Veterans' Pain Care Organizational Improvement Comparative Effectiveness (VOICE) Study

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Table of Contents

STUDY ABSTRACT

Study Title

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Background and significance

Long-term opioid therapy became a mainstay of chronic pain management over the past two decades, despite a lack of evidence for effectiveness. Now, in response to evidence that opioid therapy is associated with serious dose-related harms, clinicians and health systems are challenged to achieve a patient-centered shift in pain management from over-reliance on long-term opioid therapy to more effective use of evidence-based pain treatment approaches. Clinicians and health care decision-makers face gaps in evidence however for how to achieve these goals. Our approach is informed by patient partners who emphasized the primary need for individualized pain care and support to achieve improved pain outcomes. Accordingly, our central focus is on optimizing pain care, which we see as the first and most important step toward patient-centered opioid dose reduction.

Study aims

The overall objective of this research is to improve effectiveness and safety of pain management among patients with chronic pain. This 12-month pragmatic randomized trial will compare two pain care delivery strategies, which differ substantially in comprehensiveness and resource intensity, to improve pain and reduce opioid use among Veterans. We will also conduct an opioid tapering strategy substudy that will examine comparative effectiveness of tapering with or without the option for buprenorphine rotation in the high-dose subgroup of study participants.

Aim 1: To compare telecare collaborative pain management versus integrated pain team management for improving pain and reducing opioid use in VA patients on long-term moderate to high-dose opioids for chronic pain.

Aim 2: To compare standard taper options versus expanded taper options for improving pain and reducing opioid use among VA patients on long-term high-dose opioids for chronic pain.

Secondary Aim: To understand patients' and clinicians' experiences with the study interventions and identify strategies to enhance future implementation and dissemination of effective pain care interventions.

Study design

This is a pragmatic comparative effectiveness trial at ten VA sites to compare two distinct interventions augmenting primary care management of chronic pain for patients on long-term opioid therapy. Randomization at the individual patient level will assign patient participants to either 1) telecare collaborative management (TCM) or 2) integrated pain team (IPT) management arms for 12 months. In both arms, patients receive pain care and opioid taper planning tailored to preferences and adjusted as needed to achieve individualized treatment goals. Among participants in a high-dose subgroup, the opioid taper strategy substudy will examine comparative effectiveness of tapering with or without the option for buprenorphine rotation.

Intervention and comparators

The TCM arm uses a medication management approach delivered by a clinical pharmacist care manager in collaboration with a consulting physician to address common barriers to effective

pain medication management in primary care. The IPT arm uses a biopsychosocial management approach delivered by an interdisciplinary team and emphasizes multimodal pain management and behavioral activation. For participants who agree to opioid dose reduction or discontinuation, opioid tapering will be conducted in both arms. Participants receiving moderate-doses (20-69 ME mg/day) will receive standard taper options, which incorporate shared decision-making to guide medication selection and rate of dose changes. Patients on high-dose opioids (≥70 ME mg/day) will be randomized to standard options or expanded options. The expanded options arm differs from standard options only in that it includes the additional option of buprenorphine rotation.

Study population

VA primary care patients receiving long-term moderate to high-dose opioid therapy for chronic pain of at least moderate severity will be eligible. Long-term is ≥ 90 consecutive days. Moderate to high dose is ≥ 20 morphine-equivalent (ME) mg/day. For subgroup definition, high-dose is ≥ 70 ME mg/day. Exclusion criteria are cognitive impairment; unstable or severe untreated psychiatric disorder; severe unstable or end-stage medical disease; suspected controlled substance diversion; and inability to communicate by telephone.

Outcomes

The primary study outcome is pain response at 12 months, defined as a 30% improvement in the Brief Pain Inventory (BPI). The main opioid dose outcome is 50% reduction in opioid daily dose. The main composite outcome is the proportion with 30% improvement in pain and 50% decrease in opioid daily dose, representing dual improvements in pain and opioid safety. We will assess secondary patient-relevant outcomes including function, quality of life, symptoms (e.g., depression, anxiety, sleep, fatigue), and adverse effects.

Analytic methods

All participants will be assessed in the arms to which they are assigned. An estimated sample size of 970 patients from 10 sites provides 80% power for a 2-sided chi-squared test comparing pain response rates for TCM and IPT if IPT adds 10% to the response rate, and > 85% power if IPT adds 11% to the response rate. We will use all follow-up data in repeated-measures logistic regression modeling 30% reduction from baseline in BPI scores. For the second aim, we estimate 80% power power to detect small to moderate effects (Cohen d or standardized difference) in mean BPI scores of 0.35 or more.

We will evaluate heterogeneity of treatment effects in 5 pre-specified subgroups that may be differentially responsive to treatment, at greater risk for opioid harms, or more likely to have difficulty reducing opioids (patients treated with high-dose opioids and those with depression symptoms, post-traumatic stress symptoms, potential substance use disorder (SUD), and fibromyalgia symptoms). We will use repeated-measures linear regression to examine interactions of subgroup with treatment assignment.

1. STUDY OBJECTIVES

1.1 Primary Objectives

1.1.1 Aim 1

Aim 1 is to compare telecare collaborative pain management (TCM) versus integrated pain team (IPT) management for improving pain and reducing opioid use in VA patients on long-term moderate to high-dose opioids for chronic pain.

All participants will be randomized to one of two care management approaches: 1) TCM or 2) IPT. To assess improvement in pain and reduction in opioid use, we will compare TCM versus IPT groups on three main outcomes. First, the primary outcome is pain response, defined as a 30% improvement in Brief Pain Inventory (BPI) total score from baseline to the final study outcome assessment at 12 months. Our second main outcome is opioid daily dose reduction of 50% from baseline to 12 months, based on VA pharmacy dispensing data. The main composite outcome is the proportion with both a pain response and opioid dose reduction, representing dual improvements in pain and regimen safety.

1.1.2 Aim 2

Aim 2 is to compare standard versus expanded taper options for improving pain and reducing opioid use among patients on high-dose opioid therapy at baseline.

Participants in the high-dose therapy subgroup will be randomized to receive one of two opioid taper arms: a) standard options or b) expanded options, which includes the additional option of buprenorphine rotation. To assess the primary outcome of pain severity, we will compare standard versus expanded options groups on mean BPI total scores. Between-group differences in opioid daily dose and the composite pain response and opioid dose reduction outcome will also be examined. We hypothesize that offering the option of buprenorphine rotation will improve BPI scores and reduce opioid daily dose.

1.2 Secondary Objectives

1.2.1 Subgroup analyses

We will examine differential response to TCM and IPT among subgroups of study participants. Subgroups are not mutually exclusive and are defined as presence (yes/no) of the following characteristics at baseline:

- High-dose opioid therapy (≥ 70 ME mg/day)
- Depression symptoms
- Post-traumatic stress symptoms
- Potential SUD
- Fibromyalgia symptoms

We hypothesize that IPT will be superior to TCM in the following subgroups: high-dose opioid therapy, depression, post-traumatic stress, and SUD.

1.2.2 Secondary outcomes

We will examine intervention effects on the following additional patient-reported outcomes:

- Pain intensity
- Pain interference with function
- Quality of life
- Adverse symptoms
- Fatigue
- Sleep
- Mental health
- Substance use
- Use of nonpharmacological therapies

We will examine intervention effects on the following additional opioid dose outcomes:

- Proportion with 25% dose reduction from baseline to 12 months
- Proportion with any dose reduction from baseline to 12 months
- Mean dose change from baseline to 12 months
- Proportion with dose escalation (increase in opioid daily dose of ≥ 25% from baseline to 12 months)

1.2.3 Predictors of variation

We will examine variation in intervention effects by sex, study site and time over the course of enrollment, as well as moderation of effects by relevant covariates.

1.2.4 Implementation Process Evaluation

Aim 3 is to understand patients' and clinicians' experiences with the study interventions and identify strategies to enhance future implementation and dissemination of effective pain care interventions.

Data will be gathered to examine patients' and clinicians' perceptions of the interventions; to describe the context and processes of intervention delivery; and to assess potential for long-term sustainability and widespread dissemination of the interventions. Data collection methods will include in-depth semi-structured interviews with patient and clinician participants and other VA employees; unstructured conversational interviews with researchers, clinicians, and stakeholders; and observation of research and intervention implementation processes.

Goals of this approach are threefold: 1) to increase the relevance of the primary research findings to patients, clinicians, and health care decision-makers; 2) to increase the likelihood of timely translation of research findings into diverse practice settings; and 3) to generate information to guide interpretation of primary trial findings. In addition to scientific reports and manuscripts, products of this process evaluation will include an

implementation toolkit (developed in collaboration with study partners) to support implementation of successful study interventions in diverse practice settings.

2. BACKGROUND AND RATIONALE

2.1 Chronic Pain and Opioid Therapy

Chronic pain affects approximately 100 million Americans, with an estimated $560-635 billion in annual health care and lost productivity costs. Furthermore, three of the top five causes of years lived with disability are painful conditions—back pain, neck pain, and other musculoskeletal disorders. Starting in the early 1990s, improved awareness of the burden of pain and concern about pain under-treatment drove a generalized expansion in opioid analgesic prescribing. Tragically, this expansive prescribing has triggered a new epidemic of opioid-related deaths and addictive disorders, while meaningful progress toward the original goal—reducing the burden of pain—has not been demonstrated.

For many patients receiving long-term opioids for chronic pain, potential harms of continuing opioid therapy outweigh benefits. Indeed, benefits of long-term opioid therapy are often elusive. Most patients receiving long-term opioid therapy continue to experience severe pain and functional limitations. Counter to prior assumptions, studies have found that higher opioid doses are not associated with corresponding improvements in analgesic response. Patients prescribed higher-dose opioids may have worse quality of life than those receiving low-dose or no opioids.

The frequency and severity of opioid-related harms among patients receiving long-term opioid therapy for pain are increasingly evident. Harms stemming from pharmacological properties include tolerance and physical dependence in most persons with long-term exposure and addiction in a substantial minority. Further, opioid involvement in respiratory control mechanisms can cause unpredictable fatal respiratory suppression when dosages are miscalculated or increased rapidly, too many pills are taken, or other drugs or conditions interact to potentiate opioid effects or cause buildup of toxic levels. Prescribed opioid dosage seems to be a major driver of risk for these and other harms.

For patients with chronic pain on long-term opioid therapy, pain management should involve attention to both improving pain and reducing risk for opioid-related harms. Evidence supports the effectiveness of a wide variety of non-opioid therapies for improving chronic pain outcomes, but response to treatments is variable and individual therapies typically generate only partial improvement. Thus, multi-modal integrated care is favored as the optimal pain management approach.

Unfortunately, little evidence is available for strategies to reduce or discontinue opioid therapy while managing pain. Although comprehensive pain rehabilitation programs have demonstrated success, expansion of these programs to accommodate vast numbers of patients on long-term opioid therapy is not likely. As most patients on opioid therapy for chronic pain are treated in primary care settings, evidence is needed for strategies to support deliver improved pain and opioid management in primary care.

2.2. Study Rationale

Our work has identified numerous barriers to improving pain and opioid management in primary care, including ineffective communication, patient and provider knowledge deficits, limited time and appointment availability, and insufficient resources in terms of clinical staff,

assessment tools, and treatment pathways. The 2014 NIH Pathways to Prevention opioids for chronic pain panel concluded that individual clinicians "are often overburdened and have insufficient resources," so "systems of care must facilitate implementation" of pain and opioid management guidelines.

In VA, national pain management and opioid safety initiatives direct local facilities to increase use of nonpharmacological pain care and improve opioid management, but clinical leaders at each facility must decide how to achieve these objectives. As in non-VA health care settings, clinical leaders need direct and high-quality evidence to guide decisions about how to allocate finite resources to achieve dual goals of improving pain while reducing opioid use. This study compares two systems of care strategies that each use patient-centered approaches to address barriers to improved pain and opioid management in primary care.

Our overall approach is informed by our engagement with patient partners, who strongly emphasize the primary need for individualized pain care and longitudinal support to achieve pain management goals. A second point of partner emphasis was the need to address potential mistrust toward a health care system that initiated many Veterans on long-term opioids and now could be seen as pulling "the rug out from under [them]." Accordingly, the central focus of our interventions is on optimizing pain care. Likewise, our primary outcome is improvement in pain.

2.2.1 Rationale for TCM intervention

TCM is the low-intensity pain management intervention. It is based on the three component model, initially developed as a structured approach to addressing primary care barriers to depression care and subsequently extended to pain care. In the TCM arm, the central care provider is a pharmacist care manager who has regular follow-up visits with the patient and delivers care in collaboration with a consulting physician and the primary care team.

TCM effectiveness for chronic pain has been demonstrated in multiple trials. In the SCOPE trial of TCM vs. usual care for chronic pain, participants in the TCM arm were nearly twice as likely to have a clinically important improvement in pain at 12 months. A pre-specified subgroup analysis found a positive response to the intervention among the third of study participants who were on opioids at baseline. TCM has not been specifically tested as an approach to achieve opioid dose reduction, but it was easily extended to include opioid tapering in the VA-funded SPACE trial.

In patient-facing and public-facing materials (e.g., study brochure, recruitment letter), TCM will be referred to as "pharmacist pain care."

2.2.2 Rationale for IPT intervention

IPT is the higher-intensity pain management intervention. It is based on the biopsychosocial model, which is the dominant heuristic to explain chronic pain as a complex phenomenon determined by biological inputs, as well as factors such as mood, cognitions, relationships, and health care systems issues. In the IPT arm, an interdisciplinary team delivers biopsychosocial care emphasizing multimodal pain management and behavioral activation.

IPT effectiveness is supported by indirect evidence from trials of other interdisciplinary pain programs and observational evidence from similar programs implemented in VA.

RCTs have demonstrated the effectiveness of a variety of interdisciplinary pain programs that combine medical, psychological, and exercise approaches, as in the IPT arm. Further, several observational reports suggest that IPT clinics can improve care. For example, the Integrated Pain Clinic at the West Haven VA—staffed by a physician, psychologist and physical therapist—demonstrated improvement in patient and provider pain treatment satisfaction.

In patient-facing and public-facing materials (e.g., study brochure, recruitment letter), IPT will be referred to as "integrated pain care."

2.2.3 Rationale for expanded taper options intervention

All patients in the study will receive standard information about opioid tapering, which typically involves gradually decreasing daily doses of opioids over time. Patients randomized to the expanded options arm will receive information about buprenorphine rotation as an optional component of their personal treatment plan. Patients who opt in to buprenorphine rotation will complete a separate informed consent process for the buprenorphine rotation research protocol.

Rotation to buprenorphine, a partial opioid agonist with analgesic properties similar to those of other opioids, may help patients reduce opioid use by effectively treating the opioid withdrawal syndrome while allowing more rapid dose reduction. Opioids cause physical dependence in most persons with long-term exposure. In physical dependence, interrupting or stopping opioids causes unpleasant withdrawal symptoms, which include increased pain and dysphoria and sometimes opioid craving. These problems are major barriers to opioid discontinuation, both for persons who use opioids illicitly and for those who take prescribed opioids. Slowly reducing opioid doses over time (usually over months) can prevent development of withdrawal symptoms, but some patients on high opioid doses may prefer a more rapid approach facilitated by buprenorphine rotation.

In patients with opioid use disorders, strong evidence from multiple RCTs supports buprenorphine effectiveness for achieving sustained abstinence from illicit opioids. Observational evidence suggests buprenorphine is similarly effective for successful discontinuation of full-agonist opioids in patients on long-term opioids for pain and that patients transitioned from high-dose opioids to buprenorphine often have improved pain/function and decreased opioid AE.

3. STUDY DESIGN

3.1 Overview of Study Design

This is a pragmatic comparative effectiveness trial that will enroll VA primary care patients receiving moderate or high-dose opioid therapy for chronic pain of at least moderate severity. The study will be conducted at ten VA sites. A central coordinating center will identify potentially eligible patients based on dose and duration of opioid therapy and conduct screening interviews by telephone. Eligible and interested patients will be scheduled for an enrollment visit with their local site coordinator. After providing written informed consent, patient participants will be randomly assigned at the individual level to either TCM or IPT, stratified according to their baseline opioid daily dose (moderate or high). In TCM, a pharmacist care manager optimizes medication management in collaboration with a consulting physician; in IPT, an interdisciplinary team delivers biopsychosocial care

emphasizing multimodal therapy and behavioral activation. In both arms, participants receive patient-centered care over 12 months, with specific pain treatments and opioid taper decisions based on individual clinical assessment and shared decision-making. All patients in the moderate-dose subgroup will be assigned to receive standard opioid taper options. Patients in the high-dose subgroup will be randomized to either standard or expanded (including buprenorphine rotation) taper options. Patients, clinicians, and local site research personnel will be unmasked to treatment arm assignment. Masked outcome assessors at the coordinating center will conduct telephone interviews at 3, 6, 9, and 12 months to collect patient-reported outcomes. If participants are unable to complete 6 or 12-month telephone interviews, they will be offered an alternative mode for completion of outcomes—an abbreviated questionnaire sent by mail. Opioid dose and adverse event outcomes will be extracted from the electronic medical record.

3.2 Pragmatic Features

Pragmatic trials combine the strength of randomized treatment assignment with design elements intended to maximize applicability of findings to diverse patient populations and clinical practice settings. With the goal of maximizing pragmatism, we applied the PRECIS-2 tool for trial design to assess the consistency of our design choices with our overall goals. We take a highly pragmatic approach to eligibility, setting, organization of care delivery, flexibility of intervention delivery, flexibility of intervention adherence, and analysis.

The approach to intervention delivery is particularly pragmatic. TCM and IPT elements are defined in terms of "core" and "optional" components. During the first year of the study, each site will partner with key patient, clinician and administration stakeholders to establish their core and optional components based on site resources, preferences, and feasibility. Volunteer VA clinicians will be trained in the TCM and IPT care delivery models and will deliver the study interventions.

The least pragmatic elements of the design are follow-up intensity and recruitment. Given the importance of patient-reported outcomes in pain research, we plan frequent follow-up contacts and telephone assessments by masked coordinating center staff to reduce ascertainment bias, minimize missing outcome data, and reduce participant attrition. For recruitment, we will use a proven centralized approach to achieve the target sample size while oversampling women.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria to be enrolled:

- Moderate or high-dose long-term opioid therapy (≥ 20 ME mg daily) for chronic pain
- Chronic pain of at least moderate severity (defined as pain that is present for ≥ 6 months and with a score on the PEG 3-item pain measure of ≥ 5)
- Willingness and anticipated availability to participate for 12 months

4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation:

- Dementia diagnosis or moderate-severe cognitive impairment.
- Unstable or severe untreated psychiatric disorder, including severe untreated substance use disorder and active suicidal ideation
- Unstable or end-stage medical disease that would interfere with participation, including cancer requiring active treatment and life expectancy < 12 months
- Documentation of suspected controlled substance diversion
- Inability to communicate by telephone

4.3 Recruitment, Enrollment, and Study Arm Assignment

4.3.1 Recruitment overview

This study will employ both centralized and local site-based recruitment approaches. As for our prior studies, a customized study tracking program will support coordinated completion of research tasks, including preparing recruitment mailings, scheduling participant contacts, and randomizing participants. This program will be located on a secure network drive behind the VA firewall and will be accessible only to approved study personnel.

The centralized approach will use monthly data extractions to identify potentially eligible patients, followed by mailed invitations and telephone follow-up for eligibility screening. Prior to the start of recruitment at each site, local site investigators will inform local primary care providers (PCPs) about the study and request blanket permission for coordinating center personnel to approach eligible patients in their panels. Each month, a subset of the preliminarily eligible patients will be selected for contact using the centralized mail-then-call approach. Active monitoring of monthly eligibility and enrollment rates will allow adjustment of the number of patients contacted each month to maintain target enrollment rates. The initial approach will be based on our estimate that 75% of telephone-contacted patients will be eligible and 33% of eligible patients will agree to enroll. If estimated rates prove accurate and 33% of eligible patients enroll, we will need to contact approximately half (i.e., 7550) of the preliminarily eligible patients over the course of enrollment.

The local site-based recruitment approach will be based on clinician referrals. Local site study personnel will inform local site clinicians of the study using generalized outreach (e.g., presentations at clinical team meetings) and/or targeted outreach (e.g., providing clinicians with lists of their potentially eligible patients). Any clinician may refer their own patients to the study, including those who decline to provide blanket permission for patients to be recruited from their panels.

The study will not engage in nontargeted direct-to-patient advertising because patients are unlikely to know whether they meet the opioid dose criteria (and the vast majority of patients with chronic pain do not). Patients may directly approach study personnel seeking to enroll if they find out about the study, for example through word-of-mouth from other patients or a brochure provided by a local clinician; this is expected to be uncommon. Patients who self-refer to the study will be screened in the same manner as those who are referred by their clinicians.

4.3.2 Study population and sampling considerations

Women are underrepresented in US Veteran populations. To achieve better representation, we will oversample women by inviting all preliminarily eligible women and only a sample of men with the centralized recruitment approach. If estimated enrollment rates are accurate, we will enroll female participants at approximately twice the rate of their prevalence in the population. Local site study personnel will also reach out to women's health clinicians to encourage referrals of female patients.

We plan pre-specified analyses to assess heterogeneity of treatment effect in the following patient subgroups: high-dose opioid therapy, depression symptoms, post-traumatic stress symptoms, potential substance use disorder (SUD), and fibromyalgia symptoms.

To ensure we enroll enough patients on high-dose therapy to have adequate power for Aim 2, we will oversample this group. We will not oversample other patient subgroups, but anticipate that oversampling women will increase the prevalence fibromyalgia as it is a female-predominant condition.

To take maximum advantage of the study's geographic diversity, we will attempt to enroll similar numbers of participants at each site. Monthly monitoring of eligibility, contact, and enrollment rates will be done for the study overall and by site. The number of patients contacted each month will be adjusted to maintain overall target enrollment rates. If enrollment rates are lower than expected at an individual site, site-specific factors will be addressed as indicated. If needed, site-specific enrollment targets will be adjusted to achieve overall enrollment targets; for example, this could include increasing recruitment contacts at a successful high-volume site to make up for lower-than-expected enrollment at another site.

4.3.3 Eligibility pre-screening

Potentially eligible patients will be identified through pre-screening searches of VA datasets. This pre-screening will be done centrally by data team members at the coordinating center, creating monthly lists of potentially eligible patients by site.

Pharmacy dispensing data will be used to identify patients on long-term moderate-to-high dose opioid therapy, defined for prescreening purposes as meeting the following criteria:

- ≥ 84 days' supply of qualifying opioid analgesic dispensed within the 90 days prior to the date of eligibility assessment; and
- Opioid daily dose ≥ 20 ME mg in the prior 90 days

To avoid recruiting patients with dementia, unstable psychiatric disorder, or those being treated for pain due to active cancer or terminal disease or for opioid use disorder, patients will not be selected if they have any of the following:

- Any chemotherapy, radiation oncology, hospice care, dementia clinic, adult day clinic, current nursing home residence, or opioid treatment program visit in the year prior to the study period
- Any diagnosis of dementia
- Active CPRS flag indicating high risk for suicide

- Limited life expectancy health factor at any visit in the past 12 months

To maintain a steady enrollment rate, only a selection of potentially eligible patients from permitting PCPs at active study sites will be contacted each month by the coordinating center for centralized recruitment. Selected preliminarily eligible patients will be given a study ID number and their names, addresses, and telephone numbers will be loaded into the study tracking application.

4.3.4 Centralized recruitment procedures

Coordinating center personnel will mail recruitment letters in batches to each new group of preliminarily eligible patients identified through the centralized pre-screening process. These letters will describe the study and include signatures of the PI and local site PI, as well as instructions for how to opt out of further contacts. Twelve days after each mailing (i.e., one week after letters are expected to arrive), study personnel will call patients to determine interest in participating and further assess eligibility.

4.3.5 Local site-based recruitment procedures

The lists of potentially eligible patients for each site will also be used to support local site-based recruitment. Local study personnel will use these lists for targeted outreach to local site clinicians, providing them with information about which of their patients are potentially eligible and reminding them about the study prior to upcoming appointments with potentially eligible patients. Clinicians will be encouraged to discuss the study with their patients and inform the local site study personnel if the patient is interested in discussing study participation. Study personnel will follow-up with referred patients in-person or by telephone, depending on availability and patient preference.

When patients are individually referred or self-referred, study personnel will check the pre-screening list of potentially eligible patients. If the patient is on the list, he or she will be considered preliminarily eligible. If the patient is not on the list, study personnel will conduct a brief chart review for eligibility criteria. When patients are determined to be preliminarily eligible, they will be given a study ID number and their names, addresses, and telephone will be loaded into the study tracking application.

4.3.6 Eligibility interview

When potentially eligible patients agree, a structured computer-assisted eligibility interview will be conducted to assess patient-reported inclusion and exclusion criteria. This will include the following:

- Pain chronicity
- Pain severity (PEG 3-item scale)
- Current SUD treatment or untreated SUD
- Availability for telephone interviews and clinical visits over 12 months
- Participation in current research or clinical programs that might conflict/overlap

When patients complete the eligibility interview and are determined to be eligible and interested in participating, study personnel will schedule the patient for an appointment with the local site coordinator/research assistant. Eligible patients who are unsure about

participation will be encouraged to discuss the study with their clinical care providers and given the option of a future follow-up recruitment call.

4.3.7 Eligibility chart review

As a final eligibility assessment step, local study site personnel will use a structured chart review form to conduct a brief review of recent clinic notes. This final step will look for evidence of exclusion criteria that may not be captured in prior steps. In case of uncertainty about eligibility (for example, in a patient with cancer and unclear prognosis), the patient's clinical providers will be consulted prior to enrollment. The chart review will examine evidence of the following eligibility criteria:

- Currently prescribed opioids (inclusion)
- Dementia (exclusion)
- Current life-threatening medical disease (e.g., active cancer treatment, end-stage organ failure) (exclusion)
- Documented suspicion of controlled substance diversion (exclusion)
- Severe untreated mental health or substance use disorder, active suicidal ideation (exclusion)

Local study personnel will also use the chart review to look for current or impending enrollment in conflicting or overlapping local clinical programs (e.g., intensive pain management program) or research studies.

4.3.8 Enrollment

Eligible patients will have an enrollment appointment with local site study personnel. This enrollment appointment may be conducted in-person, via VA video-telehealth technology, or by telephone, per patient preference and local availability. At this initial appointment, the local site study coordinator or research assistant will provide additional study information, answer any questions, and complete the informed consent process with the patient.

For in-person appointments, patients will be given a folder, pen, pillbox with the study logo, and a $5 VA canteen service voucher (regardless of whether they join the study). The voucher will allow the patient to purchase water, coffee or a refreshment while they review materials. Local sites will also provide a travel payment to offset transportation costs; these will be paid via pre-paid debit card to patients who attend an in-person enrollment appointment, regardless of whether they enroll in the study. Local sites may opt to give all patients the same flat travel payment (between $20-50) or use a tiered system based on distance from patients' home.

For appointments conducted by video or telephone, study personnel will mail the patient a packet containing folder, pen, pillbox with the study logo, pre-paid debit card (containing no value, to be used for incentive payments after each completed study interview) and two copies of the informed consent document and HIPAA authorization forms. Study personnel will ask patients to sign one copy of the consent form and HIPAA authorization and mail it back, using a study provided postage-paid envelope. Patients will be instructed to keep the second copy. Upon receipt of the signed informed consent and HIPAA authorization forms from the participant, the local study coordinator/research

assistant will keep them on file, per local policy. She/he will make a copy of the signed consent and HIPAA authorization forms and mail them back to the patient for his/her records.

Participants are not considered enrolled until the signed written informed consent and HIPPA authorization forms are received. If the signed consent and HIPAA authorization forms are not received within 14 days, study personnel will follow-up with the patient by telephone to determine interest in participation and troubleshoot problems with the forms or mail. Replacement copies will be provided, if needed. If the signed consent/HIPAA forms are received after 45 days, baseline outcome measures must be repeated prior to randomization. If study personnel do not succeed in contacting the patient by 45 days after the enrollment visit, no additional attempts will be made.

4.3.9 Randomization

After obtaining the written informed consent document (either in person or upon receipt of the original mailed copy) and completing the baseline interview, the local site coordinator/research assistant will initiate randomization using the study application randomization form. The randomization code will not be visible to personnel conducting randomization and can be completed only once per study ID, preventing study personnel from influencing treatment allocation. This process will simultaneously inform the coordinator and participant of the primary study arm assignment.To prevent patients from feeling pressured to taper opioids, the taper option assignment will be revealed only when participants agree to discuss options for opioid dose reduction. Regardless of whether the taper intervention is delivered, participants will be evaluated in their assigned arm.

Patients will be randomized within site and opioid dose (i.e., moderate or high) categories, in permuted blocks of size 4 or 8, to balance the proportions of participants with moderate-dose and high-dose opioid therapy in the intervention arms. Those in the moderate-dose group will be randomly assigned, with equal likelihood, to intervention arms. Those in the high-dose group will be randomly assigned, with equal likelihood, to intervention and tapering strategy combinations.

4.3.10 Masking

Participants will not be masked to treatment arm assignment due to the complexity of the intervention strategies. Local site treatment teams and local site study personnel will also be unmasked. To reduce risk of biased outcome ascertainment, all personnel conducting outcome assessments will be masked to treatment arm assignment.

5. STUDY INTERVENTIONS

5.1 Intervention overview

Patient participants will be randomly assigned to either telecare collaborative management (TCM) or integrated pain team (IPT) arms for 12 months. In both arms, patients receive pain care and opioid taper planning tailored to preferences and adjusted as needed to achieve individualized treatment goals. Core and optional components of each arm are listed in Table 1. In both arms, pain management approaches and medications are provided by volunteer clinicians as in usual VA care. No experimental therapies will be used, other than the buprenorphine rotation protocol, which is described in Section 5.6.

All patients will receive individualized information and recommendations related to their pre-existing opioid therapy, with timing determined by individual needs and preferences. When interested in reducing or discontinuing opioids, all patients will receive information about standard opioid tapering options, which involve gradual opioid dose reduction. Patients on high-dose opioids (≥ 70 ME mg/day) who are randomized to the expanded taper options arm will additionally receive information about the option of rotating to buprenorphine.

Table 1: Core and optional components of IPT and TCM interventions

	IPT arm		**TCM arm**	
	Core	**Optional**	**Core**	**Optional**
Defining elements	Interdisciplinary team care planning, multimodal pain therapy, behavioral activation sessions	N/a	Clinical pharmacist care management; structured symptom monitoring; pain medication optimization	N/a
Team members	At least 3 clinical disciplines, including a medical provider; a mental health therapist; and a clinical pharmacist and/or rehabilitation clinician	Other specialist or generalist clinicians. If team does not include a rehab clinician as a core member, a rehab point-of-contact should be identified	Clinical pharmacist; consulting physician	N/a
Team processes	Weekly case review meetings of all core team members	Scheduled or as-needed interval communication within team and with primary care	Weekly case review meetings of core team members	Scheduled or as-needed interval communication within team and with primary care
Pain care modalities	Individual behavioral activation (goal setting, MI/CBT) sessions; multimodal pain care planning; opioid taper support	Specific therapies per individual needs and local resources (e.g., group behavioral therapy, exercise therapy, complementary therapies)	Pain medication management; opioid taper support	Nonpharmacological therapies through usual care per local availability
Initial visit	Initial visit with medical provider and mental health therapist*	Medical provider and mental health therapist may see patient together or sequentially; initial visit may include other team members	Initial visit with pharmacist care manager*	Initial visit may include consulting physician

Follow-up visits	At least 2 visits* with medical provider (at least one within initial 3 months); 8 behavioral activation visits** with mental health therapist	Additional visits with any IPT clinician	At least 5 follow-up visits** with pharmacist (monthly x 2, then at least every 3 months)	Additional follow-up visits
Core common elements	Collaboration with primary care teams; patient-centered communication and study informational materials; shared decision-making about opioid dose reduction and pain therapies; individualized opioid taper assessment, preparation, and implementation.			

Any visit may be conducted in-person, by video, or by telephone if appropriate per local resources/policies and patient preferences. *Face-to-face (i.e., in-person or video) visits are the preferred mode. **Telephone visits are the preferred mode.

5.2 Common intervention elements

The TCM and IPT interventions share several common approaches and processes, including the following:

- Collaboration with primary care teams. During the study, TCM/IPT intervention clinicians will assume primary management of chronic pain care for patients enrolled in the study; however, both interventions are intended to supplement, rather than replace, primary care pain management. Intervention clinicians in both arms use structured CPRS templates to guide visits. Care management notes entered into CPRS are the primary method of communicating with the primary care team, consistent with usual practice in VA. If indicated by clinical or safety issues, clinical intervention teams will communicate directly with the patient's primary care or mental health team.
- Patient-centered informational materials. Patient-centered communication will be supported by development of informational materials. These materials will be used by clinicians in both intervention arms.
- Shared decision-making. Both arms will use a shared decision-making approach to guide pain treatment and opioid dose reduction. Shared decision-making is an approach to clinical decisions that involves bidirectional information exchange, interactional deliberation about options, and agreement on a course of action.
- Individualized opioid taper preparation. Clinicians in both intervention arms will manage pain with non-opioid therapies while assessing interest in and readiness for opioid dose reduction/discontinuation at each follow-up visit. When patients indicate interest in opioid dose reduction or in learning more about the process, detailed information about opioid tapering options will be provided. We anticipate participants will require a variable number of visits to develop readiness for opioid dose reduction/discontinuation, so timing of the process will be highly individualized. This approach allows patients time to establish trusting relationships and become more informed and activated.

5.3 Telecare Collaborative Management (TCM) Intervention

5.3.1 TCM defining elements

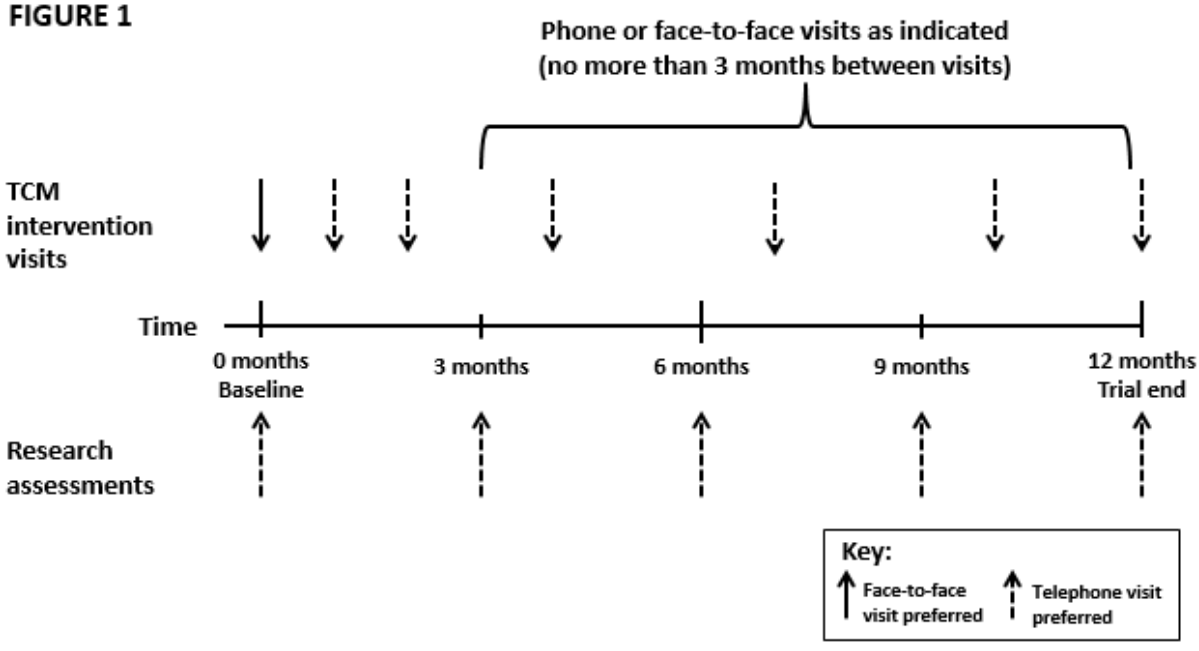
The TCM intervention arm has two defining elements: pharmacist care management, structured symptom monitoring and pain medication optimization.

- Pharmacist care management: A clinical pharmacist care manager delivers medication therapy and facilitates communication among the patient, primary care team, and collaborating physician.
- Structured symptom monitoring: At each TCM visit, the care manager will conduct a structured assessment using brief tools and a checklist of common adverse symptoms. Patients will be queried about progress toward their individual functional goals.
- Pain medication optimization: Medication management in the TCM arm will be operationalized as a series of medication trials undertaken using a shared decision-making approach. After each change in medication, the presence or absence of a clinical response will be assessed. This information will be used to support deliberation about whether to continue or change pain medications, including opioids.

5.3.2 TCM visit schedule

An overview of TCM visit timing, along with research assessment interview timing, is presented in Figure 1. All visits may be completed using any mode (in-person, video, or telephone); when applicable, the preferred mode for each visit type is indicated in the figure and text below.

FIGURE 1



The first TCM visit with the care manager will scheduled as soon as possible after study enrollment and randomization. Face-to-face (i.e., in-person or video) is preferred for the initial visit. First visit tasks include the following:

- Obtain history of current and past pain medication use, including opioid use, adherence, adverse effects, and response.
- Administer initial structured assessment battery including PEG pain scale; PHQ-4 depression and anxiety screener; and 3-item modified Prescribed Opioids Difficulties Scale (PODS)
- Establish initial pain management goals
- Provide pain management information; discuss initial options
- Discuss readiness for opioid dose reduction and any opioid-related goals; explore ambivalence about opioids; complete signs of opioid risk elevation (SORE) checklist; provide specific advice related to any safety or adherence concerns; discuss taper options if appropriate.
- Document visit on TCM initial visit template

Follow-up visits with the care manager will be scheduled monthly for the following two visits; subsequent visits will be scheduled according to individual needs during the remainder of the 12-month intervention, with a maximum of three months between visits. Most follow-up visits will occur by telephone, although participants will have the option of face-to-face visits. Subsequent visit tasks include the following:

- Administer structured follow-up assessment battery including PEG pain scale; global impression of change rating; PHQ-4 depression and anxiety screener
- Assess progress toward pain management goals; revise goals when appropriate
- Assess adherence, adverse effects, and response to medication therapy
- Determine whether a medication change should occur, based on structured shared decision-making approach.
- Provide pain management information; discuss options
- Discuss readiness for opioid dose reduction and any opioid-related goals; explore ambivalence about opioids; complete SORE checklist; provide specific advice related to any safety or adherence concerns; discuss taper options when appropriate.
- Documentation of visits on TCM follow-up visit template

The final intervention visit will be scheduled as soon as possible after the 12-month outcome assessment interview. Prior to this visit, an individual study summary will be prepared for each exiting participant and an initial plan for medication transition will be developed. The final intervention visit will include the following:

- Review of study summary, including treatment history and progress toward individual goals during the study

- Education about the transition plan and initial steps to implement the plan
- After the visit, the individual study summary and transition plan will be documented in a final templated note with the PCP as cosigner.

5.3.3 TCM medication management

The general approach for medication management includes three steps: 1) individualized assessment, 2) patient education, and 3) shared decision-making. Main considerations for medication change decisions are the presence of pain response, defined as improvement in PEG score, patient global impression of change, and progress toward individual goals; adverse effects; and patient desire for change in medications. Medications may be discontinued, adjusted, or continued with the addition of adjunctive drugs, depending on the patient's individual history of medication use (including dosing, scheduling, and adherence), therapeutic response, and adverse effects. Principles for medication initiation and adjustment include the following:

- First-line choice will depend on prior medication trials, comorbidities, and adverse effect profiles.
- Adjuvant drugs will be used alone or concurrently with first and second-line drugs when appropriate.
- One medication will be adjusted at a time.

If medication changes are made, the care manager will mail a letter outlining those changes, along with an updated medication list.

5.3.4 TCM team processes

The pharmacist care manager is the central care provider and will communicate directly with the patient via face-to-face and telephone visits, as well as mailed communication. Case review meetings of the care manager and consulting physician will be held at least weekly to review progress with pain management, adverse effects, and any clinical problems. During the final year of intervention, as the number of active study participants decrease at each site, the site PI, in consultation with the team clinicians and coordinating center fidelity monitoring team, may change the frequency of case review meetings to less than weekly (but at least once/month).

The local site study coordinator/research assistant (or in their absence, coordinating center staff or local site PI/co-investigator) will attend these meetings. Medications will be prescribed or recommended by intervention clinicians according to individual patient needs. Medications will be dispensed through the local VA outpatient or VA centralized mail order pharmacy according to usual medication dispensing processes.

5.4 Integrated Pain Team (IPT) Intervention

5.4.1 IPT defining elements

The IPT intervention arm has three defining elements: an interdisciplinary team, multi-modal pain management, and behavioral activation sessions.

- Interdisciplinary team: Three or four types of clinicians are core to interdisciplinary clinic models described in the literature or implemented within VA—medical providers (physician or NP/PA); psychologists or other mental

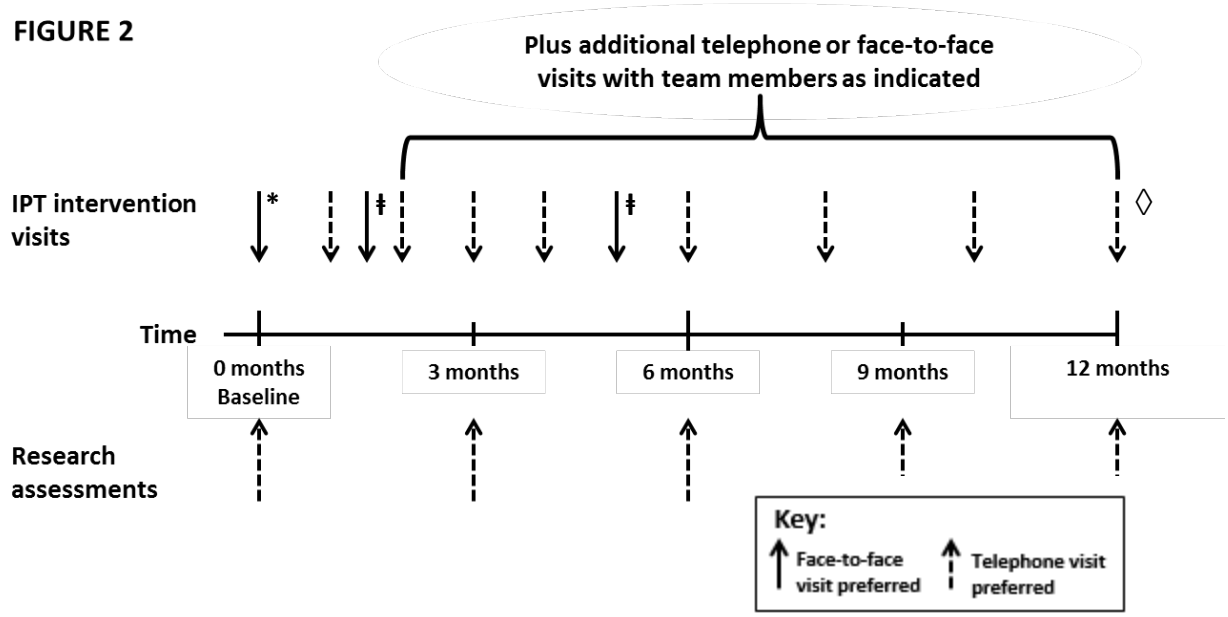
health therapists; clinical pharmacists; and rehabilitation clinicians (e.g., physical therapist, occupational therapist). IPT must have at least three types of clinicians in this study, including a medical provider and a mental health therapist. The third required position may be held by a clinical pharmacist and/or a rehabilitation clinician. Additional clinicians with pain expertise may also be included. If a rehabilitation clinician is not included in the core team, a rehabilitation clinician should be identified as a point-of-contact or "friend" of the team to facilitate clinical referrals and communication with rehabilitation services.

- Multi-modal pain management: The IPT arm will use a multi-modal approach that targets biopsychosocial contributors to pain and disability.
- Behavioral activation sessions: IPT clinicians will use MI communication techniques to engage patients, starting with eliciting core values and functional goals and developing individual pain care plans at the initial visit. Brief individual follow-up sessions conducted by the IPT mental health therapist will use MI and cognitive behavioral therapy (CBT) techniques to support patients' progress toward individual self-management goals. Delivery of specific CBT modules will be at the discretion of the clinician, based on individual patient needs.

5.4.2 IPT visit schedule

An overview of IPT visit timing, along with research assessment interview timing, is presented in Figure 2. All visits may be completed using any mode (in-person, video, or telephone); when applicable, the preferred mode for each visit type is indicated in the figure and text below.

FIGURE 2



***** Initial IPT visit: face-to-face (i.e., in-person or video) is preferred; required clinicians are medical provider and mental health provider; may be interdisciplinary visit or sequential visits.

ǂ Follow-up IPT visit: face-to-face is preferred; required clinician is medical provider; one must occur in first 3 months, second required follow-up visit may occur anytime (shown in figure at month 5 as example).

◊ Final IPT visit: may be telephone or face-to-face; any IPT clinician; after 12-month research assessment.

The first IPT visit (face-to-face preferred) will be scheduled as soon as possible after study enrollment and randomization. At this visit, the participant will meet with the IPT medical provider and mental health therapist, together or sequentially. First visit tasks include the following:

- Obtain history of current and past opioid and non-opioid pain medication use, non-pharmacological therapies, and self-management techniques and adherence, adverse effects, and response to each
- Administer initial structured assessment battery including PEG pain scale; PHQ-4 depression and anxiety screener; and 3-item modified PODS.
- Provide information on the biopsychosocial model of chronic pain, non-pharmacological pain management options, and opioid harms
- Develop pain care plan based on individual values and functional goals
- Discuss readiness for opioid dose reduction and any opioid-related goals; explore ambivalence about opioids; complete SORE checklist; provide specific advice related to any safety or adherence concerns.
- Complete initial MI session focused on pain care plan
- Document visit and pain care plan on IPT initial visit template

Follow-up IPT visits will be scheduled with individual IPT clinicians based on individual patient needs, including at least two follow-up visits with the medical provider (face-to-

face preferred; at least one in the first three months). The content of visits will be determined based on individual circumstances, but will include the following tasks:

- Administer structured follow-up assessment battery including PEG pain scale; PHQ-4 depression and anxiety screener
- Assess progress toward pain care plan goals (i.e., functional pain goals and opioid goals)
- If appropriate to visit, discuss readiness for opioid dose reduction and any opioid-related goals; explore ambivalence about opioids; complete signs of opioid risk elevation (SORE) checklist; provide specific advice related to any safety or adherence concerns; discuss taper options if appropriate.
- Document visits on IPT follow-up template

Follow-up behavioral activation sessions will be scheduled every month for the first six months and every 1-2 months for the remainder of the intervention period (i.e., ≥ 8 sessions). These will be brief (15-20 minute) telephone sessions unless the patient prefers face-to-face follow-up. Visit tasks include the following:

- Assess progress toward pain care plan goals and behavioral targets; build motivation for change; address ambivalence
- Share decision-making on action items that may result in further commitment to or modification of pain care plan
- Deliver CBT modules per individual needs
- Document visit on pain coaching follow-up template

A final intervention visit will be scheduled as soon as possible after the 12-month outcome assessment visit. The final visit may be conducted by telephone or face-to-face by any IPT clinician. Prior to this visit, an individual study summary will be prepared for each exiting participant. Final intervention visit tasks include the following:

- Review of study summary, including treatment history and progress toward pain care plan goals during the study
- Education about the transition back to primary care
- After the visit, the individual study summary and transition plan will be documented in a final templated note with the PCP as cosigner.

5.4.3 IPT pain management

The pain care plan is the guiding document for IPT pain management. Starting with the initial visit, IPT clinicians will elicit patients' core values and functional goals and collaborate with the patient to develop a pain care plan aligned with these values and goals. Specifically, the pain care plan will include up to three pain management approaches, including specific evidence-based therapies and self-management techniques, and up to three opioid harm reduction approaches, such as reducing the opioid dosage. Principles for pain care planning include the following:

- Patients will generate goals in collaboration with the clinical team

- Goals will be specific, measurable, action-oriented, realistic and time-bound
- Goals will be linked to multiple pain management approaches
- Goals will be focused on patient activation and self-management and not dependent on actions of health care providers

5.4.4 IPT team processes

Case review meetings including all core IPT members will be held at least weekly to review progress with pain management, adverse effects, and any clinical problems. Additional intra-team communication strategies suitable for each individual site will be determined prior to enrollment at each site. The local site study coordinator or research assistant (or in their absence, coordinating center staff or local site PI/co-investigator) will attend these meetings. During the final year of intervention, as the number of active study participants decrease at each site, the site PI, in consultation with the team clinicians and coordinating center fidelity monitoring team, may change the frequency of case review meetings to less than weekly (but at least once/month).

5.5 Standard Taper Intervention

All participants who are interested in learning about opioid dose reduction or discontinuation will receive information about standard opioid tapering options. In the TCM arm, the pharmacist care manager will provide initial information; in the IPT arm, the medical provider will usually be the one to provide initial information. Because evidence is lacking for any particular approach to opioid tapering, the standard taper intervention is based on guideline recommendations and our own clinical experience. The standard taper intervention incorporates shared decision-making about the following decisions:

- Taper target: Participants may choose to identify a target opioid dose and a tapering plan to achieve that target; alternatively, they may choose an open-ended approach, in which dose reduction is undertaken and re-evaluated one step at a time.
- Dose reduction rate: Both the size and the frequency of dose reductions may be individually determined. Guidelines suggest tapering 10-50% of the original dose per week, but more gradual tapers are preferred by many patients.
- Medication selection: In many cases, gradually reducing doses of original opioid medication is the most straightforward approach; in some cases, switching to a different opioid with greater dosing flexibility or availability of lower dosages is preferred. When patients take more than one opioid medication (in most cases, a short-acting formulation plus a long-acting formulation), either may be tapered first.

Patients will be provided with written informational materials and a written taper calendar with instructions. The taper plan will be documented in CPRS.

5.6 Expanded Taper Intervention

Participants who are randomized to the expanded options arm and interested in learning about opioid dose reduction or discontinuation will receive information about buprenorphine rotation as an optional component of their taper plan.

5.6.1 Buprenorphine rotation protocol overview

Patients who opt in to buprenorphine rotation will complete a separate additional written informed consent process specific to the buprenorphine rotation protocol. A buprenorphine-certified prescribing clinician will provide detailed buprenorphine education and manage the actual buprenorphine rotation for patients who choose this approach. If the buprenorphine prescriber is not a member of the assigned intervention team, an intervention clinician (i.e., TCM clinical pharmacist, IPT medical provider, or IPT clinical pharmacist) will provide initial information about standard taper and buprenorphine rotation approaches before referring to the buprenorphine prescriber. The local site coordinator (or other study staff approved to obtain informed consent) will conduct the informed consent process and work with the assigned intervention team and buprenorphine prescriber to ensure the protocol is followed throughout this process.

5.6.2 Buprenorphine regulatory issues

Although multiple buprenorphine formulations are FDA-approved, we plan to use the sublingual buprenorphine-naloxone formulation (i.e., Suboxone) that is most available in VA. The purpose of including naloxone, an opioid antagonist, in the formulation is to deter abuse of the medication by injection. If the combination medication is injected by a person with an opioid agonist in their system, the naloxone causes a precipitated withdrawal. When the combination medication is taken sublingually as prescribed, naloxone does not interfere with buprenorphine effects.

Sublingual buprenorphine-naloxone is currently FDA-approved for medication assisted therapy in opioid use disorder by physicians and mid-level providers who have completed a training program and received DEA certification. Use of sublingual buprenorphine-naloxone for physical opioid dependence due to prescribed long-term high-dose opioid therapy for chronic pain in patients who may not have addiction is an “off-label” unapproved use. FDA has determined that study use meets all of the following criteria for exemption from IND in 21 CFR part 312.2(b):

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- The investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent.
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

Although the DEA clarified in 2004 that prescribers may use buprenorphine-naloxone off-label for pain without DEA certification, we will have at least two buprenorphine-certified prescribers at each study site; one will be the primary prescriber in charge of the protocol and at least one will serve as a back-up prescriber. These buprenorphine-certified prescribers may or may not be members of the IPT or TCM team. If a prescriber is not a member of a patient's clinical intervention team, his or her role in the patient's care will be limited to managing buprenorphine rotation as a consultant in collaboration with the team.

At sites lacking two willing and already DEA-certified buprenorphine-naloxone prescribers, we will facilitate training to certify additional prescribers. Dr. Becker will run the 4-hour SAMHSA sponsored training webinar using video-linked interactive technology at no cost to participants. (The additional required training is available on-line at a time of the participant's choosing). An abbreviated interactive training will be provided to intervention pharmacists to ensure they are familiar with the buprenorphine rotation protocol and able to describe it in understandable terms to patients. Prescribers and intervention pharmacists will be trained in the specifics of the study protocol.

5.6.3 Buprenorphine rotation management

Decisions about how to initiate buprenorphine should be individualized, considering patient needs and preferences, as well as prescriber experience and local resources. Patients may initiate buprenorphine at home or in clinic. There are two methods for rotating from full-agonist opioids to buprenorphine: a traditional method and a newer method of microdose up-titration. In the traditional method, full-agonist opioids are stopped entirely prior to starting buprenorphine. Case series suggest that patients usually prefer tapering rapidly over 2-5 days, rather than discontinuing abruptly. The interval between last dose of the full-agonist opioid and the first dose of buprenorphine-naloxone depends on the duration of action of the full-agonist opioid. In most cases, 12-18 hours is appropriate for short-acting opioids. For long-acting opioids, a longer interval is typically needed, from approximately 18-24 hours for morphine SA to approximately 48-72 hours for methadone. Patients on methadone should first taper down to 30 mg daily dose of methadone, per standard protocol. Patients using the traditional rotation method are advised they will experience opioid withdrawal symptoms during the interval after stopping full-agonist opioids and before starting buprenorphine.

In the microdose up-titration method, buprenorphine is started at very low doses several days before the full-agonist opioid is stopped. Buprenorphine is up-titrated over several days (typically 3-5 days) and then the full-agonist opioid is discontinued once buprenorphine is at a therapeutic dose. Case series demonstrate that the microdose up-titration method is well-tolerated; in our clinical experience, some patients on long-term opioid therapy for pain prefer this approach because they do not have to experience opioid withdrawal symptoms before initiating buprenorphine.

Precipitated opioid withdrawal is the main potential adverse effect of buprenorphine-naloxone rotation; it is avoided if participants follow the initiation protocol. When using the traditional rotation method, the most critical point patients need to understand is that the "old" opioids must be out of their system before buprenorphine-naloxone initiation. This means they need to wait for the onset of at least moderate withdrawal symptoms.

When using the microdose up-titration method, the critical point is to start at a very low dose and increase according to instructions over several days. All patients will be provided detailed written and verbal information about opioid withdrawal symptoms and about precipitated withdrawal. Understanding will be confirmed by teach-back.
For patients who complete a rotation to buprenorphine-naloxone, decisions about subsequent buprenorphine management during and after the study will be made on an individual basis. Factors that will be considered include outcomes of therapy, patient preferences, and presence of a buprenorphine prescriber willing to continue prescribing beyond the study period. Options include the following:

- Continue on buprenorphine-naloxone;
- Taper off and completely discontinue opioids; or
- Rotate back to a full-agonist opioid. In this case, the full-agonist opioid will be started at a lower dose due to incomplete cross-tolerance.

5.6.4 Buprenorphine protocol consent process

Patients who are randomized to expanded taper options will receive initial information about buprenorphine rotation from their intervention clinician (i.e., TCM clinical pharmacist, IPT medical provider, or IPT clinical pharmacist). Those who are interested in learning more will be scheduled for a visit with a buprenorphine prescriber. This visit may be conducted in-person, by video, or by telephone per patient preference and local site visit availability. Face-to-face (in person or video) visits are preferred, but telephone visits are acceptable if allowed by current regulations and policies. This visit will include assessment of buprenorphine appropriateness, discussion of risks and benefits of buprenorphine rotation, and provision of buprenorphine educational materials and resources. The local site coordinator (or other study staff approved to obtain informed consent) will attend this visit if acceptable to the patient or meet with the patient and prescriber as soon as possible (in person, via video or telephone) afterwards to ensure the study protocol is followed (e.g., informed consent process is completed before buprenorphine is prescribed). If the prescriber determines buprenorphine is clinically appropriate and the patient would like to proceed with buprenorphine rotation, the local site coordinator (or other study staff approved to obtain informed consent) will complete the buprenorphine informed consent process.

To ensure patients make a fully informed decision about the buprenorphine protocol, written informed consent for the buprenorphine protocol will occur after the initial visit with the buprenorphine prescriber. Timing of the informed consent process may be immediately after this visit or at a later date if the patient would like additional time to consider.

For buprenorphine protocol appointments conducted by video or telephone, study personnel will mail the patient buprenorphine informational materials and two copies of the informed consent document prior to the appointment. Study personnel will ask patients to sign one copy of the consent form and mail it back, using a study provided postage-paid envelope. Patients will be instructed to keep the second copy. Upon receipt of the signed informed consent form, the local study coordinator/research assistant (or other study staff approved to obtain informed consent) keep it on file. Study staff will

make a copy and provide it to the local research pharmacy. A signed copy will also be mailed back to the patient.

5.6.5 Buprenorphine visit schedule

The initial buprenorphine visit with the buprenorphine prescriber may occur by any mode allowable by current regulations, as described above, but face-to-face (i.e., in-person or video) is preferred. First visit tasks include the following:

- Obtain history of current opioid use; assess buprenorphine risk factors (including risk for pregnancy if applicable)
- Provide standardized buprenorphine educational materials and resources
- Use shared-decision making to determine whether to proceed with buprenorphine rotation
- Document visit on buprenorphine initial visit template

Following buprenorphine initiation, structured follow-up will occur at three time points: 2 days, 1 week, and 3 weeks after initiation. These visits may occur by telephone or face-to-face, as appropriate. Patients will be instructed on whom to contact for problems or concerns occurring between visits. After the three structured visits, follow up will occur according to the assigned TCM or IPT intervention. Most follow-up visits will occur by telephone, although participants will have the option of face-to-face visits. Follow-up visit tasks include the following:

- Assess medication response and adverse effects, including withdrawal symptoms as appropriate
- Administer standard satisfaction questions
- Provide additional education and counseling as needed
- Document visit on buprenorphine follow-up visit template

5.7 Intervention Management of Adherence and Adverse Effects

5.7.1 Clinical monitoring of opioid adherence

The approach to opioid monitoring will augment, rather than replace, primary care management. Prior to the initial visit, intervention teams will review prior drug testing results and opioid fill patterns and determine whether local and national VA monitoring requirements have been met. If a patient is past due for any monitoring tasks, intervention clinicians will work with the primary care team to complete them. In addition, the PDMP will be checked and checklist of opioid non-adherence behaviors will be completed at each medication management visit.

5.7.2 Clinical management of opioid-related risk and opioid adherence problems

Intervention clinicians will facilitate use of opioid risk reduction strategies, including use of naloxone rescue kits, which are recommended by CDC guidelines for patients on moderate-to-high dose opioid therapy.

If opioid adherence problems are identified, they will be evaluated and addressed by intervention clinicians with the goals of improving both pain management and safety. Nonadherence behavior will be discussed at intervention case review meetings and an

individualized monitoring plan will be developed to aid in diagnosing and addressing the underlying cause of the behavior. This plan may include: a) education; b) medication adjustment; c) additional study or primary care visits; d) review of state PDMP database; e) urine drug testing; f) shorter prescription intervals; or g) referral to a mental health or addiction clinician.

5.7.3 Clinical management of opioid use disorder (OUD)

Intervention clinicians will be instructed to evaluate patients with symptoms or signs of OUD or other SUD to establish a diagnosis. OUD diagnostic criteria will be included in study templates for easy reference. The opioid dose reduction strategies proposed in this study are not sufficient treatment for opioid use disorder, so intervention clinicians will facilitate evidence-based addiction treatment for participants who receive an OUD diagnosis during the study. Depending on local site resources and usual care processes, addiction treatment may be integrated with primary care or may be delivered in an addiction specialty clinic. Regardless of the setting and degree of addiction care integration, intervention clinicians will collaborate with addiction treatment providers to maximize coordination of care for study participants. Participants who are diagnosed with OUD will continue to receive non-opioid analgesic and non-pharmacological therapies for their pain in their assigned TCM or IPT pain management arm. OUD will not be cause for withdrawal from the trial.

5.7.4 Clinical management of adverse effects

Medications will be prescribed and monitored by intervention clinicians according to usual standards of care and relevant clinical guideline recommendations. Prior to the start of trial enrollment, intervention clinicians involved in medication management will be provided with additional training on medication indications, contraindications, and interactions. Specific training will be provided to intervention clinicians on care of reproductive-aged women, including women who are pregnant, lactating, or could possibly be pregnant. Study medication management reference documents and educational tools will be available to all intervention clinicians on the study SharePoint site. The study pharmacist coordinator will ensure study medication management guidance is up-to-date and available throughout the study and will serve as a resource for intervention clinicians at all sites.

Study note templates will include prompts to perform medication reviews, query about contraceptives and potential of pregnancy, and consider potential drug interactions. Study educational materials will address common/important benefits and risks of medications. Educational materials for reproductive-age women will address common/important issues related to pain medications and pregnancy.

Study templates will also include prompts to inquire about treatment-related side effects and adverse symptoms. Intervention clinicians will manage these symptoms according to usual standards of clinical care, offering treatment for minor injuries and adjusting or discontinuing therapies as appropriate.

5.8 Intervention Fidelity

Delivery of intervention components will be tracked to ensure that patient participants at each site receive the core elements of each intervention and also to describe heterogeneity in intervention implementation and use of optional elements across sites. Intervention-specific

CPRS note templates will generate centrally retrievable electronic data elements (i.e., health factors), allowing us to measure the number and types of study visits attended by participants and examine aspects of intervention intensity and fidelity.

The research team will monitor fidelity to core intervention elements throughout the active intervention phase of the trial. Data generated from use of note templates and other sources will be used to populate internal study fidelity reports. Fidelity reports will include summary data across and within sites. Reports will be reviewed and discussed at least every 6 months on all-site meetings and DSMB meetings. If site or intervention arm-specific problems are identified, these will be addressed with involved research personnel or intervention clinicians.

5.8.1 IPT motivational interviewing (MI) fidelity

Because behavioral activation sessions are a defining element of the IPT intervention, fidelity to MI principles in these sessions will be assessed using the Motivational Interviewing Treatment Integrity (MITI, v 4.2) coding instrument. The MITI will be used to rate audio-recordings of a sub-sample of audio-recorded behavioral activation telephone sessions. For this pragmatic trial, fidelity monitoring will focus on training in initial sessions; later assessments will allow better understanding of intervention processes. Interventionists will be instructed to record all sessions to avoid selection bias (e.g., only providing "good" sessions to the research team). For the initial several months after the start of study enrollment, we will randomly select 10% of the recorded behavioral activation sessions. Two co-investigators will use the audio-recordings to code sessions for MI fidelity. After IPT clinicians demonstrate MI competency based on MITI ratings, we will continue to monitor MI fidelity in 5% of randomly selected visits. Finally, 1% of sessions coded with the MITI will be double-coded to establish inter-coder reliability.

5.9 Intervention Discontinuation and Transitions of Care

TCM/IPT intervention clinicians will assume primary management of chronic pain care for patients while they are participants in the study. Chronic pain management by the intervention clinicians will last 12 months unless the patient does not want to continue for the full 12 months. Patient participants may elect to discontinue active intervention participation for any reason at any time.

Patients will be encouraged to receive their chronic pain care from the TCM/IPT throughout their participation in the study; however, patients will not be restricted from seeking pain care from their PCP or other providers. Patient participants may continue in the study regardless of adherence to intervention protocols.

Chronic pain care will be transitioned from intervention clinicians back to the PCP when the patient completes participation in their assigned intervention. For most patients, this transition will occur at the scheduled end of their 12-month study participation after the final intervention visit. For patients who stop active participation in the intervention of their own accord, this transition will occur when they indicate their desire to discontinue participation.

Regardless of when and why the transition back to the PCP occurs, intervention clinicians will retain responsibility for chronic pain care (e.g., active medications, referrals) until the PCP accepts responsibility for the patient's pain care (i.e., the handoff is complete). The processes outlined below will be used to ensure continuity of care:

- Intervention clinicians will place a templated summary clinical care note in the patient's medical record with the patient's PCP added as a cosigner.
- Intervention clinicians will check the state prescription monitoring program and include information about outside prescriptions in the transition note.
- Intervention clinicians will contact PCPs directly to discuss anticipated transition needs or challenges. PCPs will be encouraged to contact intervention clinicians with any concerns.
- Patients will be encouraged to contact their intervention clinicians if they have any questions or concerns about the transition in their pain care.
- If intervention clinicians are prescribing medications at the end of the patient's study participation period, an updated prescription order will be entered in the medical record by the intervention prescriber and flagged for the PCP to sign. If needed to prevent gaps in medication availability, a limited medication supply will be prescribed by the intervention prescriber to cover patient needs until the PCP resumes prescribing.

6.STUDY DATA COLLECTION

6.1 Data Collection Overview

Three types of data will be collected for research purposes: 1) patient-reported measures; 2) administrative data; 3) qualitative data.

6.2 Patient-reported measures

Patient-reported measures, including outcomes and covariates, will be collected by interview at baseline and at 3, 6, 9, and 12 months. The baseline interview will be conducted by the local site study coordinator or research assistant after the patient provides verbal informed consent and before randomization. Follow-up outcome assessments will be conducted as telephone interviews by coordinating center research personnel who are masked to treatment arm assignment. Visual aids will be mailed to participants in advance so they can follow along with the interviews. If participants are unable to complete 6 or 12-month telephone interviews, they will be offered the alternative of completing mailed paper questionnaires. Participant responses will be recorded on machine-readable paper questionnaire forms, which will be subsequently double-scanned into an electronic database. Interviews are completed with the most critical measures first, to prevent missing core outcome data in case of interruption.

6.2.1 Timing and duration of assessment interviews

Full-length assessment interviews will be conducted at baseline, 6 months, and 12 months. The duration of assessment interviews will be approximately 60 minutes at baseline and 45 minutes at 6 and 12 months. A small participant payment ($50 each) will be provided after each of these interviews. A nominal token of appreciation (e.g., jar opener with study logo) will be sent to participants before the 12-month interview.

Abbreviated assessment interviews addressing core outcome measures will be conducted at 3 and 9 months. The duration of these abbreviated interviews will be approximately 15-20 minutes. A small participant payment ($25 each) will be provided after each abbreviated interview.

Timing of follow-up assessment interviews will be based on the date of the baseline interview. Follow-up assessments may be completed up to 30 days early when extenuating circumstances (e.g., planned travel or move) suggest that data may be otherwise lost. 3 and 9 month assessments may be completed up to 30 days late. 6 and 12 month assessments may be completed up to 60 days late. Data from assessments completed outside of these time windows will not be included in primary analyses.

If the first intervention visit is delayed >30 days after baseline assessment date, participants will be asked to repeat core baseline measures (administered by masked assessors), prior to the first intervention visit. A small participant payment ($25 each) will be provided after the abbreviated, repeat baseline interview.

At the end of the 12-month interview, the assessor will ask for permission to re-contact the Veteran, either for a qualitative interview (described below in 6.4.1) or other future interviews; participants will be reminded these future interview(s) are voluntary.

6.2.2 Alternative patient-reported assessment procedures

If assessment burden becomes a problem for participants at any point during the study, the option of completing a minimum assessment composed of core outcome measures will be offered. If participants are unable to complete interviews by telephone, a self-complete machine-readable paper questionnaire will be mailed. Participant payments will be provided as described above.

6.2.3 Description of patient-reported measures

Consistent with guidelines for outcome assessment in pain clinical trials, we will assess multiple domains, including pain intensity, function, and symptoms and adverse events, using validated patient-reported measures. Patient-reported outcome domains and data collection schedule are presented in Table 2.

Table 2: Patient-reported outcome assessment schedule

	Schedule (month)				
Measure	**0**	**3**	**6**	**9**	**12**
Pain, pain characteristics	X	X	X	X	X
Health related quality of life	X	X	X	X	X
Functioning	X	X	X	X	X
Adverse effects	X	X	X	X	X
Fatigue/sleep	X		X		X
Mood (e.g., anxiety, depression, PTSD)	X		X		X
Substance use	X				X
Predictors/explanatory variables	X		X		X
Use of health care services/self-care practices	X		X		X
COVID-19 questions	X	X	X	X	X

6.3 Administrative Data

6.3.1 Data sources

National VA datasets and the environment for analyzing them are provided by VA Informatics and Computing Infrastructure (VINCI). A VINCI project workspace will be used to access data, construct covariates, and perform primary and secondary analyses.

We will use administrative data to determine eligibility, covariates and outcomes, including the following:

- Patient eligibility criteria from outpatient pharmacy and inpatient and outpatient data domains
- Relationships of patients and primary care providers from PCMM domain
- Patient demographics from patient data domain
- Patients distance and drive time from VA facilities from geographic access data sets created by the planning services and support group
- Physical and mental health diagnoses from inpatient and outpatient data domains
- Prescriptions and drug dispensing from outpatient pharmacy domain
- Pain treatment variables from outpatient and lab chemistry data; outpatient pharmacy data; and outpatient, procedure code, and fee basis data domains
- Hospitalizations, ED visits, and SUD treatment admissions from inpatient, outpatient, procedure code, and fee basis data domains
- COVID-19 test results

6.3.2 Opioid dispensing data

Opioid dose outcomes and medication covariates will be assessed using VA outpatient pharmacy dispensing data. Opioid daily dose at any given time will calculated as the mean dose over the prior 90 days, so the main opioid dose outcome will therefore be an average dose over the final 90 days of the study intervention period. To provide information about dose after the intervention is complete, our final dose assessment time-point will be three months after the end of the study. Established conversion tables will be used to calculate morphine-equivalent (ME) mg.

6.3.3 Pain treatment data

Receipt of pain-related services outside of intervention visits will be estimated by capturing specialty, rehabilitation, and mental health visits. Complementary therapies are not all well captured in VA databases, but therapies with specific codes (e.g., acupuncture) will be assessed. Other complementary services may be variably recorded under general codes; for example, yoga could be coded as a recreational therapy visit. To maximize our capture of VA complementary therapy service delivery and validity of these data across sites, local study personnel at each site will be asked to inventory local complementary therapy availability and clinical coding practices on an annual basis; these inventories will be reviewed by the coordinating center data and statistical team and considered in administrative data extraction and cleaning protocols.

6.3.4 Intervention treatment data

Data will be collected on intervention visits to describe the care provided, as well as fidelity to the intervention arms (see 5.8). Intervention clinic visit notes will be used to count the number of intervention visits (face-to-face, video and telephone) in both arms over the study period. Structured notes will be designed to generate data objects that can later be captured from administrative data to describe intervention processes.

6.4 Qualitative Data

Qualitative process evaluation data will be gathered to examine patients' and clinicians' perceptions of the TCM and IPT interventions; to describe the context and processes of intervention delivery; and to assess potential for long-term sustainability and widespread dissemination of the interventions.

6.4.1 In depth interviews with patient participants, clinician participants, and other VA employees

A purposeful sample of patient participants in both the TCM and IPT intervention arms will be interviewed by telephone after their study participation is complete. We will purposefully select participants who are diverse in terms of age, sex, race/ethnicity, study site, and level of participation in the intervention (defined by the number of intervention visits completed during 12 months). The data team will provide names of potential participants based on demographic characteristics, assigned arm, and level of participation; interviews will take place within approximately three months after completing the study intervention. A semi-structured interview guide will be used. Questions will address experiences with the interventions, perceptions of the value and convenience of the interventions, what (if any) aspects of the intervention were most or least influential in terms of their personal treatment outcomes, and any recommendations for improvements. Interviews will be audio-recorded and transcribed. Data collection will continue until theoretical saturation is reached. Based on recommendations for qualitative sampling, we expect to conduct 15 interviews for each study arm, for a total of approximately 30 patient interviews.

In addition, a separate sample of VOICE participants across both intervention arms will be interviewed by telephone about COVID-19 pandemic-related experiences that could be relevant to their pain and pain care. Interviews will be conducted using an original semi-structured interview guide following the same approach described above for other patient interviews. We anticipate conducting approximately 30 additional interviews.

A purposeful sample of clinician participants will be interviewed. Intervention clinicians at different sites, in both arms, and with differing roles will be asked to participate. Interviews will be one-time events and will be timed to obtain information about intervention implementation; therefore, they may be done before, during, or after intervention participation. Interview questions will address reactions to the intervention, perceptions of effects of the intervention on patient outcomes, key facilitators and barriers to maintaining the interventions as standard clinical practice, and recommendations for changes to the intervention to increase the "fit" of the intervention into the clinic. Clinicians will also be asked about effects of increased use of telehealth. To inform possible future implementation efforts, the interviews will also focus on perceptions of the facilitation method for implementation of the interventions in order to determine whether the level of facilitation was sufficient for high fidelity implementation, whether it created an undue burden on clinical personnel and any changes that could be made to improve facilitation.

In addition, up to 46 VOICE clinicians involved in discussing buprenorphine as part of the expanded taper options intervention will be interviewed about their perspectives on buprenorphine and experiences with discussing buprenorphine. Buprenorphine-related clinician interviews are expected to take 30-60 minutes. If clinicians are also completing

the main interview described above, buprenorphine-related interview questions may be asked at the same session or at a second separate interview session, depending on logistics and the preferences of the clinician being interviewed.

Finally, selected additional local site clinicians, administrative staff, and other VA employees will be interviewed during the study as part of the process evaluation. These additional VA employees will be selected based on their positions and experience with the study, with the goal of obtaining a diverse array of perspectives on intervention implementation processes. Unlike the patient participants and clinical participants described above, these employees will not have prior participation in the study. Study investigators will identify potential participants and Minneapolis coordinating center personnel will send invitations by email. Employees who agree to schedule an interview will be informed of the study purpose using an information sheet, provided the opportunity to have questions answered, and asked to provide verbal consent. Interview questions will address facilitators and barriers to maintaining the interventions as standard clinical practice, recommendations for changes to the intervention to increase the "fit" of the intervention into clinical practice, burden on clinical personnel, and any changes that could be made to improve implementation.

6.4.2 Informal interviews and observation

The study process evaluation team will collect data on study implementation processes using participant observer and unstructured conversational interview techniques. They will attend and observe meetings, including investigator meetings, local site rollout meetings, and intervention clinician team meetings. In the context of these meetings and other interactions, they will gather data from investigators, intervention clinicians, and stakeholders using unstructured conversational interview questions. Data will be recorded in the form of field notes.

7. STATISTICAL ANALYSIS

7.1 Sample Size Considerations

For our power calculations, we used an effective sample of at least 776 patient participants (at least 80% of initial sample size of 970) for the comparison of 12-month outcomes.

7.1.1 Power estimates for primary analyses

Prior research observed 50% of patients achieving a 30% or greater reduction in BPI at one year with a TCM intervention. Assuming a similar response rate for TCM at a significance level of 0.05, a sample size of 970 enrolled participants provides 80% power for a 2-sided chi-squared test comparing pain response rates for TCM and IPT if IPT adds 10% to the response rate, and > 85% power if IPT adds 11% to the response rate. For the second aim examining adding buprenorphine to the tapering protocol, with an unadjusted 0.05 significance level, the estimated proportion of the sample on high-dose therapy (35%) will result in approximately 135 participants per treatment group and provide > 80% power to detect small to moderate effects (Cohen d or standardized difference) in mean BPI scores of 0.35 or more.

7.1.2 Subgroup power estimates

A difference of 1 unit in BPI is considered clinically significant and the SD of the BPI scores is typically about 2 units. A sample size of 776 participants at the 12-month

assessment will provide > 80% power for detecting a clinically meaningful difference in intervention effects across subgroups with prevalence of at least 40%, assuming a Bonferroni corrected significance level of 0.01. For a 1.2-unit difference in intervention effects, the study will have > 85% power for subgroup prevalence of 25% or more. Within a subgroup, the study will have > 80% power to detect an intervention effect of 1 unit or more for subgroup prevalence of > 25% and a 0.01 significance level. These power calculations for comparisons of 12-month outcomes consider just the data for this assessment point as a worst-case scenario. The repeated measures analyses discussed below should have power greater than discussed here for comparing the 12-month outcomes. Based on preliminary data, we anticipate the proposed sample size will provide adequate power for planned assessments of the HTE for all planned subgroups; if prevalence of any subgroup is <25%, assessment of HTE across subgroups will be exploratory.

7.2 General Analytic Approach

We will use an intent-to-treat approach, including all patient participants in the arm to which they were originally assigned. Preliminary descriptive analyses will summarize the distributions of the relevant baseline measures for each arm together with outcome distributions across the assessment points. We will summarize completeness of the outcome assessments and examine associations between completeness and the baseline measures as well as pain measurements, receipt of pain medicines outside the VA, and VA service utilization over the follow-up period. In previous and ongoing studies using similar eligibility criteria and follow-up structure, we have observed outcome completion rates in excess of 95% at each assessment time-point and > 98% of participants have provided outcomes at one or more follow-up time-points. Initial analysis will use all available follow-up data and subsequent sensitivity analyses will examine the potential effect of response bias.

7.3 Statistical Analysis of Primary Aim

We will use all follow-up data in a repeated-measures logistic regression modeling 30% reduction from baseline in BPI scores at the quarterly follow-up assessments. The regression model will use assigned intervention, assessment point, and their interaction as explanatory measures. Assessment points will be incorporated as random effects, with non-zero means and an unstructured covariance, to model potential correlation among outcomes for individuals. Our primary assessment of intervention effects will examine differences in the log odds of attaining a 30% reduction in BPI at the 12-month assessment using a two-sided Wald test (0.05 significance level), together with the corresponding model-based odds ratio point and confidence interval estimates.

To assess the sensitivity of these initial analyses to response bias, we will fit a series of weighted selection model analyses. Each analysis will use an EM algorithm to estimate weights to assign to potential values of the missing outcomes for use in logistic regression. The regression will model the log odds of a reduction in BPI at 12 months using the assigned intervention and relevant baseline measures as predictors. The EM algorithm will jointly use a logistic model for observation of the 12-month outcome to iteratively update the weight estimates. These latter logistic models will be varied to use different combinations of the following variables—12-month outcome, intervention, observation and value of the outcome at prior assessments, and baseline covariates together with pain measurements and services utilization over the follow-up period—as predictors to consider different potential missing at

random and missing not at random mechanisms generating the missing data. The approach outlined above will also be used to examine differences in reduction in opioid use at 12 months, the combination of pain reduction and opioid use reduction, and the BPI severity and interference subscales.

7.4 Pre-Specified Subgroup Analyses

We will examine variation in the intervention effects on the change in BPI within clinical subgroups defined by presence or absence at baseline of the subgroup status/conditions described above. For each subgroup measure, we will fit a repeated-measures linear regression modelling change from baseline in BPI at the quarterly follow-up assessments using assigned intervention, assessment point, subgroup indicator and all interactions between these three measures together with baseline BPI score and its interaction with assessment point as explanatory measures. Assessment points will be incorporated as random effects, with an unstructured covariance, to model potential correlation among outcomes for individuals. Our primary assessment of an interaction between intervention and the subgroup measure will use the model-based two-sided Wald test for an interaction at the 12-month assessment, using a 0.005 significance level. Weighted selection model analyses similar to those described above will examine sensitivity of 12-month results to response biases.

7.5 Secondary Analyses and Analysis of Secondary Outcomes

If the proportion of patients in the standard options arm achieving the 50% dose reduction outcome falls in the range 20%-70%, the anticipated sample size will provide 80% power to detect between-group differences in the range of 14 and 17%. The study will have this same level of power for comparable differences in the proportions achieving a 25% dose reduction and proportions with any dose reduction. We will have 80% power for assessing small to moderate differences of 0.35 SD in mean dose change.

The secondary dose escalation outcome is defined as a proportional increase in daily dose of $\geq$ 25% from baseline to 12 months. If 5-15% of participants meet this dose escalation outcome, we will have 80% power to detect between-group differences of 7-8%.

In addition, we will assess between-group differences in the pain-related function, pain intensity, quality of life, fatigue and sleep, mental health measures, and physical symptoms over the follow-up period. We will fit separate repeated-measures linear regressions modelling change from baseline at the follow-up assessments using assigned intervention, assessment point and their interaction together with the respective baseline score and its interaction with assessment point as explanatory measures. Assessment points will be incorporated as random effects, with an unstructured covariance, to model potential correlation among outcomes for individuals. The primary assessment of an intervention effect on a particular outcome will use the model based 2-sided Wald test for a difference at the 12-month assessment together with the point and confidence interval estimates for the mean difference in change from baseline.

We will examine variation in effects by sex, study site and over the course of enrollment, as well as moderation of effects by relevant covariates. Analyses will be similar to the subgroup analyses described above.

7.6 Analysis of Tapering Strategies

Among the subset of participants on high-dose opioid therapy at baseline we will modify the analyses discussed above by adding the tapering assignment as an explanatory measure to the

model structure in the same manner as the TCM/IPT measure is included in the models. We will use comparable testing and estimation approaches to assess whether the expanded tapering option results in better outcomes in this subpopulation.

7.7 Analysis of Adverse Events

Information about hospitalizations, ED visits, SUD admissions, and other adverse events will be extracted from VA administrative data. We will compare intervention arms with respect to the 1) proportion of individuals reporting any hospitalization, ED visit, and SUD admission and 2) number of hospitalization, ED visit, or SUD admissions per person at a) each assessment time-point and b) overall using, respectively, Pearson chi-square tests and, given the reasonable large sample in each arm, large sample normal approximation based z-tests. Similar comparisons will be made between other adverse events. We will also break these comparisons out by baseline dosage and assignment to the expanded taper options arm.

8. PROJECT MANAGEMENT

8.1 Project Management Overview

The overall study structure includes a central study coordinating center located at the Minneapolis VA and ten VA sites where patients will be enrolled and receive the interventions. The coordinating center will manage core research activities including centralized recruitment and outcome assessment; engagement activities; data management, programming, and statistical analysis; data and safety monitoring; and regulatory compliance. Local sites will enroll patients and implement the interventions. Local site study personnel include local site investigators and at least one local site study coordinator. Local study coordinator absences or vacancies may be covered by other local approved study staff or coordinating center staff if needed. Intervention clinicians are VA employee volunteers who are being trained and evaluated; those who are not co-investigators will be considered research participants themselves.

8.2 Study Application

The coordinating center data team will create a customized web-based front end application to support research tasks. The “front end” is a secure web page on the VA intranet, but the actual data “back end” is stored on a secure VA server maintained and regularly backed up by Region 2 of VA Office of Information Technology. Only approved specific study personnel are granted access to this application.

A user manual will be created as a guide for all study personnel. Contact information for patients selected for participation will be stored in the database. Additional tables will be created for scheduling and tracking study contacts. Coordinating center data team personnel will control access to the study application and provide access to research personnel at the coordinating center and local sites according to their research scope of practice. Study personnel will use the application to complete tasks including preparing recruitment mailings, conducting standardized eligibility screening, scheduling participant contacts, randomizing participants, and recording completed outcome assessments and adverse events.

8.3 Local Site Facilitation

During the start-up phase at each site, the study leadership team will support establishment of intervention clinical teams using an implementation facilitation approach. This will include the following activities:

- Assignment of each local site to a designated facilitator (Drs. Krebs, Seal, and Becker) for ongoing interactive problem-solving and support
- Development of detailed local site implementation plans
- Conduct of pre-implementation local site visits to accomplish the following objectives:
    - Describe rationale for the study and evidence for the interventions through research presentations and local stakeholder briefings
    - Develop relationships with local stakeholders and clinicians
    - Identify local site implementation challenges and opportunities
    - Refine local site implementation plans, including timetable
- Establishment of cross-site collaborative groups to support local site clinical champions and clinician intervention teams

8.4 Local Site Rollout

Enrollment at individual local sites will be initiated on a rolling basis once sites have met all criteria for enrollment launch. We plan to initiate enrollment at 1-3 sites per month over 3-5 months, with the order of launch depending on local site readiness.

The PM will coordinate training for study coordinators and research assistants at all sites. The Minneapolis coordinating center team will use audio-visual resources to conduct "mock" consent sessions and share them with sites as a training tool. Ongoing training will be provided throughout the study as new personnel come onboard or if questions or issues arise at local sites.

Prior to beginning enrollment at each site, the PI and overall study project manager (PM) will meet with the local site PIs and coordinators to ensure they fully understand informed consent, randomization, and data management procedures. A local site start-up checklist of required approvals and trainings will also be completed. Prior to initiating enrollment at any local site, all of the following criteria must be met:

- Approvals obtained from the VA Central IRB (i.e., the Local Site Investigator application), the Research & Development committee of record, and any additional regulatory bodies as required at the local site (e.g., University IRB)
- Site study coordinator and investigator(s) trained in study research protocols, including informed consent, randomization, adverse events reporting and other data/safety monitoring procedures
- Intervention clinician teams established and trained in clinical background, intervention protocols, documentation templates, educational materials, study resources, and local site protocols for clinical coverage

8.5 Cross-Site Communication

Current protocol, informed consent, and study intervention documents will be maintained on the study SharePoint site. All amendments and modifications to the protocol, the informed consent form, and the HIPAA authorization will be promptly communicated to local sites by email. Regular cross-site study meetings will include discussion of any anticipated or recent changes to the study protocol and procedures.

8.6 Local Site Contingency Plans

In case of significant delays in meeting enrollment launch criteria, despite facilitation efforts, site discontinuation and replacement will be considered. Consideration of site discontinuation or replacement will be discussed with engagement partners and PCORI staff prior to making a decision. If a decision is made to change a site, prior approval will be requested from PCORI as outlined in the contract for the funded research project.

9. IMPLEMENTATION PROCESS EVALUATION

9. 1 Process Evaluation Overview

Goals of the implementation process evaluation are threefold: 1) to increase the relevance of the primary research findings to patients, clinicians, and health care decision-makers; 2) to increase the likelihood of timely translation of research findings into diverse practice settings; and 3) to generate information to guide interpretation of primary trial findings. In addition to scientific reports and manuscripts, products of this process evaluation will include an implementation toolkit (developed in collaboration with study partners) to support implementation of successful study interventions in diverse practice settings.

9.2 Process Evaluation Questions

The RE-AIM and PARIHS frameworks related to dissemination/implementation were used to facilitate identification of questions related to the context of study sites and the process of implementing the interventions. Implementation process evaluation questions include the following:

- What was the level of organizational readiness relative to the clinical interventions, including staff's related perceptions/attitudes?
- What barriers or facilitators to the successful implementation of the study protocol were found (e.g., to what extent were clinic staff and leadership perceived as visibly supportive)?
- How were the interventions received by patients (e.g., how many of the selected patients actually participated in the interventions and were they different from those who did not)?
- How were the interventions received by patients who did participate actively (e.g., in terms of completion vs. drop-out rates and perceptions of usefulness to their treatment)?
- Were the study interventions provided with high fidelity?
- What, if any, recommendations do patients or clinicians have for changes to the interventions that they feel would improve the "fit" or effectiveness of the interventions?
- To what extent did facilities plan to sustain the interventions following completion of the study? If they planned to sustain an intervention, what barriers did they anticipate? How did they plan to modify the intervention from the original study protocol to address those barriers? If they did not plan to sustain an intervention, what considerations or barriers led to that decision?

9.3 Process Evaluation Methods

Qualitative or basic quantitative data will be collected as appropriate to each question. Approaches include the following:

- Evaluation team observations: Each study site will have an assigned member of the implementation evaluation team to take observational notes of interactions as described in Section 6.4.2.

- Information on patient recruitment and completion rates: Recruitment rates will provide an estimate of how appealing the interventions are to the targeted patients. Patients who decline study participation in the intervention will be asked their reason for declining. Intervention completion vs. drop-out rate will also provide information on acceptability of the interventions. Demographic and clinical data will be examined for the purpose of comparisons of decliners to enrollees and intervention completers to drop outs.

- Fidelity monitoring: In the event of negative findings (no intervention effect) for an intervention arm, it is essential to rule out implementation failure as a cause. Fidelity will be assessed as described in Section 5.8.

- Patient semi-structured interviews: A subset of participants enrolled in each study intervention will be interviewed at the end of their intervention participation as described in Section 6.4.1.

- Semi-structured interviews with clinician participants and other VA employees: A sample of clinicians directly involved in the interventions and other VA clinical and administrative staff at enrolling sites will be interviewed at the end of the intervention period as described in Section 6.4.1.

9.4 Qualitative Analysis

Qualitative data from the evaluation team observational notes and the transcribed semi-structured interviews will be analyzed by intervention evaluation team members, who are all experienced with qualitative data coding and analysis. They will review the transcripts and develop an initial coding list. They will each code an initial set of documents using the initial coding list, adding codes as new insights emerge. Consensus coding meetings will be held for review of consistency in coding. Inconsistencies will be resolved through mutual discussion. When evaluation team members have reached consistency in coding, remaining documents will be coded by one team member with 20% cross-coded by a second team member. Transcripts and codes will be entered into a software package designed to handle unstructured qualitative data (NVivo) to facilitate identification of themes and supporting quotations. Inductively derived themes will be compared with the elements identified by the PARIHS successful implementation model and RE-AIM dissemination model to further facilitate analysis and interpretation. All process data will then be triangulated, where appropriate, and used to answer the targeted questions and facilitate interpretation of summative findings.

10. DATA & SAFETY MONITORING PLAN

10.1 Overview of Data and Safety Monitoring Procedures

The proposed study confers a low level of risk, similar to routine health care. All participants will be followed with regular clinical intervention visits that will include monitoring of treatment response, adherence, and side effects.

At each site, intervention clinician teams will meet weekly to review participant progress, including pain and medication management, adherence, and adverse events. The study site

coordinator/research assistant (or in their absence, coordinating center staff or local site PI/co-investigator) will attend these meetings when possible to ensure adverse events and research-related problems and issues are appropriately identified and reported. Local site investigators and coordinators will meet regularly with the study leadership committee and coordinating center personnel. Local site study personnel will be expected to notify the study PI, PM, or other designated coordinating center personnel of serious adverse events, noncompliance, or other study related problems as soon as they are identified.

Coordinating center personnel will ensure appropriate reporting of adverse events (AEs) and other problems to the IRB, DSMB, funder, and local sites. The study application will be used for tracking AEs and generating standard reports.

10.2 Data and Safety Monitoring Board (DSMB)

A DSMB will review and evaluate study data related to participant safety, data integrity, and study conduct during the active enrollment and intervention phases of the trial. The DSMB will be convened and the first meeting will be held within 60 days after enrollment of the first trial participant. A DSMB charter will be finalized and approved at the first meeting. Members will be four clinical investigators and experts and will include at least one physician investigator, at least one pharmacist, and at least one biostatistician. One DSMB member will serve as DSMB Chair. Subsequent meetings will be held approximately every 6 months during the active intervention phase of the trial.

The DSMB will review aggregate and individual participant data related to safety, data integrity, and overall conduct of the trial and will provide recommendations to continue, modify, or terminate the trial. Termination or modification may be recommended on the basis of serious safety concerns, non-compliance with human safety regulations, or serious protocol violations. The DSMB will not review interim analyses of effectiveness.

10.3 Frequency of Data and Safety Monitoring

Coordinating center personnel will compile a data and safety monitoring report every six months during the active enrollment and intervention phases of the study. Reports will be submitted to the DSMB two weeks prior to each meeting. Reports will include the following:

- Description of serious adverse events, research-related problems, and protocol violations, including outcomes and follow-up
- Summary report of all adverse events
- Summary of recruitment outcomes, including rates of contact, refusal, and enrollment
- Summary of study progress toward milestones, including enrollment and outcome assessment targets
- Withdrawal rates, reasons for withdrawals
- Fidelity to interventions overall and across sites
- Study publications and reports

10.4 Known Risks and Potential Harms

Risks of interventions are similar to those in usual care. Medications and non-pharmacological therapies will be selected based on individual needs in both arms and are

not experimental in nature. Only the buprenorphine rotation protocol (described in 5.6) is considered an experimental treatment.

10.4.1 Known risks of study interventions

Participants may experience adverse effects of pain medications prescribed in the course of the study. Medications are FDA-approved and have known adverse effects; benefits and risks of medication changes will be discussed with patients as in usual practice.

Patients may experience withdrawal symptoms and other temporary discomfort due to reducing opioid doses or switching from one opioid medication to another. Intervention clinicians will educate participants about withdrawal symptoms, take precautions to prevent withdrawal, and manage symptoms if they occur.

Participants may experience adverse effects of non-pharmacological pain management therapies recommended in the course of the study. Non-pharmacological therapies (e.g., yoga, home exercise programs, psychotherapy) have known adverse effects, most of which are mild and transient. Benefits and risks of recommended therapies will be discussed with patients as in usual practice.

10.4.2. Known risks and potential harms associated with the underlying condition or study population

All participants will have chronic pain and be on long-term moderate-to-high dose opioid therapy at baseline. Long-term opioid therapy is associated with physiologic adaptations, including tolerance, dependence, and a withdrawal syndrome. Opioids have serious known risks, including respiratory failure, opioid use disorder, and death. Higher doses of opioids are associated with greater risks of depressive disorder, opioid use disorder, respiratory failure, suicide, and overdose death.

Chronic pain typically has a fluctuating course characterized by intermittent episodes of symptom exacerbation and improvement.

The study population is also expected to have a substantial pre-existing burden of physical and mental health comorbidity.

10.4.3 Known risks in pregnancy and lactation

Because the study is comparing care delivery strategies and no specific medication or treatment is required in any arm, pregnant women will not be excluded. Medications used in this study have variable safety profiles in pregnancy and lactation. Opioid withdrawal during pregnancy may increase risk of miscarriage and preterm labor.

For women under age 50, potential for pregnancy will be discussed prior to initiating medications or opioid tapers. If women are pregnant, lactating, or could possibly be pregnant, contraindicated medications will not be prescribed. Opioid tapering in women who are pregnant or suspected to be pregnant will be done in consultation with appropriate women's health providers, such as the patient's obstetrician. If indicated, intervention clinicians will facilitate pregnancy testing or initiation of effective contraceptive methods. Women who are pregnant or for whom pregnancy cannot be reasonably excluded will not be prescribed buprenorphine-naloxone.

10.5 Definitions of Potentially Reportable Events and Problems

- An adverse event (AE) is any untoward physical or psychological occurrence in a human subject participating in research. An adverse event does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention or research assessment.
- A serious adverse event (SAE) is an AE that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect, or for which medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome.
- A serious problem is a problem in human research or research information security that may reasonably be regarded as a) presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or b) substantively compromising a facility's human research protection or research information security programs. Examples of such problems include the following:
    - Situations that require action to prevent immediate hazard to subjects or others
    - Problems described in a VA Pharmacy Benefits Management alert relevant to human subjects
    - Inappropriate access, loss, or theft of documents or equipment containing PHI
    - Unauthorized destruction of research records
    - Use or connection of unauthorized equipment (e.g., non-VA thumb drive, unauthorized personally owned equipment) to store, process, or transmit VA research-related PHI
- An unanticipated or unexpected event or problem is an occurrence that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in the protocol-related documents and the characteristics of the study population.
- Related events or problems are occurrences that may reasonably be regarded as caused by, or probably caused by, the research.
- An unanticipated problem involving risks to participants or others is an occurrence that meets all the following criteria: 1) unexpected (as defined above); 2) related to participation in the research (as defined above); and 3) suggests the research places participants or others at a greater risk of harm (including physical, psychological, economic, social, or legal harm) than previously known or recognized.
- Serious noncompliance is a failure to adhere to requirements for conducting human research that may reasonably be regarded as a) presenting a risk of substantive harm to the safety, rights, or welfare of human research subjects, research personnel, or others; including their rights to privacy and confidentiality of identifiable private information; or b) substantively compromising a facility's human research protection or human research oversight programs

- A protocol deviation or violation is an act of noncompliance with the VA Central IRB-approved protocol or other requirements for conducting human research.

10.5.1 Assessment of adverse events

AEs will be systematically evaluated by study personnel at each site, with oversight by the coordinating center. In addition, medication-related symptoms and side effects will be extracted from templated intervention visit notes.

10.5.1.1 Hospitalizations or deaths

Local site PIs and site coordinators will monitor for hospitalizations and deaths using two main methods. First, site coordinators will enter enrolled patients in a personal CPRS patient list. Use of these lists generates automated notifications of VA hospital admissions, discharges, and deaths. Second, site coordinators/research assistants (or in their absence, coordinating center staff or local site PI/co-investigator) will attend weekly case review meetings and query clinicians at each meeting about any hospitalizations, deaths, or clinically-important AEs they learned about in the course of their clinical visits with participants.

Clinicians will also be asked to notify their site coordinator or site investigator via telephone or encrypted email if they learn of a patient's death (same business day), hospitalization, or other clinically-important AEs. If the coordinating center is notified by patient or family member of a hospitalization or death, coordinating center personnel will notify the applicable local site coordinator (via encrypted email) within one business day.

Local site coordinators/research assistants (or in their absence, coordinating center staff) will obtain medical records as needed for investigators to determine the nature and severity of adverse events, as described in section 10.6. If a hospitalization occurs at a non-VA facility, study personnel will obtain non-VA records from CPRS or, if needed, contact the community-based hospital to request records associated with the event. Participants will be asked to sign a release of information form if records are needed from a non-VA facility.

10.5.1.2 Assessment of treatment-related symptoms

Participants will be asked about medication related symptoms at each research assessment interview (3, 6, 9, and 12 months).

A checklist addressing common medication-related AE is incorporated into intervention follow-up note templates, along with an open field for reporting additional AE. Symptoms recorded in note templates will be retrievable for summary reporting.

10.5.2 AE/SAE tracking

Site coordinators/research assistants (or in their absence, coordinating center staff assisting site PI) will be responsible for entering AE information into a site-specific AE report tool on the study's secure sharepoint site. Each site's AE report tool is visible only to the local site PI and coordinator/research assistant, study leadership, and authorized coordinating center personnel. AEs will be updated in real time and coordinating center personnel may pull reports for all sites as needed.

10.6 Reporting of AEs and Research-Related Problems

10.6.1 Unanticipated and related deaths

Intervention clinicians and local site coordinators will notify the local site PI on the same business day (via encrypted email or phone) if they learn of a patient's death by any cause. Local site PIs will make the determination if a death is related to the research or is unanticipated. Local site PIs who are not physicians will consult with Dr. Krebs, Becker, or Seal for this determination for all participant deaths. In addition, any local site PI who is unsure whether a death is related to the research or unanticipated, will consult with Dr. Krebs, Becker, or Seal.

Deaths that are unanticipated and related to the research will be reported by local site study personnel immediately to the Central IRB (by calling 877-354-3130). Written notification to the VA Central IRB must follow within 5 business days of becoming aware of the death. Additionally, the local site PI or local site coordinator will notify the coordinating center (via encrypted email or telephone) if they learn of any patient's death, regardless of relationship to the research, and will add to their site's AE reporting tool.

These events must also be reported to PCORI within 10 days after reporting to the IRB.

10.6.2 Unanticipated and related SAE

Local site principal investigators and study coordinators will meet at least weekly. Local site PIs will determine whether events are related to the research or unanticipated. SAE that are unanticipated and related to the research will be reported in writing by local site study personnel to the VA Central IRB within 5 business days of becoming aware of the event. If a local site PI is unsure whether an event is related to the research or unanticipated, he/she will consult with Dr. Krebs, Seal, or Becker.

These events must also be reported to PCORI within 10 days after reporting to the IRB.

10.6.3 Serious and related unanticipated problems involving risks to participants or others

Serious and related unanticipated problems will be entered into the site-specific adverse event report tool on the study's secure sharepoint site. Each site's report tool is visible only to the local site PI and site coordinator, study leadership, and authorized coordinating center personnel. Serious problems will be updated in real time, and coordinating center personnel may pull reports for all sites as needed.

Serious problems that are both unanticipated and related to research will be reported in writing to the VA Central IRB within 5 business days of becoming aware of the event. If a local site PI is unsure whether an event is related to the research or unanticipated, he/she will consult with Dr. Krebs, Seal, or Becker.

These events must also be reported to PCORI within 10 days after reporting to the IRB.

10.6.4 Noncompliance and protocol deviations

Noncompliance and protocol deviations the site-specific adverse event report tool on the study's secure sharepoint site. Each site's report tool is visible only to the local site PI and site coordinator, study leadership, and authorized coordinating center personnel. Deviations will be updated in real time, and coordinating center personnel may pull reports for all sites as needed.

Apparent serious or continuing noncompliance will be reported in to the VA Central IRB within 5 business days of becoming aware of the event. Protocol deviations or other noncompliance that are likely to substantially adversely affect the rights, safety, or welfare of research participants; participants' willingness to continue participation; or integrity of research data will be reported in writing to the VA Central IRB within 5 business days of becoming aware of the event. If a local site PI is unsure whether an event is related to the research or unanticipated, he/she will consult with Dr. Krebs, Seal, or Becker.

These events must also be reported to PCORI within 10 days after reporting to the IRB.

10.6.5 Improper use or disclosure of research data

Improper research data use or disclosure will be reported to local VA Information Security Officer (ISO) and Privacy Officers within one hour, regardless of whether the occurrence meets criteria for prompt IRB reporting.

10.6.6 Communication of prompt reports to local sites

SAEs, serious problems, and protocol deviations that have the potential to affect implementation of the study at multiple sites will be communicated to all engaged participating sites using encrypted email or telephone calls to local site PIs and coordinators. Acknowledgement of receipt will be requested from local sites.

10.6.7 Study termination or suspension

This study has no pre-specified endpoints that would trigger immediate suspension of research. If termination or suspension is triggered by unexpected events (e.g., SAE, serious noncompliance, major information security violations, loss of funding), the PI will email notification to local site facility directors and to local site approving bodies (including local site IRB and R&D committees), along with Central IRB and PCORI, within 5 business days. Additionally, the PI will provide local sites with detailed information about procedures to ensure continuation of appropriate clinical care for research participants.

10.7 Data Management

10.7.1 Data Quality

To maximize the reliability of outcome assessment and reduce the prevalence of missing data, a dedicated team of masked coordinating center personnel will conduct all follow-up outcome assessments by telephone. Participant responses will be recorded on machine-readable paper questionnaire forms created using Teleform software. Questionnaires containing machine-readable patient-reported data will be scanned by research assessment personnel. Experienced data team members will train the outcome assessors and supervise the data scanning and verification process. Each completed form will be reviewed for completeness and stray marks before scanning. To ensure accuracy, each questionnaire form will be scanned twice, with verification performed by two people per document. Discrepancies will be resolved by comparing the different values against the survey document. Accuracy of completed datasets will be additionally verified by comparing values in the dataset to those on the original forms for randomly selected study identification numbers, representing 5% of all participants. Once accuracy is verified, SAS software will be used to generate databases. Consistency checks will be performed to check for out of range values and quantify the amount of missing data.

10.7.2 Privacy and Confidentiality

All study procedures, including the consent process and face-to-face intervention visits, will occur in private areas at each participating VA facility. Telephone assessment interviews will be conducted by study personnel in research offices at the Minneapolis VA to ensure auditory privacy.

To ensure confidentiality of data collected, we will assign patients unique study identifiers for tracking study data. Patient names, social security numbers, addresses, and other personal identifiers will be restricted to authorized personnel for limited necessary uses. The link between study identifiers and personal identifiers will also be protected and limited to authorized personnel. Only the study identification number will be used for data analysis and other uses of study data, such as reports to IRB.

Study data will be reported only in aggregate in any reports or publications; no names or identifiable details of study participants will be used in any reports or publications resulting from this study.

10.7.3 Information security

All study personnel are trained on the protection of research data; only study authorized personnel will have access to records. Study personnel will be allowed research database and study application access only as needed to accomplish authorized study duties within their scope of practice. Authorized study personnel will be oriented to appropriate use of the study research application and database. Research data access will be removed promptly when authorized personnel leave the study.

All electronic data will remain on secure VA servers, in secure electronic folders throughout the study. Study files are kept on secure servers within folders that are only accessible by IRB-approved personnel. Study files that contain any identifiable information are further secured to a smaller group of IRB-approved personnel who may see PHI. These listings are regularly reviewed by the project manager.

Cross-site communication involving PHI will be accomplished by using encrypted VA email or secure shared electronic folders whenever possible. Communication of PHI by fax will be used only when more preferred methods are infeasible.

Local ISO and Privacy officers will be notified within one hour of improper research data use or disclosure, and will be consulted throughout the study if any issues or questions arise.

Payments to patient participants will be in the form of a pre-paid debit card, issued via the University of Minnesota (UMN) Controller's Office. The UMN pre-paid debit card program requires subjects' first and last name, mailing address, and date of birth. This information is uploaded to the UMN vendor via a secure website (reviewed by VA ISOs).

Paper files will be kept in locked cabinets within secured areas.

10.8 Regulatory and Administrative Compliance

10.8.1 Institutional Review Board (IRB) approvals

The protocol and associated documents will be reviewed and approved by the VA Central IRB (CIRB) before trial recruitment begins. Prior to enrollment of patients at each local

site, approvals must be obtained from the CIRB (i.e., the Local Site Investigator application), the facility's Research & Development committee of record, and any additional regulatory bodies as required at the local site (e.g., University IRB).

All amendments to the project or changes in the informed consent will be submitted to the VA Central IRB for review and approval prior to implementation, except if necessary to avoid immediate hazard to participants. Any changes implemented as a result of an immediate hazard will be promptly reported to the VA Central IRB as a project deviation and an amendment submitted if determined necessary. All required local facility approvals will be obtained before amendments or modifications are implemented.

10.8.2 ClinicalTrials.gov registration

The study ClinicalTrials.gov identifier is NCT03026790. The PI is the responsible party for registering and updating the study record in the Protocol Registration and Results System (PRS). The record will be updated as follows:

- Within 30 days of a change to recruitment status data elements
- Within 30 days of a change to completion date
- At least every 6 months, even if no changes

10.8.3 Reporting to PCORI

PCORI is the study funder and not a "sponsor." Study documents will refer to PCORI as a funder, not a sponsor, of the research.

10.8.3.1 Report submission

The following reports will be submitted to PCORI, as outlined in the research funding contract:

- Interim progress reports (every 6 months)
- Draft final research report
- Final research report
- Final progress report

10.8.3.2 Data and safety monitoring

Approved minutes for each DSMB meeting will be submitted in interim progress reports, along with a summary of any significant data & safety monitoring issues that occurred in the reporting period.

Serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) related to the research study will be reported to PCORI no later than 10 days after the problem is reported to the IRB.

Any decision, finding, recommendation, action or direction of the IRB, DSMB, or other regulatory or oversight body relating to any serious unanticipated problem will be reported to PCORI within 10 days.

10.8.3.3 Required notifications

PCORI will be notified within 30 days of the following occurrences:

- Absence of PI for > 3 continuous months

- Absence of Key Personnel for > 3 continuous months or change in overall effort ≥ 25% of approved effort
- Conflicts of interest that emerge during the contract term

10.8.3.4 Changes requiring PCORI approval

If any of the following changes are planned, a request will be submitted to PCORI prior to implementation:

- Significant change in the scope, specific aims, protocol, or milestones
- Significant change in approach, methodology, or number of participants
- Transfer of PI
- Significant new contracting or transferring project effort
- Naming new key personnel or PI
- Decrease in the annual percentage effort of a PI that exceeds a variance of 25% of the approved effort
- Budget adjustments in salaries of Personnel or for Travel that exceed 25% of the total amount approved for the budget category
- Deviation from PCORI Methodology Standards

10.8.4 Research records retention

All records will be retained in accordance with the VHA Records Control Schedule 10-1 (May 2016) and will be destroyed in accordance with VHA regulations (under guidance of local Information Security Officer and Privacy Officers).

10.8.5 Completion of local site engagement

When study activities requiring local site participant interaction are complete, local site PIs, coordinators, and facility directors will be notified by email that the study no longer requires engagement of the local facility. A closeout meeting and checklist will be completed with local site PIs and coordinators at the time of closeout at each site.

11. DISSEMINATION AND DATA SHARING

11.1 Submission of Primary Study Results

The PI will submit reports of primary analysis results to PCORI and to ClinicalTrials.gov, as outlined in the research funding contract.

11.2 Peer-Reviewed Publications

A study publication committee will coordinate planning, preparation, submission, and tracking of publications and will provide internal guidance on authorship. Electronic copies of accepted peer-reviewed manuscripts will be made publicly available on PubMed Central, consistent with the PCORI policy on Public Access to Journal Articles Presenting Findings from PCORI-Funded Research.

PCORI will be notified prior to the publication/presentation date and within 30 days of acceptance of all presentations and peer-reviewed publications related to this research.

VA will be notified at the time of acceptance of all scientific publications or presentations, in accordance with VHA Handbook 1200.19.

11.3 Results Reporting to Study Participants

Study results will be reported directly to research participants by mailing a lay summary of results. This will be reviewed and approved by the study's Veteran Engagement Panel prior to mailing.

11.4 Dissemination of Additional Research Products

Informational materials, intervention manuals, and other research products will be provided to PCORI as outlined in the research funding contract. The study team will strive to disseminate these products as widely as possible.

11.5 Data Sharing Plan

A complete, cleaned, de-identified copy of the final data set used in conducting the analyses will be made available within one year after the completion of the study, in accordance with ORD Data Management and Access Plan (DMAP) requirements of January 1, 2016. This relatively new requirement includes different ways to share research data; we plan to make available either a de-identified, anonymized dataset or a limited dataset that can be shared pursuant to a data use agreement appropriately limiting use of the dataset and prohibiting the recipient from identifying or re-identifying any individual whose data are included in the dataset.

12. STUDY GOVERNANCE

12.1 Leadership Committee

Erin Krebs, Karen Seal, and William Becker constitute the leadership committee and will collaborate closely to ensure the ethical, timely, and scientifically rigorous conduct of the entire multi-site project.

Primary and shared responsibilities are as follow:

- Scientific direction and research protocol: Oversight and decision-making will be shared by all members of the leadership committee.
- Administrative, regulatory, and technical matters: This includes human subjects and research regulatory compliance matters, coordinating center activities, and data management and statistical services. Oversight is the primary responsibility of Dr. Krebs, who will be responsible for day-to-day decision-making. Decisions about substantial changes or issues, such as those that may potentially affect scientific direction, protocol adherence, or ability to meet study milestones, will be made by the full leadership committee.
- Budget: Dr. Krebs is primarily responsible for ensuring appropriate allocation of funds. Decisions about substantial changes or issues, such as those that may potentially affect scientific direction, protocol adherence, or ability to meet study milestones, will be made by the full leadership committee.

Decisions of the leadership committee will be made by consensus. Disagreements will be resolved through discussion, including co-investigators and study personnel if appropriate. The PCORI program officer will be consulted in the case of any major disagreement related to the scientific direction, protocol adherence, or ability to meet study milestones.

12.2 Other Committees

12.2.1 Engagement

- Responsibilities: Recruiting, selecting, and interviewing patient engagement panel members. Identifying best practices for study initiating and sustaining stakeholder engagement and engagement evaluation. Other activities related to engagement.
- Membership: Joseph Frank, Benjamin Morasco, Agnes Jensen, Erin Krebs
- Reporting: Reports to leadership committee through Dr. Krebs

12.2.2 Implementation evaluation

- Responsibilities: Finalizing protocol for process evaluation (to be approved by leadership committee). Collecting process evaluation data through observation and interviews. Analyzing and interpreting results of process evaluation. Developing dissemination products.
- Membership: Hildi Hagedorn, Karen Seal, Natalie Purcell
- Reporting: Reports to leadership committee through Dr. Seal

12.2.3 Data

- Responsibilities: Finalizing data collection and management protocols. Monitoring study recruitment, enrollment, outcomes, and fidelity data. Reviewing data and statistical resources in relation to study milestones. Reviewing study data analysis plans.
- Membership: David Nelson, Sean Nugent, Allyson Kats, Agnes Jensen, Erin Krebs
- Reporting: Reports to leadership committee through Dr. Krebs

12.3.4 Publications

- Responsibilities: Establishing guidelines for authorship and for review, approval, and tracking of proposed data analysis plans, presentations, and publications. Reviewing study data analysis plans and presentation/publication drafts in collaboration with the data committee.
- Membership: TBD
- Reporting: Reports to leadership committee through Dr. Krebs

PROTOCOL REVISION HISTORY

Version Number: 1.0
Version Date: December 30, 2016

Version Number: 2.0
Version Date: May 15, 2017

Summary of Revisions: Added information about local site recruitment (4.3.2), buprenorphine rotation protocol and IND exemption (5.6), qualitative data collection (6.4.1), local site rollout (8.3, 8.4, 8.6), process evaluation (9), ClinicalTrials.gov registration (10.8.2), and study governance (12). Removed certificate of confidentiality. Edited for clarity throughout.

Version Number: 3.0
Version Date: September 8, 2017

Summary of Revisions: Changed title of study. Revised eligibility criteria and provided detail on consent visit (4.3.4-4.3.6); revised and clarified intervention details (5.1, 5.3, 5.4); added and revised buprenorphine rotation details (5.6.1-5.6.5); revised IPT fidelity monitoring (5.8.1) plan; clarified adverse event data collection and analysis for outcomes (6.2.3, 7.7) and assessment, tracking, and reporting for human subjects monitoring (10.5.1, 10.5.2, 10.6); added UPIRTSO definition (10.5); revised incentive payment data information (10.7.3). Edited for clarity/consistency of terminology throughout.

Version Number: 4.0
Version Date: November 20, 2017

Summary of Revisions: Revised requirements for IPT team members (5.3, 5.6.3); simplified/revised description of patient-reported outcome assessment (6.4.5); changed baseline interview process (6.4). Edited for clarity/consistency throughout.

Version Number: 5.0
Version Date: March 6, 2018

Summary of Revisions: Added travel pay for enrollment visit (4.3.6); edited section numbering (5.1 – 12.2).

Version Number 6.0
Version Date: June 22, 2018

Summary of Revisions: Minor inclusion criteria revision (4.1.); refined definition exclusion criteria (4.2); revised and reorganized content and subsections to distinguish local and central recruitment procedures and improve clarity (4.3); revised enrollment visit and informed consent procedures to allow for VA Telehealth option (4.3.8); revised IPT visit schedule description for

clarity (5.4.2); revised protocol language throughout to clarify local tasks that may be done by local study personnel (rather than study coordinator specific).

Version Number 7.0

Version Date: February 5, 2019

Summary of Revisions: Added option to complete patient reported outcomes by mailed paper questionnaire (3.1 and 6.2).

Version Number 8.0

Version Date: April 12, 2019

Summary of Revisions: Revised definitions of "moderate to high dose" opioid therapy from ≥ 50 ME mg to ≥ 20 ME mg/day; revised "high dose" from ≥ 100 ME mg to ≥ 70 ME mg daily (Abstract, 1.2.1, 4.1, 4.3.3, 5.1).

Version Number 9.0

Version Date: September 13, 2019

Summary of revisions: Removed "24 month period" from recruitment section (4.3.1); ; revised protocol language throughout to clarify tasks that may be done by coordinating center or other study personnel if local study staff are unavailable; clarified other local study staff authorized to obtain consent (5.6); updated buprenorphine management section to clarify approach to buprenorphine initiation may be individualized by prescribing clinician (5.6.3); added prescription monitoring program check and documentation of outside medications to transition of care process (5.9); added visual aids for follow-up outcome assessment interviews (6.2); added nominal token of appreciation prior to 12 month interview (6.2.1); made small word changes/edits for clarity.

Version Number 10.0

Version Date: November 25, 2019

Summary of revisions: Updated number of sites from nine to 10 in multiple locations; revised estimated sample size and related power estimates (abstract, 7.1, 7.5); revised pre-specified subgroups (abstract, 1.2.1, 4.3.2).

Version Number 11.0

Version Date: May 28, 2020

Summary of revisions: Added repeat core baseline interview if first intervention visit is delayed (section 6.2.1); added COVID-19 questions to assessments (section 6.2.3); added COVID test results to administrative data collection (section 6.3.1).

Version Number 12.0

Version Date: October 20, 2020

Summary of revisions: Updated aim 2 outcome language consistent with previous changes in version 10.0 (abstract, section 1.1.2); clarified process for mailing signed documents when informed consent is not conducted in-person (sections 4.3.8, 4.3.9, 5.6.4); added telephone option for enrollment and intervention visits (sections 4.3.8, 5.1, 5.3.2, 5.4.2, 5.6.4, 5.6.5); clarified timing of qualitative interviews (section 6.4.1).

Version Number 13.0

Version Date: December 17, 2020

Summary of revisions: Clarified issues related to delays receiving signed informed consent/HIPPA authorization forms after virtual enrollment visits (section 4.3.8); added allowance for less frequent case review meetings in final year of intervention (section 5.3.4 and 5.4.4.); clarified processs for clinician reporting of adverse events (section 10.5.1.1).

Version Number 14.0

Version Date: April 22, 2021

Summary of revisions: Add patient interviews about COVID-19 pandemic-related experiences; add telehealth questions to clinician interviews (section 6.4.1).

Version Number 15.0

Version Date: August 16, 2021

Summary of revisions: Add clinician interviews focused on buprenorphine (section 6.4.1).

Version Number 16.0

Version Date: February 1, 2022

Summary of revisions: Clarification that baseline interview will be after the patient provides verbal informed consent and before randomization (section 6.2). Written consent is required prior to randomization (section 4.3.9).