation barriers, or competing demands-a problem that clinicians often cite as a reason for choosing treatment plans that center around medication.[25,26, 27] Providers also experience barriers to referring patients to CBT-CP. including lack of knowledge about the efficacy of CBT-CP or concern about not having enough time to discuss this option with patients during the visit.[28] Given the multiple barriers to CBT-CP treatment, VHA would benefit from innovative strategies to ensure that patients receive the pain self-management support that they need.

Mobile health (mHealth) approaches to CBT-CP. Technology such as interactive voice response (IVR) offers a way to increase access to evidence-based pain care, including CBT-CP. IVR monitoring and self-care assistance are central components of COPES. Here, the term mHealth refers mainly to communication between health systems and patients using IVR calls. Because mHealth services have low marginal costs, they can reach large numbers of patients to provide support for health behavior

change.[29] More than 50 studies have demonstrated that patients provide reliable and valid information about psychiatric symptoms and substance use via IVR and other mobile health technologies.[30-33] mHealth interventions can improve self-management behaviors[34,35] and outcomes of chronic illness care.[36] We propose a model for taking advantage of mHealth services to deliver evidence-based CBT-CP to improve patients' functioning in a way that could promote non-pharmacological management of chronic pain without the burden of in-person visits to a medical center. However, successful implementation of this model will require not only a means to surmount known geographic, convenience, and resource limitations, but will also need to encourage and support patient engagement and provider referral and identify unknown barriers and facilitators to uptake.

Co-Operative Pain Education and Self-management (COPES):

This trial is informed by the widely-recognized gap between evidence of effectiveness of CBT for chronic pain management and equitable and timely access to it. A desire to address these gaps has informed the proposed trial. Our interest in comparing the real-world outcomes of COPES (IVR-CBT-CP) and synchronous CBT-CP is rooted in determining if there is clear evidence of superiority and thus, cause to recommend one treatment over the other. Alternatively, if there is not superiority; then providers can rely on patient preference and local availability to determine what is offered to patients. Additionally, identification of patient characteristics (e.g., age, gender, pain features, co-occurring conditions) that predict or moderate a positive response to CBT for chronic pain (in either form) or induce preferential response to one treatment relative to another can meaningfully guide policy and clinical decisions. Finally, identification of the organizational, provider and patient-level barriers that prevent referral and widespread patient uptake of these approaches could improve our ability to engage patients initially and to sustain their participation over time.

2.2 Study Rationale

Evidence related to IVR-delivered CBT for chronic pain. The central proposed intervention, IVR based CBT for chronic pain was recently examined in a non-inferiority trial by our group.[37] The COPES (Cooperative Pain Education and Self-Management) efficacy trial randomized VA patients with chronic back pain to receive either a) in person-CBT-CP: 10 weekly in-person individual CBT sessions with a therapist for chronic pain or b) IVR-CBT-CP: 10 weeks of daily IVR calls with weekly pre-recorded personalized feedback messages about their progress. Patients in both groups received CBT self-care support manuals, and both the "in-person CBT-CP" and "IVR CBT-CP" interventions included 10 CBT modules covered at the rate of one per week that covered the same pain coping skills. Patients in both groups

were also provided a pedometer and instructed to increase their daily step counts by 10% each week. All participants received brief automatic nightly IVR calls to assess pedometer-measured step-counts and other pain-related outcomes. At 12 weeks post enrollment, statistically significant improvements in physical functioning, sleep quality, and physical quality of life relative to baseline occurred in both treatments, with no advantage for either treatment (Figure 1). Post-treatment, 33% of subjects receiving in-person CBT reported clinically meaningful improvement in pain intensity of at least 30%, compared to 19% receiving IVR-CBT (p=0.19).[5] For physical functioning/disability, 35% of participants in in-person CBT and 45% in IVR-CBT reported a reduction of at least 30% (p=0.43).[5] Additionally, the "IVR CBT" participants reported step count increases that were comparable to the increases observed in "in-person CBT." Overall, across all participants, an average increase of 2,072 steps per day was observed from baseline to follow-up; this equates to an increase of approximately one mile of walking per day. Additionally, IVR-CBT patients received 2.3 (95% CI: 1.0, 3.6) more weeks of treatment than patients attending in-person sessions, and patients were equally satisfied with IVR and in-person therapy.[5] Finally, participants were proactively assessed each week for study-related adverse events. Forty-six participants experienced 92 related and unrelated AEs (COPES=40, In-person CBT=52). Most related AES were small increases in pain from exercise. The number of AEs was not significantly different by treatment group (p=0.44). Only two serious AEs were reported, but judged by the IRB to be unrelated to study participation.

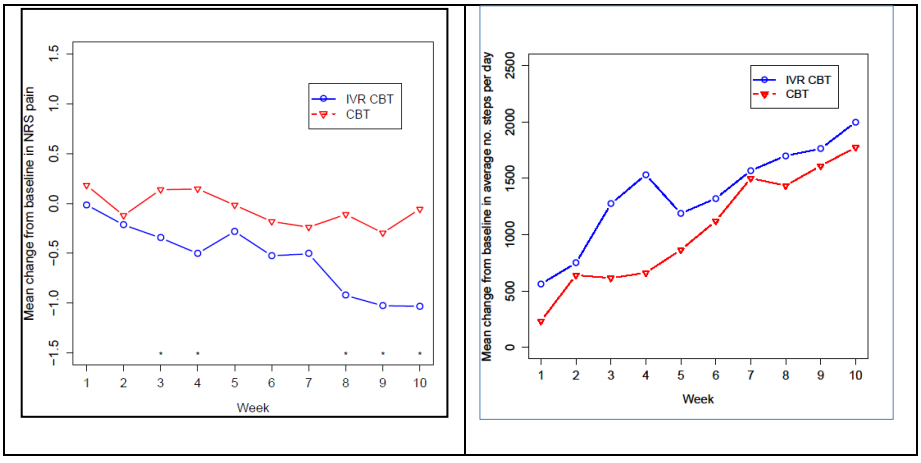


Figure 1. Pain Intensity (left panel) and daily steps (right panel) reported among VHA patients with back pain randomized to in-person CBT (red line) vs. IVR CBT (blue line).

The proposed project will be the first large scale pragmatic trial designed to directly evaluate the relative effectiveness of an asynchronous CBT intervention for the management of chronic musculoskeletal pain delivered in "real life" clinical practice settings compared to "standard" CBT involving intensive outpatient psychotherapy with providers previously trained to deliver this treatment. As such, this project stands to change the care of Veterans, and by extension, others with chronic musculoskeletal pain, by demonstrating the feasibility of a low burden, cost-effective intervention that overcomes many known organizational, provider and patient-level barriers to accessing effective pain self-management interventions.

The clinical impact of the treatment will be evaluated in terms of its effectiveness, reach and cost, both in absolute terms and relative to other available treatments, thus providing invaluable information beyond that obtained from our prior efficacy and implementation trials. Our approach was chosen to identify the most effective treatment that patients will engage in and that is feasible for the healthcare system to provide.

3. STUDY DESIGN

This is a randomized hybrid type 1 pragmatic superiority trial comparing a technology-based form of CBT-CP that patients can do from their homes (COPES IVR-CBT_CP) versus synchronous CBT-CP delivered by a VA clinician. to examine the strengths and weaknesses of an IVR-based form of CBT-CP called Co-Operative Pain Education and Self-management (COPES) versus synchronous CBT-CP provided by clinicians previously trained through VHA's evidence-based psychotherapy program.

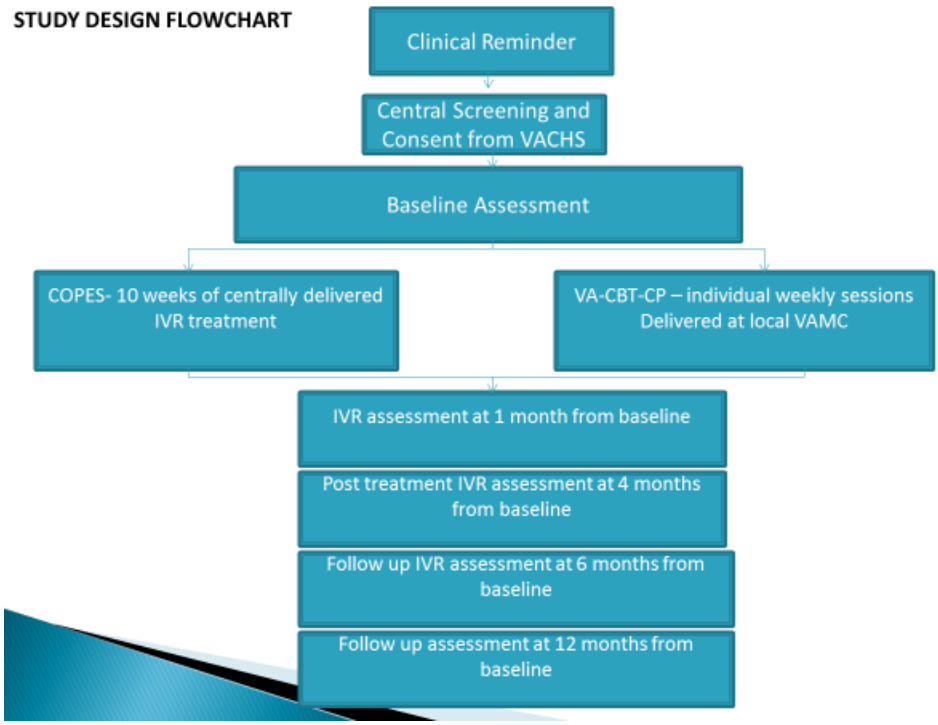
Eligible patients will be identified from the EHR. The electronic health record will be used to collect information on referred patients for analysis and contains reliable information on diagnoses, medications prescribed, and patients' clinical history and demographics, a limited number of demographic items will be confirmed via telephone screening.

The study will occur in 9 Women's Health-Practice Based Research Network (WH-PRBN) sites selected during the UG3 planning period on the basis of site quantitative metrics and a diagnostic process evaluation. The study sample will be drawn from patients with an electronic health record (EHR) derived a) musculoskeletal diagnosis and b) 2 or more reports of pain of ≥4 on the pain numeric rating scale (NRS) occurring within the past 12 months. After receiving a referral from a site clinician or patient self-referral, study staff at the centralized coordinating center at VA Connecticut Healthcare System (VACHS) will contact patients by telephone, and assess patient interest and consent eligible patients. All randomized patients will be asked to complete an automated telephone assessment prior to beginning treatment and 1, 4, 6, and 12 months after beginning, through the study IVR system.

Patients randomized to COPES (IVR-CBT) will be enrolled in the daily IVR monitoring system and participate in 10 weeks of pain self-management treatment with asynchronous therapist feedback skills as well as completing the assessments over 12 months. COPES treatment is managed by the coordinating center at VACHS. Patients who are randomized to in- person CBT-CP will receive treatment at their local VA by a local CBT-CP clinician and will also participate in completing assessments on the IVR system for a duration of 12 months at the time points specified above.

A total sample size of 610 subjects (305 per group) would provide 80% power to detect a mean difference in BPI interference of 0.55 between COPES and CBT-CP at 4 months using a two-sided t-test at significance level alpha=0.05. To account for an expected attrition rate of 20% in each group, we will enroll a total of 764 participants (382 per group) with a target of half of the participants being female.

Below is diagram of participant flow through the project:



4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants. The study sample will be drawn from patients with an EHR derived a) ICD-10 pain-related musculoskeletal diagnosis and b) 2 or more reports of pain of ≥4 on the pain numeric rating scale (NRS) occurring within the past 12 months, as used in prior trials [41] and who are

receiving care at a selected site within the WH-PBRN. Data from our Musculoskeletal Diagnoses (MSD) cohort show 5,237,763 patients in VHA care had a musculoskeletal diagnosis between 2000-2011 with the most common diagnoses being non-traumatic joint disorder (27%), back disorder (25%), and osteoarthritis (21%). We expect the incident cases captured after 2011 to follow this same pattern. Approximately 20% of Veterans in the cohort had 2 or more concurrent MSDs. Among patients entering the cohort in 2011, 47% reported a score of ≥ 4 on the 0 (no pain) to 10 (worst pain imaginable) on the pain intensity NRS at an outpatient or inpatient encounter. In 2011, 7.7% of patients in the MSD cohort were women, 74% non-Hispanic White, 15% were African American, and 5% were Hispanic. Given the prevalence of chronic musculoskeletal pain in VHA, there will be more than an adequate number of eligible patients to meet our enrollment target of 764. Because we have a sub-aim to test for differences in outcomes between men and women and women only represent approximately 8% of VHA patients, we will oversample women. Our final sample target will be 50:50 men to women. We will not stop recruitment of male Veterans if we exceed the 382 target number, but will continue to recruit both men and women until the total enrollment goal of 764 is reached We have elected to spread recruitment over 9 sites throughout the WH-PBRN so that enrollment targets for women will be manageable at each site (n=382 total women over 9 sites=42 women per site over 3 referral years). As a comparison, in our COPES efficacy trial[5] we recruited 28 women over 4 years, though we were not specifically attempting to increase recruitment of women. In this context, with specific focus on recruiting women, we believe that 42 per site is feasible. The number of eligible Veterans who actually engage in COPES IVR-CBT-CP or in person CBT-CP and how many sessions they attend will be examined in the proposed work (see Data Analysis 9.6 "Engagement").

Based on our UG3 work, we believe that the optimal number of sites is fewer than the originally proposed 20 sites. Proposing 20 sites was not based on a power analysis, but a strategy to spread the recruitment and treatment burden over more sites. This is not a cluster randomized trial and reducing the number of sites will not compromise our power to detect differences in the primary outcome. Moreover, as shown in Table 2, even a much smaller number of sites than originally planned will still result in reasonable recruitment targets for each site. Nine sites would require each site to enroll only 2.3 participants per month. Local site clinicians would need to provide treatment for half that number because the remainder would obtain treatment from clinicians at VA Connecticut through the IVR-based CBT-CP. We believe that approximately 9 final sites will be the most advantageous number for striking a balance between meeting enrollment targets and the additional effort required to manage and oversee more sites. Additionally, we believe that securing the most interested and well-positioned sites as opposed to sites with less interest and marginal availability of clinicians may be the most feasible and practical approach. We have 4 additional back up sites that can step in quickly if one of the initial sites is no longer eligible.

Number of sites	Total # of participants per site (total N=764)	# participants per month per site over the enrollment period
5	153	4.3
9	**85**	**2.3**
10	76	2.1
12	64	1.8
14	55	1.5
16	48	1.3
18	42	1.2
20	38	1.1

Table 2 showing recruitment by site for various numbers of sites

Despite having fewer sites than originally proposed, we believe that the selected sites are sufficiently diverse to ensure our findings will be generalizable. The sites represent all major geographic regions of the US except the southwest and sizes in terms of patient populations. According to the data provided by the WH-PBRN, the sites have a range of rurality from highly urban (Jess Brown in Chicago) to primarily rural (Jackson, MS). To further increase rural patient representation, we will recruit patients from community-based outpatient centers (CBOCs) affiliated with the selected sites. Selected sites range from predominantly white like Ann Arbor (71.3%) and Puget Sound (69.1%), to sites with majority black populations like Jackson, MS (64.1%), Jesse Brown (60.7%), and those with a plurality of black patients (Charleston, SC 48.7% black and 36.7% white). Hispanic populations range from 2.6% to 10.9% across sites, with Asian populations ranging from 0.2%-3%. The Oklahoma City site has a relatively high percentage of American Indian patients (2.8%).

Eligible patients will be identified from the EHR or patient self-referral (see 4.3 for details). The electronic health record will be used to collect information on referred patients for analysis and contains reliable information on diagnoses, NRS pain intensity score collected at medical center visits, medications prescribed, and patients' clinical history and demographics. The investigators on this team have experience conducting custom queries for research purposes, reviewing and managing data related to pain and its outcomes, and using informatics to identify patients who meet our study criteria. (Section 9.6 Data Analysis-Engagement)

4.1 Inclusion Criteria

Consistent with the guidelines for pragmatic trials[78] the eligibility criteria will be as inclusive as possible so that the study cohort represents the population of patients with chronic musculoskeletal pain receiving care in VHA. Unlike most trials of non-pharmacological interventions for chronic pain, patients with history of substance abuse disorders or active use disorders will not be excluded. Eligibility criteria are designed to identify patients with: (1) a pain-related musculoskeletal diagnosis indicated by an EHR identified ICD10 code (i.e. M54.5, M54.2, M25.561, M25.562, M25.511, M25.569, M25.512, M19.90, M17.0,M17.9, M54.16, M25.551, M51.36, M25.519, M25.552, M06.9, M79.673, M72.2, M19.91, M17.11, M79.671, M79.672,

M17.12, M48.02, MS4.9, M79.7, M54.12, G89.4, F45.42) ; (2) presence of chronic pain of at least moderate severity (two or more EHR NRS pain scores of ≥ 4 in for a period of 12 months with 30 days between occurrences);[41] (3) ability to participate safely in the walking portion of the intervention as evidenced by patient-reported ability to walk at least one block and absence of diabetic foot ulcers at the time of the enrollment call; (4) availability of a touch-tone land-line or cellular telephone.

4.2 Exclusion Criteria

Exclusion criteria will include (1) current inpatient psychiatric hospitalization for detoxification of alcohol or drugs or acute psychotic episode; (2) receipt of hospice or end-of-life palliative care because we do not believe these participants could meaningfully participate or benefit from CBT-CP and short survival time will likely limit their time in the trial leading to lowered treatment dose and high probability of missing outcome data or dementia-related diagnosis (F02.81, A81.00, F02.80, F03.90, A81.01, A81.89, A81.9, F03.91, F10.27, A81.09, A81.2, F01.50, F19.97, F01.51, G30.0, G30.1, G30.8, G23.1, G90.3, G30.9, G31.01, G31.83, G31.09) as dementias are marked by impaired memory, executive function, and inability to learn new information we do not believe these patient swill be able to learn new pain management skills and therefore they will not benefit from CBT-CP; (4) vision or hearing deficits that would impair participation verified by patient report at the time of the enrollment call (5) current participation in CBT-CP; and (6) any medical intervention that would cause a meaningful increase in pain such as surgery, chemotherapy, radiation therapy.

4.3 Study Enrollment Procedures

Recruitment. Potential participants will be recruited either by self-referral (i.e., opt out letters, toll free number from advertisements) or by provider referral. To promote self-referral, informational posters, flyers, and business cards will be placed at participating sites. Veterans who are interested in participating may refer themselves by contacting VA Connecticut study staff using a toll-free number listed on the materials. For provider referral, patients will be recruited during primary care or mental health visits in the study settings. We will use the national corporate data warehouse (CDW) data obtained from the VA electronic health record (EHR) to identify eligible patients based on ICD10 musculoskeletal diagnosis code, present of at least 2 pain reports of 4 or great in the prior 12 months, absence of palliative or hospice care, and absence of dementia diagnosis. The national CDW database will be accessed by a computerized referral alert built during the UG3 period and installed at each of the recruiting sites. The alert will query the CDW data automatically. An EHR alert to the treating provider will be visible to the

treating provider during a scheduled clinic appointment. The EHR alert will contain three elements: Notification that the patient could benefit from CBT-CP, brief messages describing CBT for pain broadly (not specifying anything about either treatment under consideration, simply stating that they are eligible for CBT for chronic pain), suggestions for presenting the referral to the patient, and a hyperlink that will automatically place the inter-facility referral to VACHS study staff when clicked. We have chosen not to discuss the possibility of referral to different forms of CBT-CP because we want the trial to mimic routine care and in routine care there would not be randomization and patients may not be able to choose their specific form of treatment (e.g., in-person, telehealth, individual, group). In cases where visit time is short or if for any reason clinicians do not want to introduce the referral to COPES/CBT-CP at that visit, providers may click a link that requests they be notified again at the patient's next visit. When patients agree to be referred or to speak to study staff to learn more about CBT for chronic pain, the provider will simply click the hyperlink embedded in the alert to generate an inter-facility consult to the study staff.

Enrollment and randomization. Patients will be contacted, screened, enrolled, and randomized in the same way whether they are self-referred or provider referred. After receiving a referral from a clinician at a study site or a voicemail from a patient self-referral, VA Connecticut study staff will contact patients by telephone, and using a semi-structured interview, assess patient interest, patient's self-reported ability to walk at least one block, presence of a landline or cellular telephone, and absence of vision or hearing loss that would interfere with participation (to confirm eligibility criteria not reliably contained in the EHR), use of complimentary and integrative health (CIH) modalities and answer any questions patients have about the intervention (see attached script) as well as review their VA medical record to confirm eligibility. If a patient is willing to obtain treatment, study staff will read the approved consent language contained in the information sheet. Patients will be specifically asked about consenting to the audio recording of their voice if they leave a message for their study therapist. The information sheet will be available to patients on our study website. The website is a resource for patients and has copies of the information sheet, the patient handbook and audio files of the relaxation exercises. Patients do not need to login and it does not collect, hold or request any PHI or patient data. Use of the website will allow patients to view a copy of the information sheet without the delay of prior mailing. If patients do not have access to the internet or if they would prefer to have a physical copy prior to consenting, we will mail them a copy and contact them at a later time for consenting. Staff may email the patient

the link to the study website or reminder for scheduled assessments upon request. Email addresses used for communication will be identified by the patient during routine staff telephone screenings or reminders. No PHI will be included in email communication. Veterans for whom an email address is available can opt-out at any time of email communication by contacting our 1-800 number. The email to Veterans will state specifically that they are to not respond as the email address is not monitored and anything they reply is not protected and the VA is not liable for. Patients will be told that they will be asked to complete an automated telephone assessment prior to beginning treatment and 1, 4, 6, and 12 months after completion in order to evaluate the treatment program. Following consent patients will then be enrolled in the study IVR system so that baseline and follow-up assessment can be obtained. After completing the baseline assessment, participants will be randomized. Patients will select a convenient time of day to receive their assessment phone calls and the IVR system will automatically leave a reminder message 1 day prior to their scheduled assessments. Patients randomized to COPES (IVR CBT-CP) will receive automated calls each evening between 6pm and 10pm at a time pre-selected by the patient to ensure that each call captures the full 24-hour reporting period. On evenings when participants miss their scheduled call, the IVR system will call again 2 additional times. Alternatively, participants may initiate a call into the system themselves. COPES patients will be instructed to go to the study website to obtain access to the patient handbook that accompanies the treatment, or one will be mailed to patients who do have Internet access. A pedometer will be mailed to COPES patients so they can engage in the graduated walking program. Patients who are randomized to synchronous CBT-CP will be referred to a site CBT-CP clinician by study staff using an electronic interfacility consult (IFC). VA Connecticut study staff will initiate an IFC for each participant randomized to synchronous CBT-CP. This IFC will be sent to the corresponding local site contact and appear in the usual referral workflow (i.e., it will appear in the same pathway as a non-study related referral to CBT for chronic pain). The VA electronic health record system automatically tracks IFCs and the referral source is automatically notified when a referred patient's consult is either declined or scheduled and closed. This will allow us to track the disposition of referred synchronous CBT-CP participants.

Randomization Participants will be randomized in a 1:1 ratio to one of the two treatments (COPES or CBT-CP). The randomization sequence will be generated by the study statistician using statistical software and concealed in the study database until the time of randomization. Randomization will be stratified by site and gender

and will be done according to a permuted block design with variable block size (4 and 6) to maintain balanced treatment assignment.

A waiver of informed consent for recruitment purposes has been obtained, for recruitment and initial study screening.
A waiver of documentation of informed consent has been obtained for the intervention. The information sheet will be available on the study website, as explained, or participants will be mailed an information sheet if they request it. Certificate of confidentiality language will be included.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Interventions- Both interventions are forms of CBT-CP, which is a widely used non-pharmacologic intervention for chronic pain and considered to be the standard of care and a first line treatment for chronic pain. We do not consider COPES (IVR CBT-CP) to be experimental. We consider it to be simply a different way of delivering CBT-CP, which is part of standard clinical care. Clinically, VA has frequently delivered CBT-CP and other psychological/behavioral interventions using various forms of technology (web, app, telehealth, video). This delivery is often done without formal testing of the efficacy of these new delivery methods. When these methods are tested they are often shown to provide benefit and perform similarly to in person treatment. Thus, we consider COPES to be an alternately delivered version of CBT-CP.

CBT-CP Interventions.

COPES (IVR-CBT-CP)

Overview. COPES (IVR-CBT-CP is a 10-week, IVR-facilitated program of CBT for chronic pain. The primary components of the intervention include: 1) a self-help handbook containing the rationale and instructions for using eight pain self-management skills, and their corresponding weekly skill practice goals; 2) a pedometer-facilitated walking program; 3) daily, automated IVR calls to collect patient-reported pain intensity and pain interference, sleep quality, pedometer-measured step count, and adherence to the pain coping skill practice ratings; and 4) weekly, two to four minute pre-recorded, personalized therapist messages based on participant IVR-reported data. The COPES IVR system provides participants the ability to automatically connect to the Veteran Crisis Line during any call. In this study, COPES will be centrally delivered from the VA Connecticut site. Participants will be given up to 14 weeks to complete treatment to allow for missed sessions

(vacations, illness).

Intake and materials. Each weekly IVR module will feature a single self-management skill (e.g., paced physical activity, stretching, or relaxation) reinforced via a companion chapter in the patient handbook. The handbook, developed for the initial COPES efficacy trial and refined prior to the ongoing COPES implementation trial, is written at the 6th grade reading level and features design strategies to enhance engagement and readability. The manual will assign a specific goal each week that promotes practice of the module's coping skill (e.g., practice deep breathing for 5 minutes each day this week). The participant will be instructed to practice that week's skill each day of the week and report via daily IVR assessment their daily skill practice completion (0=not at all completed to 10=totally completed). Participants will have access to a patient handbook through the COPES website. If patients do not have Internet access the handbook will be mailed to them. Participants will also be mailed an Omron Go Smart Model HJ-320 pocket pedometer to facilitate their participation in the walking portion of the treatment.

Daily IVR assessment calls. Prior to treatment and after the study baseline evaluation, participants will undergo daily IVR assessment of pain intensity, pain interference, pedometer-measured step counts, sleep quality, and sleep duration for seven days to establish a baseline of function. After the baseline period, participants will continue to receive daily calls for the duration of the 10-week treatment. During the treatment period two additional questions regarding pain skill practice and progress toward the weekly meaningful activity goal will be included. Patient-reported data collected on the IVR assessment calls will form the basis for therapist feedback. Calls will continue through an immediate one-week post-treatment assessment period. COPES participants will receive automated calls each evening between 6pm and 10pm at a time pre-selected by the patient to ensure that each call captures the full 24-hour reporting period. On evenings when participants miss their scheduled call, the IVR system will call again 2 additional times. Alternatively, participants may initiate a call into the system themselves. Study staff automatically receive alerts when participants do not respond to their first call or do not respond to two consecutive daily calls. During the IVR call, participants may directly access the VHA suicide crisis line by press 777# from the main menu or leave a message for their COPES therapist.

Pedometer-Assisted Graduated Walking Program. The COPES intervention includes a graduated walking component supported by daily reporting of pedometer-measured step counts.[37] Participants will report their daily step count during the daily IVR assessment. Each week, a new daily step target will be calculated by adding 10% to

the prior week's average daily step count and that target will be communicated to participants during the weekly personalized, asynchronous therapist feedback.

Meaningful Activity Goal. Participants will learn the basics of goal setting using the SMART (specific, measurable, achievable, relevant, and timely) framework in the introductory handbook module. They will be asked to generate a weekly meaningful activity goal using this format. These goals will focus primarily on increasing productive, pleasant, or social activities with others. This goal will be reported to the therapist during an automated IVR daily call, and participants will be asked to report on the degree to which they made progress toward this goal via the IVR system later in the week. If a participant misses that call, the therapist will not have the piece of information for the therapist feedback that week. Additional attempts to collect this data will not be made.

Asynchronous therapist feedback. Therapists will use data collected from daily IVR assessment calls to inform a 2-4 minute *personalized* feedback message for each participant. The message will be pre-recorded and left on the final day of each week. Procedures for developing feedback scripts, feedback script examples, and suggestions for common patient circumstances have been developed in prior trials and are included in a COPES therapist manual. Participants will be alerted to the feedback when they receive their nightly automated call and they may access or replay these messages as often as they like. Should they miss their scheduled call, they will be alerted to the waiting message during their next interaction with the IVR system. The IVR system is also designed to allow participant and therapist to leave messages at any time to seek clarification from therapists and to minimize any frustrations or confusion that may lead to attrition.

Centralized intervention delivery. COPES will be delivered from VACHS to all study sites. No additional clinicians will be placed in the study sites. Drs. Higgins, Driscoll, and Edmond all have experience delivering COPES in one of our current or previously funded trials and will train new COPES therapists. Because COPES can be delivered centrally, by a core group of therapists who receive consistent training and use therapist manuals and feedback scripts to further standardize treatment provision, COPES can be provided with a high degree of fidelity to the original treatment and is less subject to drift than synchronous treatments. After therapists complete the training period, we will continue to monitor treatment fidelity and provide specific feedback to therapists regarding their delivery of the intervention in 30% of sessions.[71] We will also track time to treatment, dose (number of weeks engaged), time to completion, and treatment completion (yes/no).

Synchronous CBT-CP. VHA Evidence-Based Psychotherapy CBT-CP[18] (referred to as in person CBT-CP) is a 10-session intervention containing skills similar to those contained in COPES (IVR- CBT-CP). In general, patients attend weekly, individual, 50-minute treatment sessions with a previously trained CBT-CP therapist. Synchronous CBT-CP will include individual or group in-person treatment and virtual treatment provided by VA video connect (VVC), Zoom, Skype, telephone, or other similar platforms that allow the patient and clinician to have real-time interaction, A detailed therapist manual[18] (https://www.va.gov/painmanagement/docs/cbt-cp_therapist_manual.pdf) provides pain education, case examples, and session by session guidance on treatment delivery. Following an initial assessment session, patients learn one pain coping skill per week. Patients set goals with their therapists and are asked to regularly practice the pain coping skills they are learning in treatment at home. Therapists give feedback regarding goal accomplishment. Although all CBT-CP therapists have undergone training and demonstrated CBT-CP specific competencies, it is anticipated that they will still display a range of experience and skill in delivering the intervention and maintaining fidelity to the treatment manual. In the spirit of pragmatic trials, we will not attempt to impose fidelity to the treatment manual, or provide specific training or feedback, but will monitor the quality of treatment delivery. Using electronic health record clinical notes we will track participant time to treatment, dose (number of weeks engaged), time to completion, treatment quality, and treatment completion (yes/no). Thus, in person-CBT-CP will be delivered as it would in usual clinical practice.

5.2 Handling of Study Interventions

Centralized intervention delivery. COPES (IVR CBT-CP) will be delivered from VACHS to all study sites. No additional clinicians will be placed in the study sites. Because COPES can be delivered centrally, by a core group of therapists who receive training and use therapist manuals and feedback scripts to further standardize treatment provision, COPES can be provided with a high degree of fidelity to the original treatment and is less subject to drift than synchronous treatments. The therapist manual and treatment script library is part of the manual of procedures for the intervention.

Control Condition: Synchronous CBT-CP. VHA Evidence-Based Psychotherapy CBT-CP[18] (referred to as CBT-CP) is a 10-session intervention containing skills similar to those contained in COPES. Synchronous treatment will include individual or group in-person treatment and virtual treatment provided by VA video connect (VVC), Zoom, Skype, telephone, or other similar platforms that allow the patient and

clinician to have real-time interaction, We will not try to alter local adaptations, though we will assess for their presence prior to site enrollment and we will examine each participant's EHR to determine the treatment they received (platform, individual/group). During the site selection interview process we ask about local adaptations (group, telehealth administration of CBT-CP and number of treatment sessions). We will send sites an email inquiry 3 times per year to assess for any new adaptations. A detailed therapist manual[18] developed and published by VA provides pain education, case examples, and session by session guidance on treatment delivery. It is available at the VA Evidence-based Psychotherapy website. Following an initial assessment session, patients learn one pain coping skill per week. Patients set goals with their therapists and are asked to regularly practice the pain coping skills they are learning in treatment at home. Therapists give feedback regarding goal accomplishment. CBT-CP will be delivered as it would in usual clinical practice.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

We anticipate that patients will continue to engage in usual pain care. Information about participants' use of inpatient and outpatient care will be obtained from the EHR (see Table 4). We will extract from the EHR instances of pharmacological and non-pharmacological pain care received by COPES and CBT-CP participants beginning at randomization (baseline). Because complementary and integrative health (CIH) interventions and pain-specific psychological interventions are not uniformly coded and can therefore be difficult to identify in the EHR, we will work with study sites during the UG3 planning phase to identify local pain care offerings and coding practices for these interventions. One of the final steps will be collecting information regarding CIH offerings at the site and specific coding practices for these offerings. This information will be obtained through a combination of a survey and informational interview with local site personnel. We will assess experience with the most common CIH interventions during the screening assessment call using the PMC3 harmonized measure. We will ask patients about pain treatment received outside of VHA.

Table 4 Components of Usual Pain Care

EHR Identified	**Treatment identified with local input**
Physical therapy	CBT-CP
Injections	Yoga
Chiropractic care	Mindfulness meditation and Mindfulness-based Stress Reduction

TENS	Acceptance and commitment therapy (ACT)
Spinal cord stimulator	Pain school or other behavioral + PT or exercise
Pain Clinic	Tai Chi
Physiatry	Massage
Emergency and urgent care	Acupuncture
Opioid pain medication dispensed	
Non-opioid pain medication dispensed	

5.3.2 Required Interventions

n/a.

5.3.3 Prohibited Interventions

As noted in the exclusion criteria, participants who are engaging in CBT-CP or interventions that would likely produce pain will be excluded (e.g., surgery).

5.4 Engagement, Adherence, and Completion Assessment

We will track time to treatment, dose, engagement (did the participants begin treatment) as well as adherence (how many sessions did the participant attend), time to complete treatment, and completion (attend all 10 treatment sessions/weeks yes/no).

Engagement. Because the most frequent drop out point in our prior trials has been after randomization, but prior to attending any treatment sessions, we will track participant engagement (did the participant begin treatment). Patient engagement will be defined as a patient attending at least one session of CBT-CP or completing at least one treatment week of COPES.

Dose. We will track participant adherence (number of weeks engaged in IVR-CBT and number of sessions attended in in-person CBT-CP).

Completion. We will identify the number of participants who complete all 10 treatment sessions (completion=yes/no).

Engagement, adherence, and completion will be identified for COPES (IVR CBT-CP) patients by measuring number of weeks that the participant was participating in COPES (at least one call answered/week through the COPES IVR system and in synchronous CBT-CP through examining number of treatment sessions attended as

documented by treatment notes in the electronic health record. For workload credit and co-payment billing purposes all synchronous sessions are recorded in the VA electronic health record. Study staff will collect session attendance and treatment format data at the same time that they do the post-treatment chart review for adverse events. We will perform subgroup analyses for the primary outcome and engagement.

Variable	Collection
Time to treatment from randomization (access- time to first treatment session)	Collected from electronic health record review by study RAs.
Number of treatment sessions received (burden- dose)	Number of sessions (weeks for IVR) attended
Engagement-Did participant complete one session	Collected from electronic health record review by study RAs using notes or CPT codes
Time taken to finish treatment	Number of days between randomization and last treatment session
Fidelity / quality assurance	Treatment quality checklist for both conditions. Assess presence of pain coping skill teaching, treatment session length (synchronous) skill practice, homework assignment and assessment of adherence to practice.
Treatment characteristics	Format (in-person, VVC, Skype) and mode (individual/group)
Treatment completion	Did participants complete full course of treatment (y/n)

No recruiting, consenting, randomizing, or assessment will occur at the non-engaged sites (non-engaged sites are sites where patients are recruited, but no study staff are present) so there is no need to monitor locally their activities for compliance (please see Table 3 for a list of non-engaged sites). Patients randomized to synchronous CBT-CP will receive their CBT-CP from clinicians at these non-engaged sites, but in the spirit of pragmatic trials, we will not attempt to control adherence to treatment or

fidelity, but we will monitor it. The trial is designed to assess care as it is given in the real world setting.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	EHR Data	Telephone Screening	Enrollment, Randomization	Baseline Assessment	Month 1	Month 4	Month 6	Month 12
Informed Consent Form			X					
Demographics	X	X						
Pain and comorbidities Diagnoses	X							
Current CIH Treatments received inside/outside VA	X	X						
Healthcare Utilization	X							
Current Medications	X	X						
Vital Signs	X							
Inclusion/Exclusion Criteria	X	X						
Enrollment/Randomization			X					
PEG-3				X	X	X	X	X
Brief Pain Inventory (Interference & NRS scores)				X	X	X	X	X
Insomnia Severity Index				X	X	X	X	X
Pain Catastrophizing-SF				X	X	X	X	X

Assessment	EHR Data	Telephone Screening	Enrollment, Randomization	Baseline Assessment	Month 1	Month 4	Month 6	Month 12
Pain Self-Efficacy-SF				X	X	X	X	X
PHQ-8				X	X	X	X	X
Patient Global Impression of Change					X	X	X	X
Audit-C				X		X	X	X
Treatment Satisfaction (POC)						X		
COVID-19	X			X		X	X	X
Adverse Events						X	X	X
Treatment dose, quality, and characteristics	X							

6.2 Description of Evaluations

6.2.1 Screening Evaluation

The telephone screening tool to address inclusion/exclusion criteria has been attached in Appendix III.

Consenting Procedure

A waiver of informed consent and HIPAA waiver have been obtained for electronic medical record review and telephone screening procedures. The patient information sheets for consenting to participate in the trial have been attached in the Supplement I & II. Some providers will be consented for interviews regarding the implementation of the interventions.

Screening

The telephone screening tool to address inclusion/exclusion criteria has been attached in the Supplement III.

Participants will be screened for eligibility and enrolled over the telephone. We anticipate after the screening procedures, eligible participants will move directly into enrollment in the same telephone call, although no specific time period is required.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment and randomization. Patients will be contacted, screened, enrolled, and randomized in the same way whether they are self-referred (i.e., opt out letters, toll free phone number) or provider referred. After receiving a provider or patient referral, VA Connecticut study staff will contact patients by telephone, and using a semi-structured interview, assess patient interest, patient's self-reported ability to walk at least one block, presence of a landline or cellular telephone, and absence of vision or hearing loss that would interfere with participation (to confirm eligibility criteria not reliably contained in the EHR) and answer any questions patients have about the intervention (see attached script) as well as review their VA medical record to confirm eligibility. If a patient is willing to obtain treatment, study staff will read the approved consent language contained in the information sheet and will set up the patient to receive a baseline telephone assessment. Next, after baseline completion, study staff will randomize the patient. Patients who are randomized to CBT-CP will be referred to a site CBT-CP clinician by study staff using the preferred local method.

Baseline Assessments

Demographics, outcome measures, and co-variates. We will assess demographic covariates and outcome measures by extracting the data from the EHR when possible and supplementing with automated IVR call collection of the remaining data as outlined below. A limited number of demographic items will be confirmed via telephone screening. With the exception of demographic data and treatment satisfaction, outcomes and covariates will be assessed at baseline and 1, 4, 6, and 12 months post-baseline. The four-month outcome will be the primary outcome.

EHR data. The following data will be abstracted from the EHR using methods developed and refined in the Women Veterans Cohort Study, the Musculoskeletal Diagnosis Cohort study and the Veterans Aging Cohort Study, all conducted at the PRIME Center.

Socio-Demographics. Socio-demographic characteristics of participants will be collected via VHA electronic data and the Corporate Data Warehouse on the day of randomization. Variables will include age, gender, race/ethnicity, and marital status. These same databases will also provide a record of health care encounters and coded ICD-9 or 10 data associated with VHA inpatient and outpatient encounters. .A limited number of demographic items will be confirmed via telephone screening.

Painful Conditions (MSD). We will examine the 36 most commonly used ICD-10 diagnostic codes within the musculoskeletal code (M code) grouping. In our planning period activities, we found that only 36 codes were used in 0.05% or more of VHA encounters in both 2016 and 2017. They represent spine pain, joint pain, osteoarthritis, fibromyalgia, and rheumatoid arthritis. All diagnoses will be identified via ICD-10 code, as described above, on the date that eligibility was met. We will use diagnoses that were made in the year prior to randomization.

Distance to nearest VHA facility. Using the patient's home address as indicated in the EHR, we will calculate the distance from their home to the relevant study site in miles as calculated by Google Maps.[80]

Opioid medications dispensed in morphine equivalent daily dose. Dispensed opioid medications will be extracted and converted to morphine equivalent daily dose. Opioid medications include: butorphanol, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, and tramadol.[81]

Non-opioid pain medications dispensed. Dispensed non-opioid pain-related medications also will be extracted, including topical analgesics, non-steroidal anti-

inflammatory drugs, anticonvulsants, and antidepressants (specifically, selective serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants as in Dorflinger et al.[82]).

Non-pharmacological pain care. Visits to specialty services associated with non-pharmacological pain care will be extracted from the EHR using clinic stop codes. These services include physical therapy, physiatry, multidisciplinary pain clinic, chiropractic care, CIH, pain school, and psychological interventions pertaining to pain (CBT-CP, ACT, biofeedback). Non-pharmacological pain care will be assessed in the 12 months leading up to enrollment for the baseline assessment. Subsequent assessments will include all instances of non-pharmacological pain care since the prior assessment.

Use of emergency department and urgent care, VHA services. Emergency department and urgent care visits will be extracted from the EHR using stop codes 130 and 131. We do not have access to non-VA emergency and urgent care and will not collect this data.

Mental Health and other Physical Comorbidities. Comorbid mental health diagnoses will be identified when two or more of the same outpatient diagnosis codes are assigned within 18 months, or one or more inpatient codes). Mental health conditions will include depressive disorders (i.e., major depressive disorder, dysthymia, depression due to other causes or not otherwise specified), anxiety disorders (i.e., anxiety disorder not otherwise specified [NOS], panic disorder, generalized anxiety disorder, agoraphobia with and without panic, other anxiety states), bipolar disorder, PTSD, alcohol use disorders, and drug use disorders. Other physical health conditions will be identified in the same manner. These include conditions contained on the Charlson Comorbidity Index[96].

Daily IVR assessment calls. COPES participants will a undergo daily IVR assessment of pain intensity, pain interference, pedometer-measured step counts, sleep quality, sleep duration, and positive and negative affect for seven days to establish a baseline of function for the purposes of treatment.

Substance Use Diagnosis. We will abstract from each participant's VA electronic health record current (in the past 12 months) and past diagnosis of alcohol use disorder (diagnosis prior to the past 12 months.

Synchronous treatment characteristics. A trained research assistant will review each participant's electronic medical record at the completion of treatment to collect treatment characteristics, (platform, mode), time to treatment, treatment dose, time to completion, completion (y/n), and treatment quality.

IVR-collected outcome data. In addition to passively collected EHR data, we will actively collect patient-reported outcome data using automated IVR calls at baseline,1, 4, 6, and 12 months. COPES patients will receive regular IVR assessments as part of the COPES intervention. At the baseline and follow-up periods they will be asked to complete the outcomes assessment at the end of a regularly scheduled call. CBT-CP patients will be enrolled in the IVR system after randomization and scheduled for assessment calls at baseline, 1, 4, 6, and 12 months. They will be informed of the 5-10 minute automated telephone interview to assess their pain and physical and emotional functioning, sleep, and satisfaction with their pain care at baseline and in 1, 4, 6 and 12 months. All measures demonstrate strong psychometric properties. IVR assessment allows us to collect outcomes data in a pragmatic, low burden manner, with no need for an in-person visit. We will not reimburse participants for cellphone minutes.

We will measure multiple IMMPACT-recommended dimensions of pain care,[83] including self-reported pain intensity, pain-related physical functioning, and emotional functioning. Our primary outcome will be the Interference subscale of the Brief Pain Inventory Score,[68] which is a score of patient-reported pain-related interference. The BPI has been shown to be sensitive to change and to have good reliability. Depression symptom severity will be assessed using the 8-item Patient Health Questionnaire (PHQ-8)[84] a widely-used measure with excellent internal consistency and stability. Sleep quality will be measured using the Insomnia Severity Index [86] and will assess subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Catastrophizing will be measured using the Pain Catastrophizing Scale-Short Form(PCS-SF) a 2-item self-report scale that examines thoughts and feelings people may experience when they are in pain including rumination, magnification, and helplessness.[87] Self-Efficacy will be assessed using the 2-Item Short Form of the Pain Self-Efficacy Questionnaire (PSEQ-2).[88] The Patient Global Perception of Change scale is a single item measure that quantifies a participant's overall perception of improvement since beginning treatment and the clinical importance of that improvement. Participants indicate improvement on a 7 point "much worse" to "much better" scale. This is a well-validated measure recommended by IMMPACT.[64] We will use the AUDIT-C, a reliable brief alcohol screen using a 3 month timeframe, to identify patients who are hazardous drinkers or have active alcohol use disorders.[98] We will assess non-VHA delivered pain care by asking if any pain care has been received outside VHA (yes/no), was this care paid for by VHA through fee-basis referral or the Choice Act (yes/no), and the specific modalities that have been obtained (yes/no) for physical therapy, psychiatry, pain clinic, interventional pain medicine, psychological treatments, CIH, chiropractic care, acupuncture, emergency or urgent care).

COVID-19 Assessment: We will assess each participant's COVID-19 status and its effect on their lives. These questions are recommended by the PMC3 and will be evaluated during baseline and follow-up IVR assessments. (See appendix VI).

Randomization

Randomization Participants will be randomized in a 1:1 ratio to one of the two treatments (COPES or synchronous CBT-CP). The randomization sequence will be generated by the study statistician using statistical software and concealed in the study database until the time of randomization. We will randomize participants during the enrollment call. Randomization will be stratified by site and gender and will be done according to a permuted block design with variable block size (4 and 6) in order to maintain balanced treatment assignment.

6.2.3 Blinding

IVR assessment calls are automated so all data collection is blinded. Due to the nature of behavioral interventions, neither patient or provider will be blinded to their treatment condition. The statistician will be blinded. An independent statistician will create the randomization allocation schedule and this schedule will be incorporated into the IVR system so that it will remain masked. We will work with the Yale Center for Analytical Sciences to obtain statistical support for the DSMB report preparation and meetings and other tasks that will involve unblinded data. This will allow us to have a blinded statistician.

6.2.4 Follow up Visits

Follow-up information will be collected by the IVR system; there will be no in-person visits. With the exception of demographic data and treatment satisfaction, outcomes and covariates described in the baseline will be assessed at 1, 4, 6, and 12 months post-baseline. The four-month outcome will be the primary outcome. Follow-up assessments may be collected anytime within the window of 1 week prior to the planned assessment date to one month after. In order to minimize missing data, when participant do not complete the planned IVR assessment we will attempt to collect the information using telephone interview or survey mailing to the participant's home.

Various domains of pain treatment satisfaction will be assessed using a subscale of the Patient Outcomes Questionnaire at the four month outcome timepoint. This 5-item measure shows good internal consistency and significant associations with staff and patient ratings of patient improvement.[85]

6.2.5 Completion/Final Evaluation

The final visit will be the same as the follow up visits listed above.

7. SAFETY ASSESSMENTS

Study progress and safety will be reviewed monthly. Progress reports, including patient recruitment, retention/attrition, and adverse events (AEs) will be provided to the Independent Monitor(s) semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis. The IRB and NCCIH Program Officials will receive copies of all study monitoring/audit or inspection reports within 14 day of PI receipt.

Table of reporting activities

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
Data entry quality control checks on 10% of charts	Weekly	QA Reviewer
Adherence data regarding study visits and intervention	A monthly report will be prepared containing information on those assessed. Participants will be assessed at the end of treatment and subsequent assessment points	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
AEs and rates	A monthly report will be prepared containing	PI, Internal QA Reviewer

	information on those assessed. Participants will be assessed at the end of treatment and subsequent assessment points	
	Semi-annually	Independent Monitor(s)
	Annually	NCCIH, FDA (If Applicable)
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitor (s) NIH/NCCIH, FDA (if applicable)
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer
	Annually	Independent Monitor (s), NIH/NCCIH
Unanticipated Problems	Monthly	PI, Internal QA Reviewer
	Per Policy	IRB, FDA (if applicable)

7.1 Specification of Safety Parameters

The interventions are minimal risk and in fact are two forms of guideline recommended non-pharmacological care for chronic pain already provided in the VHA system. Adverse events will be reported by patients via the IVR system and/or medical records review.

COPES (IVR CBT-CP) and synchronous CBT-CP are minimal risk interventions and CBT-CP and its variants are considered standard of care for chronic pain. COPES (IVR-CBT-CP) participants will be centrally treated at VACHS. Regular meetings will be held between the PI and study staff members who will be delivering the intervention locally from VACHS Additionally, for the synchronous CBT-CP participants study staff will review participant's electronic health records to identify AEs and UPIRSO.

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

Suicide risk assessment.

The interventions in this trial are not believed to increase suicidal ideation, and in fact may be beneficial in improving emotional functioning. However, in the course of baseline or post-treatment and follow-up assessment we may learn information about patient's suicide risk. Participants will complete questionnaire measures via the study IVR system. If they answer any questions in a manner that indicate elevated risk (PHQ-8 score >=10), they will be automatically asked by the IVR system if they would like to be connected to the Veteran Crisis line. This allows the Veteran to choose to be transferred without hanging up and making another call. We have successfully used this process in prior studies.

During any IVR call (assessment or treatment) participants have the option of connecting to the Veteran Crisis Line. Participant's primary care physician will be informed of any important discoveries made during this study that may affect the patient, their condition, or their willingness to participate in this study. If we discover that the patient is experiencing suicidal thoughts, we will share this with the primary physician immediately (VA patients are assigned to a primary care provider and this provider is noted in their electronic health record). If the participant is receiving care from a mental health provider that person will also be alerted.

Synchronous CBT-CP. VHA Evidence-Based Psychotherapy CBT-CP[18] (referred to as synchronous CBT-CP) is a 10-session intervention containing skills similar to those contained in COPES. Patients attend weekly, individual, 50-minute treatment sessions with a previously trained CBT-CP therapist. A detailed therapist manual[18], available on-line, provides pain education, case examples, and session by session guidance on treatment delivery. Therapists in this condition will use clinical judgement and follow VA suicide risk procedures as is required of all VA mental health clinicians. Therapists are required to document suicide risk evaluations and follow-up procedures. Study staff will be able to detect these events when reviewing patient electronic health record data for adverse events. Clinical action for suicide risk evaluation and management identified during synchronous CBT-CP sessions will be managed by local clinicians, not study staff.

7.3 Adverse Events and Serious Adverse Events

Definition of adverse events and unanticipated problem involving risks to subjects or others (UPIRSO): The following definitions of adverse events are included in the NCCIH toolbox DSMP information and we have adopted these same definitions for use in monitoring the safety of participants in the proposed project. We will report all AEs, SAEs, and UPIRSOs to the NCCIH and VA Central IRB as required.

Adverse event (AE): An AE is defined as any untoward physical or psychological occurrence in a human participant taking part in research. An AE can be any

unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment.

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

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

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Adverse Event (UAE): An UAE is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.

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

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

Time Period and Frequency for Event Assessment and Follow-up

Unanticipated problems will be recorded in the data collection system throughout the study. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Participants in the COPES (IVR-based CBT-CP) intervention will be asked to report any AEs weekly. At each follow-up assessment point study staff will examine participant electronic health records for the occurrence of AE/SAEs since the last assessment. Events will be followed for outcome information until resolution or stabilization.

Characteristics of an Adverse Event

Relationship to Study Intervention

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

1. Related (Possible, Probable, Definite)

a. The event is known to occur with the study intervention.

b. There is a temporal relationship between the intervention and event onset.

c. The event abates when the intervention is discontinued.

d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)

a. There is no temporal relationship between the intervention and event onset.

b. An alternate etiology has been established.

Expectedness of SAEs

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

Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)

2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL

3.Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

7.4 Reporting Procedures

Reporting of Unanticipated Problems or Adverse Events. We will adhere to all cIRB rules and NCCIH policies regarding reporting of adverse events and UPIRSOs. Details of this plan are included below. We will notify the cIRB promptly when any SAE occurs. If the incident is serious, unanticipated and /or requires revision of the Project Description and/or Consent Form, we will notify the cIRB by telephone as soon as possible and always within 24 hours and complete the Unanticipated problem form found in the NCCIH toolbox (https://nccih.nih.gov/grants/toolbox/pdfs). A formal report will be provided within two business days. Study progress including subject recruitment, completion of protocol, and adverse events will be reviewed by Eugenia Buta, PHD, study biostatistician. These results will be presented to the study PI. Please see reporting table below for information on the frequency of assessment and reporting.

Table of reporting activities

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
Data entry quality control checks on 10% of charts	Weekly	QA Reviewer
Adherence data regarding study visits and intervention	For each participant at the end of treatment or at drop-out/withdrawal A monthly report will be prepared containing information on those assessed.	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)

AEs and rates	For each participant at the end of treatment and subsequent assessment points A monthly report will be prepared containing information on those assessed.	PI, Internal QA Reviewer
	Semi-annually	Independent Monitor(s)
	Annually	NCCIH, FDA (If Applicable)
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitor (s) NIH/NCCIH, FDA (if applicable)
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer
	Annually	Independent Monitor (s), NIH/NCCIH
Unanticipated Problems	Monthly	PI, Internal QA Reviewer
	Per Policy	IRB, FDA (if applicable)

Reporting for sites- because there are no study staff at non-engaged sites, there is no site PI to report adverse events or UPIRSOs. We will collect AEs and UPIRSOs from IVR reports and review of electronic health records as described above, thus communication from local site personnel is not needed.

Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

All unanticipated problems will be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Adverse Event Reporting of Non-IND Studies

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), VA cIRB, Yale IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements. and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

7.5 Follow-up for Adverse Events

During the follow-up assessment points, study staff will retrospectively examine participants' electronic medical record to determine if AEs, SAEs, or UPIRSOs have occurred and report to the cIRB, NCCIH, the IC as outlined above

In the COPES (IVR-CBT-CP) condition, participants will be monitored weekly for the full 11 weeks of the study. All participants will be monitored using automated IVR calls at multiple study timepoints (baseline,1 4, 6, and 12 months). Safety data will only be retrospectively collected during post follow up assessments.

7.6 Safety Monitoring

We will follow NCCIH guidelines for independent monitoring
A Data and Safety Monitoring Committee (DSMC) will be appointed by NCCIH to review study progress, assess the adequacy of ongoing enrollment & site performance, ensure adequacy of data acquisition & protocol adherence and evaluate overall safety throughout trial implementation. The DSMC will meet at least annually after trial initiation. A DSMC Charter Document outlining the operating guidelines for the committee, the frequency of planned meetings and the specific data presentation format will be agreed upon during the initial meeting of the DSMC. Study reports will be created by the study data center, following a standardized format, as directed by the DSMC. The DSMC will report directly to NCCIH.

8. INTERVENTION DISCONTINUATION

If the principal investigator decides that a participant is not appropriate for the study, they could be withdrawn from the study intervention, even if they want to continue. However, consistent with an intention-to-treat study, participants will not be removed from study follow-up. This could happen if a participant no longer meets the requirements for the study, if participants are not able to do things required by the study, if it becomes medically unsafe for them to continue, or if approval to conduct the study is withdrawn. Regardless of whether or not the participant is withdrawn from this study, they will still get medical care as usual from their VA healthcare team. Withdrawal from the study does not result in any risk to the patient, thus no special procedures are planned for those who choose to withdraw on their own or who are withdrawn from the study by the PI.

Participation in this study is entirely voluntary. If a participant chooses not to enroll or withdraw after the participant has started, he/she will not be penalized in any way, nor will the quality of care received be affected. If a participant should choose to re-enroll after withdrawing, they may if they are still eligible. They may participate in the intervention up to the 14-week from baseline cutoff. If the participant decides not to participate in this study, the Veteran may receive CBT for pain or similar treatment at the local VA Healthcare System, though may need to come to the medical center for appointments rather than receive treatment by phone.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The study is a two-arm, parallel design, pragmatic, randomized clinical trial testing the superiority of IVR-based CBT (COPES) versus VHA synchronous CBT-CP for the treatment of chronic pain. Our prior efficacy trial found that COPES was

noninferior to CBT-CP and that participants attended, on average, a little over two more treatment weeks in COPES than in-person treatment, presumably due to the ease of in-home treatment attendance relative to in-person treatment. Although we did not find superiority in our original trial, COPES may be superior in less tightly controlled circumstances. In real world treatment settings, several factors may lead to patients obtaining a lower dose of synchronous CBT-CP relative to COPES. This may lead to less robust outcomes for CBT-CP than in tightly controlled efficacy trials where treatment dose, adherence and fidelity are closely monitored and regulated.

The randomization and treatment will occur at the patient level; however, the intervention will be delivered by a limited number of therapists and there may be some clustering due to patients sharing a therapist (i.e. outcomes for patients using the same therapist may be more similar to each other than outcomes for patients using different therapists). We consider this clustering both in our power calculation (section 9.2) and in our analysis plan (section 9.6).

The primary hypothesis is that COPES will be superior to synchronous CBT-CP in terms of the self-reported pain functionality outcome as measured by the interference subscale of the Brief Pain Inventory (BPI) at 4 months post-baseline. Secondary hypotheses are that COPES will be superior to CBT-CP in terms of the secondary and tertiary outcomes listed in section 9.5.2 below (including depressive symptom severity, , pain catastrophizing etc.).

9.2 Sample Size and Randomization

Assuming a standard deviation of BPI interference of 2.4 (as observed in a previous study (SCOPE)[99]), a total sample size of 610 subjects (305 per group) would provide 80% power to detect a mean difference in BPI interference of 0.55 between groups at 4 months using a two-sided t-test at significance level alpha=0.05, and 90% power to detect a difference of 0.63. To account for an expected attrition rate of 20%, we will enroll a total of 764 participants (382 per group). Half of the participants will be female.

Although the randomization will be done at the patient level, there may be some clustering due to the therapist delivering the intervention. We conducted a simulation study to investigate the effect of this clustering on power. We assumed that in the COPES arm (treatment delivered remotely by IVR) 9 therapists will be delivering the intervention (each to an equal number of subjects), and in the synchronous CBT arm 38 therapists will be delivering the intervention. Based on a prior pain trial of group cognitive behavioral treatments[97], we used an estimate of therapist-level intracluster correlation coefficient (ICC) of 0.01. Simulations (N=100000) showed that we will

have at least 84% power to detect a difference in BPI of 0.65 with an ICC of 0.01 or less using a mixed model on the outcome at 4 months with a therapist random effect.

Treatment Assignment Procedures

After receiving a referral from a clinician at a study site, VA Connecticut study staff will contact patients by telephone, and using a semi-structured interview, assess patient interest, eligibility and answer any questions patients have about the intervention. Patients will also be allowed to enroll in the study by self-referral. We will use recruitment materials (posters and business cards) to allow patients to contact us directly at our 1-800 number to request enrollment. Data on source of referral (self/provider) will be tracked in the enrollment database.

If a patient is willing to obtain treatment, and completes the baseline survey, study staff will randomize the patient. Subjects will be randomized in a 1:1 ratio to one of the two treatments (COPES or CBT-CP). The randomization sequence will be generated by the study statistician using statistical software and concealed in the study database until the time of randomization. Randomization will be stratified by site and gender and will be done according to a permuted block design with variable block size (4 and 6) in order to maintain balanced treatment assignment. Patients who are randomized to in person CBT-CP will be referred to a site CBT-CP clinician by study staff using the preferred local method identified by staff interview in the UG3 period. Participants randomized to COPES will be referred to a VA Connecticut COPES therapist.

9.3 Definition of Populations

Analyses of all outcomes will be done according to the intent-to-treat principle, that is, subjects will be analyzed in the treatment group to which they were randomized. To include all subjects in the primary analysis (including those who have only baseline assessments), our primary analysis will be a mixed model over all measurements (including baseline) with the restriction that the two groups have equal means at baseline (i.e. the primary analysis will be a constrained longitudinal data analysis). Missing data, which hinders the ability to perform a strict ITT analysis, is inevitable in this pragmatic trial. However, we will try to minimize the amount of missing data by following the National Research Council's recommendations[100]on strategies for preventing missing data in clinical trials (e.g. try to collect outcome data on subjects who discontinue therapy). Also, we have incorporated into the analysis plan (section 9.6) several sensitivity analyses for assessing the impact of missing data on the results.

9.4 Interim Analyses and Stopping Rules

We acknowledge that of the rationale for superiority of IVR CBT has diminished because instead of in-person treatment, control participants can now obtain videoconference or telephone CBT-CP from their homes. However, we still expect IVR CBT will be superior. We assume that dose will be greater in the IVR condition because patients can access treatment at any time, not just during business hours and session time is shorter reducing therapist and participant burden relative to the control condition. Time to treatment will be shorter in IVR because the centralized delivery of IVR CBT allows more efficient use of therapist resources. There is relatively little information reported in the literature about dose in videoconference treatment and none about time to treatment relative to in-person treatment so there is little information to guide these estimates more precisely. We have proposed to monitor these and other factors that we believe will continue to be different, and show an advantage for the IVR condition, as part of the trial (see below).

Monitoring Separation Between Arms: We will monitor indicator variables (below) on treatment delivery, uptake and quality to determine whether the treatment arms are diverging in ways expected to drive differences in clinical outcomes. We will continuously monitor the indicators and calculate the means and confidence intervals of each indicator for both groups and for the difference between groups. These data will be shared with the DSMB at the regularly scheduled DSMB meetings occurring every 4 months and at 50% of participant treatment completion and used to assess whether there is divergence between the treatment conditions. These data may be used to inform a future futility analyses if needed once adequate data is collected [50% participants (n=382) completed treatment].

Indicator	Description
Dose	# of sessions/weeks attended including only those with ≥ 1 session
Engagement	% who initiate treatment (attend first treatment session)
Minimal dose	% who achieve minimal dose (minimal dose=3 sessions/weeks)
Time to treatment initiation	Time from randomization to first treatment session or IVR call among those with ≥ 1 session
Quality assurance	Ratio of #skills taught/#sessions among those with ≥ 1 session

9.5 Outcomes

9.5.1 Primary Outcome

Our primary outcome will be the interference subscale of the Brief Pain Inventory (BPI) score at 4 months post-baseline, which is a measure of patient-reported pain-related interference (0-10 scale, with higher values indicating more pain) and has been shown to be sensitive to change and to have good reliability. This outcome will be collected via the IVR automated call system.

9.5.2 Secondary and Tertiary Outcomes

Secondary outcomes will include BPI interference scores at 6 and 12 month post-baseline, and other outcomes collected via IVR automated call system at 4, 6 and 12 months post-baseline: NRS pain intensity rating, PEG-3 pain scale, depressive symptom severity (PHQ-8), pain catastrophizing, Insomnia severity index, Pain Self-Efficacy scale, Patient Global Impression of Change (4 months only), treatment dose and treatment satisfaction (collected at 4 months only).. Tertiary outcomes include time to treatment, time to completion, treatment completion (y/n), treatment fidelity/quality, treatment completion (y/n), and patient engagement (a patient attending at least one session of CBT-CP or completing at least one treatment week of COPES). Details on the instruments used to collect these outcomes and their psychometric properties are provided in section 6.2.2, "Baseline Assessments."

To evaluate the intervention delivery costs of COPES and conduct a budget impact analysis. We will examine the intervention costs associated with COPES(IVR-CBT-CP) including the cost of therapist time and technology costs. We will also examine VA service use across both treatment conditions (primary care, mental health, specialty care, emergency and urgent care visits).

To conduct a process evaluation using the Consolidated Framework for Implementation Research (CFIR) and RE-AIM to guide the evaluation. We will conduct CFIR-guided interviews with coordinating site clinicians and study site clinicians and administrators to assess their experience with and views regarding the strength and weaknesses of COPES (IVR-CBT-CP) and synchronous CBT-CP interventions. We will also examine domains included in the RE-Aim model for both interventions.

9.6 Data Analyses

Quantitative Analysis. As an estimate of uptake, we will present the proportion of patients who agree to be randomized out of all who are offered referral to treatment in our study. Randomization success will be assessed by side-by-side summaries of

baseline demographic and clinical characteristics of subjects by treatment group. Analyses of all outcomes will be done according to the intent-to-treat principle.

Primary Analysis. We will test and estimate the difference between COPES and CBT-CP in terms of BPI interference by using a linear mixed-effects model which simultaneously models all available BPI interference measurements including baseline. The model will contain fixed effects for treatment (categorical: COPES vs. CBT-CP), site (categorical), gender (categorical), time (categorical: baseline, 1, 4, 6, 12 months), and the treatment-by-time interaction. The only covariates that will be included in the primary and secondary analysis (including subgroup analyses) are site and gender. We are adjusting for these 2 variables because they are used for stratification in randomization. An unstructured variance-covariance matrix will be used to model correlations among repeated measures within a subject, and a therapist random effect will be used to model the correlation of outcomes in subjects who share the same therapist. Because this is a randomized trial, in the model above we will impose the constraint that the means for the two groups are equal at baseline (that is, we will perform a constrained longitudinal data analysis). Following the CONSORT recommendations, we will not perform any test for baseline differences as these tests are not needed in a randomized clinical trial "Such significance tests assess the probability that observed baseline differences could have occurred by chance; however, we know that any differences are caused by chance" This model will allow us not only to assess the between-group difference at 4 months (primary endpoint), but also to evaluate in secondary analyses whether between-group differences are maintained over time (at 6 and 12 months). Results will be summarized as least-squares means (and their 95% confidence interval) within and between groups. The primary analysis will be conducted at significance level 0.05.

Sensitivity Analyses. If there is heterogeneity in therapist-specific time trends, then our primary analysis may have an inflated Type 1 error rate.[105] As a first sensitivity analysis, we will use the 4-month outcome as the dependent variable in a mixed model ANCOVA. The model will have fixed effects for treatment, site, gender, baseline BPI interference, and a therapist random effect. To deal with missing data, this analysis will be applied to multiple imputed datasets (see Missing Data Sensitivity Analyses section). We will check whether the conclusion from this analysis regarding the treatment effect is consistent with the conclusion from the primary analysis.

As a second sensitivity analysis, we will use a mixed model similar to the primary analysis model, except that time will be treated as continuous. We will check the linear time assumption by considering other polynomials (e.g. quadratic, cubic).

Secondary Analyses. We will use Holm's correction to adjust for multiple secondary analyses. We will also conduct a per protocol analysis as an adjunct to the ITT primary analysis defining a "dose" of treatment as having attended/answered calls for 3 treatment sessions.

IVR-collected data. Analysis of the continuous secondary outcomes collected by IVR (PEG-3, PHQ-8, Pain Catastrophizing Scale, Insomnia Severity Index, Pain Self-Efficacy Scale,) will be similar to the primary analysis. We will use a generalized mixed model for ordinal data to analyze the Patient Global Impression of Change outcome.

We will compare treatment dose (number of sessions, a count variable) and treatment satisfaction at 4 months (continuous) between groups by using a negative binomial generalized linear mixed model and linear mixed model, respectively. The models will include treatment, site and gender as fixed effects, and a random effect for therapist.

Tertiary Analysis Engagement/Dose/Completion. Patient engagement will be defined as a patient attending at least one session of CBT-CP or completing at least one treatment week of COPES. Time from randomization to treatment, time from randomization to completion, completion (y/n, a binary variable will be examined. For workload credit and co-payment billing purposes all sessions are recorded in the VA electronic health record. Study staff will collect session attendance data at the same time as they do the post-treatment chart review for adverse events. We will compare engagement, and completion between groups by using logistic generalized linear mixed models. Time to treatment and time to completion will be analyzed using Cox proportional hazards models. All models will include treatment, site and gender as fixed effects, and a random effect for therapist.

Recruitment Method: Patients will be recruited by 2 different approaches (provider referred or self-referred). We plan to examine potential differences in patient characteristics by recruitment type. First, we will present descriptive statistics for recruitment type in each treatment arm and overall in Table 1. If the sample sizes in the two recruitment type groups are sufficient (>=30 in each group), we will include a supplemental table comparing the two groups on the baseline characteristics included in Table 1. We will compare baseline continuous characteristics using a t-test or Wilcoxon rank sum test, and categorical characteristics using the chi-square test or Fisher's exact test as appropriate.

Subgroup Analyses. To test whether between-group differences in outcome vary by gender, race/ethnicity comorbid substance use disorder, and alcohol use subgroup analyses will be performed via interaction tests. For example, to perform the race subgroup analysis for the primary outcome, we will enter race, the interactions race-by-time, race-by-treatment and race-by-time-by-treatment into the primary analysis models: the last two interactions will allow us to test whether race is a moderator of the treatment effect. We will perform subgroup analyses for the primary outcome and engagement. Subgroup analyses for other outcomes and subgroups (such as PTSD, depressive disorder) may be conducted as exploratory analyses.

Missing Data Sensitivity Analyses: The inferences from the mixed model described above for the primary analysis are valid under the missing-at-random (MAR) assumption. This assumption cannot be verified based on the observed data, but we will perform sensitivity analyses to assess how results change under different missing data assumptions.

Patterns of missing data

As a first step towards assessing the potential missing mechanism, we will examine the pattern of missing data and dropout in each treatment arm (both dropout from the therapy and dropout from participating in the survey). We will tabulate all missing data patterns and percent missing data at each time point by treatment arm. Additionally, we will examine missingness by reason for dropout. We will also plot mean outcomes over time by treatment group and time of last recorded measurement (i.e., subjects who have their last assessment at baseline, subjects who have their last assessment at 1 month, etc.). This will allow us to assess patterns in outcome prior to the last recorded measurement. An association between dropout and prior values of the outcome (e.g., those with worsening or non-improving pain more likely to drop out) will indicate a possible deviation from MCAR and that some of the missingness may be MAR.

Since it is not possible to distinguish between MAR and MNAR based on observed data, we will run our primary analysis under the MAR assumption (mixed model) and conduct sensitivity analyses to see how results change under different missing data assumptions.

Baseline predictors of missing data

We will present and compare baseline characteristics (age, sex, race/ethnicity, mental and physical comorbidities) between those with missing outcome data at each follow-up time point (and at any timepoint) and those with available data. Comparisons will be done using t-tests and chi-square tests.

Sensitivity analyses under MAR

If we find baseline variables not included in the original models to be associated with missingness (which would suggest that the MAR assumption was not reasonable for the original models), then we will conduct sensitivity analyses to gauge the effect of including those baseline variables as covariates in the mixed-effect models evaluating the difference between groups.
As a second sensitivity analysis under MAR, we will use multiple imputation based on chained equations (full conditional specification (FCS) imputation approach[101]) to impute missing variables. The FCS approach is applicable to both monotone and intermittent missing data, and to both continuous and categorical variables. The imputation model will be more general than the analysis models and will include the primary/secondary outcomes measured at all time points, treatment group, all stratification variables and baseline variables. In order to use the EHR pain NRS data (measured at irregular intervals) in the imputation process, we will aggregate it at the monthly level (e.g. obtain a mean NRS for each subject and month). One hundred imputed datasets will be generated using PROC MI in SAS with the FCS method. Following Rubin's rule for multiple imputation inference, each of the simulated complete datasets will be analyzed by standard methods (using mixed models like those used for the primary analysis), and the results will be combined to produce results that incorporate missing-data uncertainty.

Sensitivity analyses under MNAR

Further sensitivity analyses appropriate under MNAR such as pattern mixture models (PMM) will be examined. PMMs allow for the fact that subjects with different dropout patterns may have different response trajectories. We will implement PMM by including dropout pattern as a categorical variable in the primary analysis model, along with its interaction with all the other variables in the model. The dropout pattern variable will be defined based on the last recorded measurement; other definitions (e.g. based on reason from dropout) will be investigated. To get an estimate of the treatment differences from the PMM, we

will compute a weighted average of the treatment differences over the dropout patterns [102]

The multiple imputation described above gives valid results only under a MAR assumption. We will also perform multiple imputation under MNAR under different assumptions. For example, we may assume that subjects who drop out early from the treatment in the experimental group (COPES) have worse BPI interference outcomes after dropping out than those who stay in the study by adding a shift of 0.5 points to their MAR-imputed outcome. We would then vary the assumption about the shift after dropping out in both treatment groups and identify which of these assumptions would change the conclusion from our primary analysis.[103]

Responder analysis (exploratory analysis). Response will be defined as at least a 30% improvement in BPI interference score from baseline to 4 months. Reduction in pain/interference of 30% or more has been shown to be clinically meaningful and is recommended by IMMPACT that the percentage of participants who receive this reduction be reported in all clinical trials of chronic pain treatments. We will investigate predictors of response by using both logistic regression and classification trees, as classification trees can accommodate a larger number of predictors (including high order interactions) than the typical logistic regression.[90] Predictors considered will include treatment, gender, race, baseline BPI interference and other baseline variables such as comorbidities.

Propensity score exploratory analysis. If the sample size allows, we will perform an analysis of the primary outcome (4-month BPI interference) that takes into account the type of treatment received in the synchronous CBT-CP group, that is, the treatment variable will be a 3-level categorical variable: video/telephone CBT-CP, in-person CBT-CP and COPES. This analysis will allow us to compare the two types of CBT-CP against each other and separately against COPES. To balance these three groups in terms of baseline covariates, we will use inverse probability of treatment weighted estimation based on propensity scores. The weights will be estimated from generalized boosted models and the estimates will represent population average treatment effects[106, 107]. At a minimum, the propensity models will include demographics, baseline values of the outcomes, and baseline medical and mental health comorbidities. Balance among treatment groups will be evaluated by standardized differences, with values >0.1 indicating imbalance. To deal with missing data, this analysis will be applied to multiple imputed datasets (see Missing Data Sensitivity Analyses section).

Resource Use. *Intervention Costs.* Therapists will use a log to record time spent in intervention-related activities for all treatment days. Therapists will record this information on the IVR system's therapist interface using an online calendar that has mandatory data fields for this information. We will regularly review completion of this field during monthly quality assurance monitoring with weekly checks in the first month of the treatment during the trial and the first month of any new therapist's tenure. A random sample of 20% of all treatment days will be used in the estimation of personnel costs. Time records will be combined with wage data from the VA Financial Management System to estimate intervention-specific personnel costs. Technology costs of the COPES IVR program include fixed costs (e.g., software development and computer maintenance) plus variable costs (e.g., minute costs for IVR calls). One-time fixed start-up costs will be reported separately. *VA Inpatient and Outpatient Service Use* data will be obtained from the Musculoskeletal Diagnoses Cohort (MSD), a project currently underway as part of the VA Connecticut Healthcare System's CREATE. The MSD is developing validated algorithms for using VA electronic health record data to identify utilization events, comorbid conditions, receipt of opioid medications, and pain screening results, for patients with pain-related diagnoses.

Intensity of Service Use. As exploratory analyses, we will compare service utilization during the 12 months post-baseline by category (e.g., dose of opioid medication dispensed (continuous variable), number of PCP visits (count), non-opioid medication dispensed (binary), non-pharmacological pain care (binary), use of emergency department (binary) and urgent care (binary)) between groups using linear/generalized linear mixed models with an appropriate outcome distribution. We will also consider two-parts models for the opioid dose and PCP visits outcomes in case of zero-inflation. We will conduct a budget impact analysis92 and will include the cost of the intervention (personnel, supplies, CBT therapist training, and IVR fixed/variable costs) as well as costs for specific medical care services likely to be affected. Data from CBT therapists time records will be combined with wage data from the VA Financial Management System to produce estimates of intervention-specific personnel costs. Costs associated with the use of specific medical care services, such as medications, will be obtained from the VA Managerial Cost Accounting (MCA) System. Cost analysis will be conducted in accordance with the guidance provided by Sullivan et al.92 including the use of sensitivity analysis and scenarios that allow for varying assumptions about intervention uptake, compliance or component costs. All resource use and cost comparisons will be adjusted for any observed differences in baseline characteristics. Because costs of resource utilization are usually skewed, alternative modeling techniques (e.g., log-transformed costs, negative binomial regression)

will be used. Information on non-VA care will be collected by automated IVR call assessment. To mitigate recall bias, we will use a two-time frame method that asks about utilization over the past 6 months and over the past 2 months with more weight given to the shorter timeframe.

Process evaluation. In order to refine and evaluate our implementation of the proposed interventions, we will conduct a formative evaluation, with implementation-focused, progress-focused, and interpretation phases. We will use semi-structured telephone, or in-person interviews conducted by a trained research assistant under the supervision of a qualitative expert. Interview guides will be developed using constructs and questions derived from the Consolidated Framework for Implementation Research (CFIR), refined based on our experience in the COPES implementation trial and tailored to the informant group being interviewed (mental health provider, primary care provider or administrator). The interview guides are being developed and piloted in the context of another approved study and when complete, the guides will be submitted to the cIRB for approval prior to use. Interviews will be audio-recorded and professionally transcribed by a VHA-approved contractor. Participants in each of the stakeholder categories (i.e., providers and administrators) will be recruited by in-person recruitment strategies or email solicitations with the assistance of the WH-PBRN site lead. Staff interviews will be conducted with clinical staff who provide clinical care and who we anticipate will be directly involved in patient referral including primary care providers (n=2 per site), mental health providers (n=2 per site), and administrators (n=2 per site). Providers will be emailed an information sheet or asked to view it on the study website which details their participation. Interviewers or staff will go over this with the provider participant and will specifically ask about consenting to the audio recording of their voice. We will record the provider's confirmation of this consent.

Qualitative analysis. We will utilize data reduction strategies[93] to sort, focus, discard and organize data to draw inferences regarding the implementation interventions in place at each facility. We will develop a template summary of data at each facility according to a small set of pre-determined domains that align with the interview guides developed for each group of respondents. Once we have developed that summary for each facility, we will create a matrix across all facilities to understand the major issues with regards to implementation. Matrices streamline the process of noting, simultaneously and systematically, the similarities, differences and trends in response across a group of informants.[94] All interviews and focus groups will be digitally recorded for verbatim transcription (either transcribed by the transcription service previously described or through VA MS Teams software and reviewed by study staff). Analysis of qualitative data will be

conducted using ATLAS.ti, a qualitative data analysis software program allowing fluid interaction of data across types and sources.

Examination of key components of the facilitation approach. Using CFIR domains and constructs[38] we will systematically consider strengths and weaknesses of our implementation strategy in the formative evaluation. We will collect qualitative and quantitative data prior to, during, and at completion of the COPES ExTRA study. We will use the RE-AIM framework to evaluate the summative success of the COPES and CBT-CP implementation. Reach will be evaluated by determining the refusal rate (percentage of those patients for whom an alert was triggered but the referral was not made and demographic characteristics of Veterans who participate versus those who do not). Refusal rates will be calculated overall and for each site.

Efficacy/Effectiveness measures are described elsewhere (BPI interference is the primary effectiveness measure). Adoption is defined as the proportion of providers at each site who report willingness to refer to the interventions and their representativeness. We will also examine demographic and qualitative formative evaluation data associated with high and low adopting sites. Implementation: We will use qualitative formative evaluation data to understand the implementation process in the study sites. We will query site staff and/or review patient EHR to determine treatment format (i.e. individual, group). Maintenance will be evaluated by examining COPES and CBT-CP 12 month outcomes. To assess system level maintenance, we will review qualitative formative evaluation data to identify potential barriers to maintenance trajectories of provider referral rates over time, and necessary areas for additional assistance.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The investigators will maintain adequate data collection mechanisms including electronically captured patient reported data from the study IVR system, approved data taken from the VA electronic health record via electronic download, and data taken from the live telephone electronic screening that is placed directly into a study database (no hand-written information is collected).

The following data will be collected from the patient electronic health record by the study data manager using the VA approved VINCI interface: demographic data, clinic visits, pain treatment, prescribed opioid and non-opioid pain

medications, and ICD-10 musculoskeletal diagnosis codes. These data will remain behind the VA firewall. These data are downloaded by VINCI staff based on data requests and provided to study staff via the VINCI interface located behind the VA firewall.

Study staff will collect information about patient engagement/adherence/completion/treatment quality for both study interventions. We will track participant adherence (time to treatment, engagement, dose, time to completion and treatment completion (yes/no). Engagement and adherence will be identified for COPES (IVR CBT-CP) patients by measuring number of calls answered on the telephone system and in synchronous CBT-CP through examining number of sessions attended in the electronic health record. For workload credit and co-payment billing purposes all sessions are recorded in the VA electronic health record. Study staff will collect session attendance and treatment format data at the same time as they do the post-treatment chart review for adverse events.

A live telephone screening call will be done with participants by research staff to confirm eligibility and some demographics. We will collect information on pain, current medical treatments being used for pain, ability to walk and balance, if the patient has a foot ulcer, the availability of a telephone to participate, if patient is undergoing detox in an inpatient unit for alcohol or substance abuse or psychiatric condition, or any other medical conditions that may impair the patient's ability to participate, sensory deficits that could interfere with participation, use of non-steroidal anti-inflammatory drugs (NSAIDs) for pain, address, race/ethnicity, gender, and marital status will collected by patient report.

Study staff are not blinded. However, collection of this information occurs prior to randomization and the randomization allocation will be concealed. These data will be entered as it is collected directly into the study database which will be held behind the VA firewall.

Most data and outcome measures will be collected from patients via our automated IVR system. Participants randomized to the IVR-COPES arm will make daily reports of their pain intensity, pain interference, sleep, steps, skill practice, and self-efficacy as described in section 6.2 Description of Evaluation. Participants in both conditions will complete the study baseline, post-treatment, and follow-up assessment measures using the IVR system. Outcome measures are described in section 6.2 Description of Evaluation. IVR data are held in the IVR system and can be viewed by approved research personnel with a web portal, and then transferred to the VA through approved methods. For patients who do not adhere to the IVR system calls for data collection, we will mail surveys or offer to collect the survey information using a real-time telephone interview with study

staff. Survey data will then be entered into the study database behind the VA firewall by blinded study staff. Paper surveys will be kept in locked filing cabinets in the office of the research coordinator at VA Connecticut.

10.2 Data Management

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents will be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

This study will use an Access or compatible database to track eligibility and enrollment. Eventually all data sources (enrollment, HER, and IVR) will be brought together in one final database that will reside behind the VA firewall. The database will be secured with password protection and will reside behind the VA firewall. Electronic communication with outside collaborators will involve only unidentifiable information. The database incorporates an electronic audit trail to show change(s) to data after original entry including the date/time and user making the change

VA Connecticut Healthcare System (VACHS) will be the coordinating center. All patients will be screened and enrolled through the staff at VACHS. Patients will be randomized to either receive the COPES (IVR-CBT-CP) treatment through VACHS or receive synchronous CBT-CP through their local facility.

Screening will be done by a telephone call from research staff at VACHS. All other assessments will be completed through the IVR system.

The clinical sites (non-engaged sites) will be responsible for referring patients to participate and to treat patients randomized to CBT-CP however they are standardly delivering this clinical treatment.

10.3 Quality Assurance

10.3.1 Training

Treatment training. In person CBT-CP therapists have all received CBT-CP training through the VA Evidence-based Psychotherapy program or commensurate training in graduate school, internship, or post-doctoral fellowship

and use the VA approved companion manual. This manual was created and published by the VA Evidence-based Psychotherapy program and is available at https://www.va.gov/painmanagement/docs/cbt-cp_therapist_manual.pdf. COPES (IVR CBT-CP) therapists use a manual, feedback scripts and are trained on providing treatment through the COPES system. This documentation is part of the manual of procedures for the intervention.

Consenting. Staff who will be consenting and screening participants use an information sheet and a telephone screening document. Staff will use a consenting checklist to ensure that all consent steps are followed. All personnel will be trained in consenting according to VA standards, be trained in monitoring the COPES system's website portal and be trained in evaluating EHR medical notes. These staff are all centrally located at VA Connecticut and overseen by the PI and study coordinator.

Additionally, all staff who will be consenting, screening or delivering treatment will be up to date on VA Privacy and Information Security Awareness, Privacy and HIPAA, and Good Clinical Practice training requirements.

10.3.2 Quality Control Committee

N/A

10.3.3 Metrics

When patients are referred to the study, they will be assigned a sequential study ID and tracked in the study database. The database will contain the disposition of the participant at each decision point (eligible/not eligible/reason not eligible, consented/declined, randomization result, number of sessions, completion of follow-ups). We will audit the database regularly to ensure that all referred patients are accounted for and the disposition of each participant is correctly captured.

Outcome measures are collected by the IVR system, the system will not allow patients to enter answers that are outside the data range for each question. If a patient does not complete follow-up assessments, staff will follow written procedures to reduce missing data including contacting patients by phone and offering the opportunity to complete measures by IVR automated call sent at the time of the contact and a mailed survey. As with our prior studies that have used an IVR system, each morning study staff check the system for alerts (e.g., a participant connected to the Veteran Crisis line, a follow-up measure was not completed, the participant left a message for staff).

10.3.4 Protocol Deviations

Meetings of the larger research group (PI, staff at engaged sites, and the VA Connecticut research team) will allow us to detect deviations from the IRB-approved protocol. No recruiting, consenting, randomizing, or assessment will occur at the non-engaged sites so there is no need to monitor their activities for compliance.

COPES and CBT-CP are minimal risk interventions and CBT-CP and its variants are considered standard of care for chronic pain. Based on previous experience with this study population, we added diabetic foot ulcer as an exclusion criterion from the study. COPES+UC participants will be centrally treated at VACHS. Regular meetings will be held between the PI and study staff members who will be delivering the intervention locally from VACHS. Additionally, for the CBT-CP+UC participants, regular meetings will be held between the PI and each site liaison. During these meetings staff will convey any issues or adverse events (AEs), serious adverse events (SAEs), unexpected adverse events (UAEs), or unanticipated problems involving risks to participants or others (UPIRSOs), that may occur at these sites and report to the cIRB within 5 days. as necessary, or at continuing review for AEs that do not meet criteria for reporting within 5 days.

During follow up (4, 6 & 12), the study coordinator will retrospectively examine participants' electronic medical record to determine if AEs, SAEs, or UPIRSOs have occurred and report to the cIRB within 5 days. as necessary or at continuing review for AEs that do not meet criteria for reporting within 5 days.

In the COPES+UC condition, participants will be monitored weekly for the full 11 weeks of the study. All participants will be monitored using automated IVR calls at multiple study timepoints (baseline,1 4, 6, and 12 months). Safety data will only be retrospectively collected during post follow up assessments.

10.3.5 Monitoring

Measurement and Reporting of Subject Accrual
Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the recruitment phase to ensure that a sufficient number of participants are being enrolled, in keeping with proposed recruitment projections, and that they meet eligibility criteria and fulfill the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table).

Study progress and safety will be reviewed as detailed in reporting table. Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor(s) semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis.

This is a minimal risk study and the intervention under investigation is guideline recommended and considered safe. There is no adverse outcome associated with patient early withdrawal and patients may access similar treatment outside the trial if they desire. Therefore, the trial does not require intensive safety monitoring. We will work with NCCIH to implement safety monitoring according to their guidelines and are included in the Data and Safety Monitoring Plan.

We will assess treatment quality/fidelity in both conditions as described above. We will track participant adherence (time to treatment, dose, number of weeks engaged in IVR-CBT and number of session attended in synchronous CBT-CP), time to completion and treatment completion (yes/no).

Engagement, adherence, time to treatment, time to completion and completion (y/n) will be identified for COPES (IVR CBT-CP) patients by measuring number of weeks that the participant was participating in COPES (at least one call answered/week through the COPES IVR system and in synchronous CBT-CP through examining the number and timing of treatment sessions attended as documented by treatment notes in the electronic health record. For workload credit and co-payment billing purposes all synchronous sessions are recorded in the VA electronic health record. Study staff will collect session attendance and format data at the same time as they do the post-treatment chart review for adverse events. A trained research assistant will review each participant’s electronic medical record at the completion of treatment to also

collect data on treatment quality. We will perform subgroup analyses for the primary outcome and engagement.

We will be using the VA Central IRB for annual reviews. At the study coordinating center (VA Connecticut Healthcare System), we will have research team meetings twice a month to review compliance of procedures of enrollment, screening and data monitoring that assessments are completed and attempted on schedule and follow up with patients who are missing assessments. Kathryn LaChappelle MPH, the project manager will oversee the preparation of the reports and present them at the regular meetings to the PI. These data will be obtained from the IVR system or from the participants' electronic health records, so we are not dependent on reports from local sites to obtain this information. The exception is changes is local CBT-CP providers or CIH offerings. To obtain this information, we will send email inquiries 3 times per year soliciting this information from sites.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

A version of this protocol and the informed consent document (Appendix I and II) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study, the VA Central IRB and the Yale University Human Investigations Committee.

11.2 Informed Consent Forms

Patients will be contacted, screened, enrolled, and randomized in the same way whether they are self-referred or provider referred. After receiving an electronic referral from a clinician at a study site or a voicemail from a patient self-referral, VA Connecticut study staff will contact patients by telephone, and using a semi-structured interview, assess patient interest, patient's self-reported ability to walk at least one block, presence of a landline or cellular telephone, and absence of vision or hearing loss that would interfere with participation (to confirm eligibility criteria not reliably contained in the EHR) and answer any questions patients have about the intervention (see attached script) as well as review their VA medical record to confirm eligibility. If a patient is willing to obtain treatment, study staff will read the approved consent language contained in the information sheet and will randomize the patient. Patients will be specifically asked about consenting to the audio recording of their voice. We will record the patients' confirmation of this consent. The information sheet will be available to patients on our study website. The website is a resource for patients and has copies of the information sheet, the patient handbook and audio files of the relaxation exercises. Patients do

not need to login and it does not collect, hold or request any PHI or patient data. Use of the website will allow patients to view a copy of the information sheet without the delay of prior mailing. If patients do not have access to the internet or if they would prefer a physical copy prior to consenting, we will mail them a copy and contact them at a later time for consenting.

11.3 Participant Confidentiality

The study has a certificate of confidentiality and the appropriate language has been incorporated into the consent document to communicate this to participants. The study will use subjects' Protected Health Information (PHI). The study will also disclose subjects' PHI to the IVR system and transcription service contractor. All privacy and security issues will be addressed in the contracts per current VA requirements and will be approved by VA prior to sharing data. The transcription service is a VA healthcare system entity. The IVR system and web portal will hold patient name, year of birth, and telephone number in order to send out scheduled calls and manage patients.

Names, addresses, telephone numbers, dates of musculoskeletal diagnoses, dates of provider referral, dates of pain scores, date of birth any age, voice recordings, and social security numbers will be collected and recorded during the course of the study and kept behind the VA firewall.

Full social security numbers are being used so that we can identify the group of Veterans who meet our basic eligibility criteria for recruitment purposes. The social security number allows us to collate data across VA data sources used to build the electronic health record data. Last four numbers of the social security number are used in our recruitment database to identify participants and access electronic medical records to ensure eligibility and to make required clinical and research related documentation. All social security numbers will be stored behind the VA firewall and only approved study staff will have access. Social security numbers are also kept separate from research records.

We have secured a contract with Tech4Research, an outside vendor, to build and maintain the information system for the COPES intervention and obtain IVR-collected outcome data. Tech4Research contracts with Amazon govcloud to host the system in their secure environment. The contracts are in compliance with VA rules of privacy and security and approved by VA.

At the conclusion of this study, all documents and electronic files containing personal or confidential data will be returned to the VA or destroyed according to

VA security procedures. In cases where data are destroyed the IVR contractor will provide data destruction certificates. Additionally, all electronic storage media used to store, process, or access study data will have all data elements removed in compliance with VA policies and procedures. The IVR contractor will not maintain any copies of VA data after the contract has concluded.

Regular study team meetings will be used to ensure that all data quality and IRB policies and procedures are being followed. This will include ensuring that (1) all participants understand, agree to, and acknowledge the information contained in the consent procedure before participating; (2) strict adherence is maintained to communication regarding the participants' right to withdraw or refuse to answer questions; (3) staff maintain confidentiality both by protecting hard-copy and electronic data collection forms and also by avoiding all unauthorized conversations about individual patients; (4) all identifying information is kept locked at all times and sensitive computer files are maintained on a secured VA server; (5) coding for ambiguous responses is handled in a way that is consistent and clear across data collectors and over time; and (6) participants are informed in writing how to contact the study PI, the study coordinator, and the relevant IRB office with any questions or concerns.

11.4 Study Discontinuation

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

12. COMMITTEES

The Pain Management Collaboratory Coordinating Center (PMC^3) will be facilitating the harmonization and conduct of this pragmatic trial along with other funded PMC projects through routine workgroup meetings and reports. We will work with PMC^3 leadership and other trial PIs to disseminate the findings of the trials.

The COPES ExTRA trial is overseen by Dr. Alicia Heapy the PI. She oversees the activities of all VA Connecticut study staff. Daily supervision and coordination of the trial is accomplished by Kathryn LaChappelle, MPH, the study manager. Twice monthly in-person or telephone research team meetings occur for VA Connecticut study staff. Safety and quality assurance monitoring will take place in this meeting as detailed in the reporting table. VA Connecticut staff will also send an email inquiry to each study recruitment site to assess any local adaptation to synchronous CBT-CP or changes in personnel 3 times per year. There are two study workgroups containing study staff and co-investigators that meet twice per month. Each workgroup has two co-chairs. All four co-chairs, the PI, and the project manager meet monthly. The work of the

study is coordinated at the co-chairs' monthly workgroup. Task are assigned to workgroups and the chair and workgroup manage completion of the task. NIH project scientist and program officers will be invited to all work group meetings.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the PMC[3]. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

We have adapted our own study procedures to be consistent to the PMC[3] policies and procedures.

A. Manuscripts, abstracts and presentations derived from COPES-ExTRA demonstration project-funded activities are designated as "COPES ExTRA" manuscripts, abstracts, and presentations.

B. A "COPES ExTRA" manuscript, abstract or presentation" deals directly with knowledge derived from COPES ExTRA funded work. The methods or results of a specific project would constitute a Demonstration Project manuscript, abstract, or presentation.

The procedures for review of publications and presentations for COPES Extra manuscript, abstract, or presentations includes review by the PI and all co-investigators. The PI approves 1) proposed publications and abstracts slated for submission; 2) penultimate drafts before they are submitted for publication; and 3) presentations before they are made in a public forum. All co-investigators will be given an opportunity for comment. If the interval specified for comments passes without feedback (2 weeks [10 business days]), assent to that version of the manuscript is assumed. The PI, with input from the co-investigators will determine authorship and authorship order. The PI and co-investigators will have 2 weeks (10 business days) to collect and forward comments and suggestions to the first author. There may be circumstances (for example, if an author is an NIH, DoD, VA staff member) wherein an NIH, DoD, VA Institute/Center (IC) for a given manuscript, abstract, or presentation would require review prior to its submission.

Final editorial authority and the decision to publish will reside with the designated co-authors, although the PMC Publications and Presentations Committee will have the right to vote on the designation of the final proposed manuscript as a "PMC Publication or Presentation."

Once a COPES ExTRA manuscript has been accepted for publication, the lead author or their designee will inform the relevant PMC3, NIH and VA Program Officials.

For COPES -ExTRA draft manuscripts, abstracts, or public presentations that include descriptions of or details about an ongoing PMC Demonstration Project other than the author's own, a draft version of the manuscript or other materials will also be routed to PMC3 staff for forwarding to the Demonstration Project Principal Investigator at least 2 weeks prior to initial manuscript submission (or resubmission involving substantive changes to the relevant section)

Once a manuscript, abstract, or presentation has been accepted for publication or presentation, the first author will inform the NIH and the PMC Publications and Presentations Committee Chair and/or designee and provide them with a final copy of the accepted publication or presentation.

We will include the following statement in publications

> Research reported in this publication was supported by [GRANT NUMBER] from the [RELEVANT INSTITUTE/CENTER/OFFICE]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

> Prior to issuing a press release concerning results, presentations, or publications derived from this research, we will notify the ICOs that supported the grant (NIH, DoD, VA) in advance to allow for coordination.

14. REFERENCES

1. Chou R, Huffman LH. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Annals of Internal Medicine.* 2007;147:492-504.
2. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. *Health Psychology.* 2007;26(1):1-9.
3. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database of Systematic Reviews.* 2012;11.
4. Stewart MO, Karlin BE, Murphy JL, et al. National dissemination of cognitive-behavioral therapy for chronic pain in veterans: therapist and patient-level outcomes. *Clin J Pain.* 2015;31(8):722-729.
5. Heapy AA, Higgins D.M., Goulet, J.L., LaChappelle, K.M., Driscoll, M., Czlapinski, R.A., Buta, E., Piette, J.D., Krein, S. L., Kerns, R.D. Interactive voice response-based self-management for chronic back pain: The cooperative pain education and self-

management (COPES) trial: A randomized clinical trial. *JAMA Internal Medicine.* in press.
6. IOM. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research..* Washington, DC: Institute of Medicine;2011.
7. Upshur CC, Luckmann RS, Savageau JA. Primary care provider concerns about management of chronic pain in community clinic populations. *J Gen Intern Med.* 2006;21(6):652-655.
8. Kerns RD, Otis, J. D., & Rosenberg, R. Veterans' reports of pain and associations with ratings of health, health risk behaviors, affective distress, and use of the healthcare system. *J Rehabil Res Dev.* 2003;40:371-380.
9. Haskell SG, Heapy A, Reid MC, Papas RK, Kerns RD. The prevalence and age-related characteristics of pain in a sample of women veterans receiving primary care. *J Womens Health (Larchmt).* 2006;15(7):862-869.
10. Gironda RJ, Clark ME, Massengale JP, Walker RL. Pain among veterans of Operations Enduring Freedom and Iraqi Freedom. *Pain medicine (Malden, Mass.).* 2006;7(4):339-343.
11. US Burden of Disease Collaborators. The state of US Health 1990-2010: Burden of diseases, injuries, and risk factors. *JAMA.* 2013;310(6):591-608.
12. *Treatment Episode Data Set (TEDS). Highlights - 2007.* National Admissions to Substance Abuse Treatment Services;2009.
13. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med.* 2007;146(2):116-127.
14. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med.* 2007;147(7):478-491.
15. Department of Health and Human Services:National Pain Strategy: A comprehensive population health-level strategy for pain. 2016. https://iprcc.nih.gov/docs/HHSNational_Pain_Strategy.pdf. Accessed August 1, 2016.
16. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep.* 2016;65(1):1-49.
17. Turk DC, Meichenbaum D, Genest M. Pain and Behavioral Medicine: A Cognitive Behavioral Perspective. New York, NY: Guilford Press. 1983.
18. Murphy JL, McKellar, J.D., Raffa, S.D., Clark, M.E., Kerns, R.D., Karlin, B.E. . Cognitive behavioral therapy for chronic pain among veterans: Therapist manual. In: Affairs. USDoV, ed. Washington, DC: .
19. Murphy JL. National Training in Evidence Based Psychotherapy for CBT for chronic pain. 2016.
20. Cucciare MA, Curran GM, Craske MG, et al. Assessing fidelity of cognitive behavioral therapy in rural VA clinics: design of a randomized implementation effectiveness (hybrid type III) trial. *Implement Sci.* 2016;11:65.
21. Kazdin AE, Blase SL. Rebooting Psychotherapy Research and Practice to Reduce the Burden of Mental Illness. *Perspect Psychol Sci.* 2011;6(1):21-37.
22. Cully JA, Jameson JP, Phillips LL, Kunik ME, Fortney JC. Use of psychotherapy by rural and urban veterans. *J Rural Health.* 2010;26(3):225-233.

23. Waller G, Turner H. Therapist drift redux: Why well-meaning clinicians fail to deliver evidence-based therapy, and how to get back on track. *Behav Res Ther.* 2016;77:129-137.
24. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA.* 2016;315(12):1240-1249.
25. Bair MJ, Matthias MS, Nyland KA, et al. Barriers and facilitators to chronic pain self-management: a qualitative study of primary care patients with comorbid musculoskeletal pain and depression. *Pain medicine (Malden, Mass.).* 2009;10(7):1280-1290.
26. Jensen MP, Nielson WR, Kerns RD. Toward the development of a motivational model of pain self-management. *J Pain.* 2003;4(9):477-492.
27. Institute A. Study of barriers to care for women veterans. 2015. Accessed February 2, 2017.
28. Ehde DM, Dillworth TM, Turner JA. Cognitive-Behavioral Therapy for Individuals With Chronic Pain Efficacy, Innovations, and Directions for Research. *Am Psychol.* 2014;69(2):153-166.
29. Waegemann CP. mHealth: the next generation of telemedicine? *Telemed J E Health.* 2010;16:23-25.
30. Moore HK, Mundt JC, Modell JG, et al. An examination of 26,168 Hamilton Depression Rating Scale scores administered via interactive voice response across 17 randomized clinical trials. *Journal of Clinical Psychopharmacology.* 2006;26(3):321-324. PMID: 16702899.
31. Perrine MW, Mundt JC, Searles JS, Lester LS. Validation of daily self-reported alcohol consumption using interactive voice response (IVR) technology. *J Stud Alcohol.* 1995;56(5):487-490.
32. Kobak KA, Taylor LH, Dottl SL, et al. Computerized screening for psychiatric disorders in an outpatient community mental health clinic. *Psychiatr Serv.* 1997;48(8):1048-1057.
33. Piette J. Interactive behavior change technology to support diabetes self-management: where do we stand? *Diabetes Care.* 2007;30(10):2425-2432.
34. Free C, Phillips G, Watson L, et al. The effectiveness of mobile-health technologies to improve health care service delivery and processes: a systematic review and meta-analysis. *PLOS Medicine.* 2013;10(1):e1001363+.
35. Bender BG, Apter A, Bogen DK, et al. Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. *J Am Board Fam Med.* 2010;23(2):159-165.
36. Bachofen M, Nakagawa A, Marks IM, et al. Home self-assessment and self-treatment of obsessive-compulsive disorder using a manual and computer-conducted telephone interiew: replication of a UK-US study. *Journal of Clinical Psychiatry.* 1999;60(8):545-549.
37. Heapy AA, Higgins DM, LaChappelle KM, et al. Cooperative pain education and self-management (COPES): study design and protocol of a randomized non-inferiority trial of an interactive voice response-based self-management intervention for chronic low back pain. *BMC Musculoskelet Disord.* 2016;17:85.
38. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci.* 2009;4:50.

39. Higgins DM, Kerns RD, Brandt CA, et al. Persistent pain and comorbidity among Operation Enduring Freedom/Operation Iraqi Freedom/operation New Dawn veterans. *Pain medicine (Malden, Mass.).* 2014;15(5):782-790.
40. Haskell SG, Ning, Y., Krebs, E., Goulet, J., Mattocks, K., Kerns, R., Brandt, C. Prevalence of painful musculoskeletal conditions in female and male veterans in 7 years after return from deployment in Operation Enduring Freedom/Operation Iraqi Freedom. . *The Clinical Journal of Pain.* 2012;28(2):163-167.
41. Haskell SG, Brandt CA, Krebs EE, Skanderson M, Kerns RD, Goulet JL. Pain among Veterans of Operations Enduring Freedom and Iraqi Freedom: do women and men differ? *Pain medicine (Malden, Mass.).* 2009;10(7):1167-1173.
42. Higgins DM DM, Carroll C, Heapy AA, Kerns RD, Bair MJ, Fenton BT, Brennan P, Burgess DJ, Piette JD, Goulet JL, Haskell SG, Brandt CA. Gender differences in correlates of pain intensity among veterans at the time of diagnosis with a musculoskeletal disorder. *Women's Health Issues.* in press.
43. Haskell SG, Mattocks, K., Goulet J.L., Krebs, E.E., Skanderson, M., Leslie, D., Justice, A.C., Yano, E.M., Brandt, C. The burden of illness in the first year home: Do male and female VA users differ in health conditions and healthcare utilization? . *Women's Health Issues.* 2011;21(1):92-97.
44. Driscoll MA, Higgins DM, Seng EK, et al. Trauma, social support, family conflict, and chronic pain in recent service veterans: does gender matter? *Pain medicine (Malden, Mass.).* 2015;16(6):1101-1111.
45. Driscoll MA HD, Garroway A, Burger A, Buta E, Brandt CA, Goulet J, Heapy A, Kerns RD, Haskell SG. Examining gender as a correlate of self-reported pain treatment use among recent service veterans with deployment related musculoskeletal disorders. *Pain Medicine.* in press.
46. Krein S, Kadri R, Hughes M, et al. A randomized trial of a pedometer-based internet mediated intervention for patients with chronic low back pain. *Journal of Medical Internet Research.* 2013;15(7):e181+. PMCID: PMC2945952.
47. Martino S. Credibility and treatment fidelity may matter in twelve-step treatment. *Am J Drug Alcohol Abuse.* 2013;39(5):273-274.
48. Martino S, Paris M, Jr., Anez L, et al. The Effectiveness and Cost of Clinical Supervision for Motivational Interviewing: A Randomized Controlled Trial. *J Subst Abuse Treat.* 2016;68:11-23.
49. Martino S, Canning-Ball M, Carroll KM, Rounsaville BJ. A criterion-based stepwise approach for training counselors in motivational interviewing. *J Subst Abuse Treat.* 2011;40(4):357-365.
50. Statistics NCfVAa. Department of Veterans Affairs Statistics at a Glance. 2016. Accessed 02/01, 2017.
51. Frayne SM, Carney DV, Bastian L, et al. The VA Women's Health Practice-Based Research Network: amplifying women veterans' voices in VA research. *J Gen Intern Med.* 2013;28 Suppl 2:S504-509.
52. Pomernacki A, Carney DV, Kimerling R, et al. Lessons from Initiating the First Veterans Health Administration (VA) Women's Health Practice-based Research Network (WH-PBRN) Study. *J Am Board Fam Med.* 2015;28(5):649-657.
53. Network WsHPBR. Women's Health Practice Based Research Network Site Characteristics. 2014.

54. Goulet JL, Kerns RD, Bair MJ, Becker W, Brennan P, Burgess DJ. The Musculoskelatal Diagnosis Cohort: Examining Pain and Pain Care amongVeterans. *Pain.* 2016;in press.
55. Abel EA, Brandt CA, Czlapinski R, Goulet JL. Pain research using Veterans Health Administration electronic and administrative data sources. *J Rehabil Res Dev.* 2016;53(1):1-12.
56. Goulet JL, Buta E, Bathulapalli H, Gueorguieva R, Brandt CA. Statistical Models for the Analysis of Zero-Inflated Pain Intensity Numeric Rating Scale Data. *J Pain.* 2016.
57. Piette JD, Krein SL, Striplin D, et al. Patient-Centered Pain Care Using Artificial Intelligence and Mobile Health Tools: Protocol for a Randomized Study Funded by the US Department of Veterans Affairs Health Services Research and Development Program. *JMIR Res Protoc.* 2016;5(2):e53.
58. Brown ST, Tate JP, Kyriakides TC, et al. The VACS index accurately predicts mortality and treatment response among multi-drug resistant HIV infected patients participating in the options in management with antiretrovirals (OPTIMA) study. *PLoS One.* 2014;9(3):e92606.
59. Miller P, Phipps M, Chatterjee S, et al. Exploring a clinically friendly web-based approach to clinical decision support linked to the electronic health record: design philosophy, prototype implementation, and framework for assessment. *JMIR Med Inform.* 2014;2(2):e20.
60. Niehoff KM, Rajeevan N, Charpentier PA, Miller PL, Goldstein MK, Fried TR. Development of the Tool to Reduce Inappropriate Medications (TRIM): A Clinical Decision Support System to Improve Medication Prescribing for Older Adults. *Pharmacotherapy.* 2016;36(6):694-701.
61. Stetler CB, Legro MW, Wallace CM, et al. The role of formative evaluation in implementation research and the QUERI experience. *J Gen Intern Med.* 2006;21 Suppl 2:S1-8.
62. Helfrich CD, Li YF, Sharp ND, Sales AE. Organizational readiness to change assessment (ORCA): development of an instrument based on the Promoting Action on Research in Health Services (PARIHS) framework. *Implement Sci.* 2009;4:38.
63. Affairs DoV. Pain management. VHA Directive 2009-053. . 2009.
64. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113(1-2):9-19.
65. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. *J Gen Intern Med.* 2007;22(10):1453-1458.
66. Lorenz KA, Sherbourne CD, Shugarman LR, et al. How reliable is pain as the fifth vital sign? *J Am Board Fam Med.* 2009;22(3):291-298.
67. Goulet JL, Brandt C, Crystal S, et al. Agreement between electronic medical record-based and self-administered pain numeric rating scale: clinical and research implications. *Med Care.* 2013;51(3):245-250.
68. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Annals of the Academy of Medicine, Singapore.* 1994;23(2):129-138.
69. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain.* 2008;9(2):105-121.

70. Taylor AM, Phillips K, Patel KV, et al. Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. *Pain.* 2016;157(9):1836-1850.
71. Ford I, Norrie J. Pragmatic Trials. *N Engl J Med.* 2016;375(5):454-463.
72. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *J Gen Intern Med.* 2009;24(6):733-738.
73. Taylor SL, Elwy AR. Complementary and alternative medicine for US veterans and active duty military personnel: promising steps to improve their health. *Med Care.* 2014;52(12 Suppl 5):S1-4.
74. Kopcke F, Prokosch HU. Employing computers for the recruitment into clinical trials: a comprehensive systematic review. *J Med Internet Res.* 2014;16(7):e161.
75. Rollman BL, Fischer GS, Zhu F, Belnap BH. Comparison of electronic physician prompts versus waitroom case-finding on clinical trial enrollment. *Journal of General Internal Medicine.* 2008;23(4):447-450.
76. O'Keeffe M, Purtill H, Kennedy N, et al. Comparative Effectiveness of Conservative Interventions for Nonspecific Chronic Spinal Pain: Physical, Behavioral/Psychologically Informed, or Combined? A Systematic Review and Meta-Analysis. *J Pain.* 2016;17(7):755-774.
77. Goyal M, Haythornthwaite JA. Is It Time to Make Mind-Body Approaches Available for Chronic Low Back Pain? *JAMA.* 2016;315(12):1236-1237.
78. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *Journal of clinical epidemiology.* 2009;62(5):464-475.
79. O'Connor SR, Tully MA, Ryan B, et al. Walking exercise for chronic musculoskeletal pain: systematic review and meta-analysis. *Arch Phys Med Rehabil.* 2015;96(4):724-734 e723.
80. Wang KH, Goulet JL, Carroll CM, et al. Estimating healthcare mobility in the Veterans Affairs Healthcare System. *BMC Health Serv Res.* 2016;16(1):609.
81. Mosher HJ, Krebs EE, Carrel M, Kaboli PJ, Weg MW, Lund BC. Trends in prevalent and incident opioid receipt: an observational study in Veterans Health Administration 2004-2012. *J Gen Intern Med.* 2015;30(5):597-604.
82. Dorflinger L, Moore B, Goulet J, et al. A partnered approach to opioid management, guideline concordant care and the stepped care model of pain management. *J Gen Intern Med.* 2014;29 Suppl 4:870-876.
83. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;1(113):9-19.
84. Kroenke K, Strine TW, Spritzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of
current depression in the general population. J Affect Disord. 2009; 114(1-3):163-73.
85. Clark ME, Gironda RJ, Young RW. Development and validation of the Pain Outcomes Questionnaire-VA. *J Rehabil Res Dev.* 2003;40(5):381-395.
86. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2000;2:297–307..

87. Nicholas MK, McGuire BE, Asghari A. (2015) A 2-item short form of the Pain Self-Efficacy Questionnaire: Development and psychometric evaluation of the PSEQ-2. J Pain, 16, 153-163
88. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One- and two-item measures of pain beliefs and coping strategies. *Pain.* 2003;104(3):453-469.
89. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med.* 1997;19(2):179-186.
90. Zhang HS, B. *Recursive Partitioning and Applications. 2nd Edition.* New York: Springer; 2010.
91. Kroenke K, Krebs E, Wu J, et al. Stepped Care to Optimize Pain care Effectiveness (SCOPE) trial study design and sample characteristics. *Contemp Clin Trials.* 2013;34(2):270-281.
92. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health.* 2014;17(1):5-14.
93. Miles MB HA. *Qualitaitve data analysis: An expanded sourcebook.* Sage; 1994.
94. Averill JB. Matrix analysis as a complementary analytic strategy in qualitative inquiry. *Qual Health Res.* 2002;12(6):855-866.
95. Kilbourne AM, Neumann MS, Pincus HA, Bauer MS, Stall R. Implementing evidence-based interventions in healthcare: application of the Replicating Effective Programs framework. *Implementation Science.* 2007;2(1):42-52.
96. Charlson, M., Szatrowski, T.P., Peterson, J.,& Gold, J.Validation of a combined comorbidity index, 1994; 47 (11) 1245-1251.
97. Lamb, S.E., Hansen, Z., Lall, R., Castelnuovo, E., Withers, E.J., Nichols, V., Potter, R., Underwood, M.R. and Back Skills Training Trial investigators, 2010. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. *The Lancet*, *375*(9718), pp.916-923.
98. Bush K, Kivlahan DR, McDonell MB, et al. The AUDIT Alcohol Consumption Questions (AUDIT-C): an effective brief screening test for problem drinking. Arch Internal Med. 1998 (3): 1789-1795.
99. Kroenke K, Krebs E, Wu J, et al. Stepped Care to Optimize Pain care Effectiveness (SCOPE) trial study design and sample characteristics. Contemp Clin Trials. 2013;34(2):270-281.
100. Council, N. R. (2010). The prevention and treatment of missing data in clinical trials, National Academies Press.
101. White, I. R., P. Royston and A. M. Wood (2011). "Multiple imputation using chained equations: issues and guidance for practice." Statistics in medicine 30(4): 377-399.\
102. Sint, K., R. Rosenheck, D. G. Robinson, N. R. Schooler, P. Marcy, J. M. Kane, K. T. Mueser, H. Lin and R. E. Investigators (2018). "Accounting for group differences in study retention in a randomized trial of specialized treatment for first episode psychosis." Schizophrenia research 195: 481-487.
103. Yuan, Y. (2014). "Sensitivity Analysis in Multiple Imputation for Missing Data." Retrieved August 30, 2018, from https://support.sas.com/resources/papers/proceedings14/SAS270-2014.pdf.

104.Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., ... & Altman, D. G. (2010). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Journal of clinical epidemiology, 63(8), e1-e37.
105. Murray, D. M., Hannan, P. J., Wolfinger, R. D., Baker, W. L., & Dwyer, J. H. (1998). Analysis of data from group-randomized trials with repeat observations on the same groups. *Statistics in Medicine*, *17*(14), 1581-1600.
106. McCaffrey, D. F., Griffin, B. A., Almirall, D., Slaughter, M. E., Ramchand, R., & Burgette, L. F. (2013). A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Statistics in medicine*, *32*(19), 3388-3414.

107. Ridgeway, G., McCaffrey, D., Morral, A., Burgette, L., & Griffin, B. A. (2017). Toolkit for Weighting and Analysis of Nonequivalent Groups: A tutorial for the twang package. *Santa Monica, CA: RAND Corporation*.

15. SUPPLEMENTS/APPENDICES

Appendix I

Appendix I. Providers Information Sheet v071018

Veterans Information Sheet v

Appendix II. Veterans Information Sheet v06.11.20

Patient Phone Script_COPES ExTRA

Appendix III. Patient Phone Script_COPES ExTRA_10.23.19

Appendix IV

Appendix IV. IVR Suicide Protocol

copes extra therapist manual 03

Appendix V. Copes extra manual 03.06.2020

PMC COVID 19 Measures v1.0_0502

Appendix VI. PMC3 COVID-19 Questions