

Protocol Supplement

Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial

This protocol supplement contains the following items:

- Summary of protocol changes
- Original IRB-approved protocol (approved May 2012)
- Original statistical analysis plan (excerpt from research proposal)

Details of the final protocol and recruitment outcomes are in the following publication: Krebs EE, Jensen AC, Nugent S, DeRonne B, Rutks I, Leverty D, Gravely A, Noorbaloochi S, Bair MJ, Kroenke K. Design, recruitment outcomes, and sample characteristics of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial. *Contemporary Clinical Trials*. 2017 Nov;62:130-139. PMID: 28893675 DOI [10.1016/j.cct.2017.09.003](https://doi.org/10.1016/j.cct.2017.09.003)

Table: Summary of protocol changes

Date	Description of change
March 2013	<p>Pre-enrollment refinement of outcome assessment batteries</p> <ul style="list-style-type: none"> • Changed measures of sleep, medication beliefs, headache, and health related quality of life domains; add treatment preference questions and other items to baseline assessment • Changed fall calendar data collection to first 6 months only • Eliminated cold pressor pain sensitivity testing at 6 months
June 2013	<p>Pre-enrollment changes to outcome assessments and intervention protocol</p> <ul style="list-style-type: none"> • Added PROMIS pain and depression measures at baseline and 3 months for ancillary NIH-funded measurement study • Revised prescribing strategies <ul style="list-style-type: none"> ○ Non-opioid arm: Adjuvants and topicals are second-line. Tramadol and non-formulary adjuvants are third-line. Will not use any typical opioids (i.e., no hydrocodone or codeine) ○ Opioid arm: Always start with IR opioid unless there is a truly compelling reason to start with SR therapy (almost never the case). Due to availability without prior authorization, oxycodone SA is a second-line option. • Clarified intervention visit content • Revised intervention medication safety and adherence monitoring protocol
February 2014	<p>Refined recruitment strategy in response to difficulty recruiting</p> <ul style="list-style-type: none"> • Increased incentive from \$40 to \$100 for in person assessments at 0, 6, and 12 months • Changed recruitment to “opt in” for Veterans > age 80 or who live >50 miles from Minneapolis VA, due to low yield of proactive recruitment
July 2014	<p>Revised opioid arm intervention approach to opioid dose adjustments</p> <ul style="list-style-type: none"> • Decided not to increase opioid doses beyond 100 ME mg (no doses > 100 mg prescribed to date)
October 2014	<p>Revised outcome assessments:</p> <ul style="list-style-type: none"> • Added brief 15-month mailed follow-up questionnaire • Eliminated fall calendar data collection due to participant and research team burden and low completion rates
April 2015	<p>Revised opioid arm intervention approach to opioid dose adjustments:</p> <ul style="list-style-type: none"> • Decided if patients have not responded to an individual opioid at a dose of 60 ME mg/day, rotate to an alternative opioid • Decided if patients have a partial response to an individual opioid, the dose may be titrated above 60 ME mg/day to a maximum of 100 ME mg/day
May 2015	<p>Revised non-opioid approach to tricyclic TCA dose adjustments:</p> <ul style="list-style-type: none"> • Redefined adequate trial as nortriptyline or amitriptyline 50 mg for minimum of 2 weeks

June 2015	<p>Revised opioid arm intervention approach</p> <ul style="list-style-type: none"> • Decided to drop methadone from prescribing strategy (not prescribed to date) • Decided to keep fentanyl in prescribing strategy as third-line therapy; if prescribed, ensure potential excess risks are communicated to patient and patient agrees to not make any independent dose adjustments
September 2015	<p>Revised prescribing procedures in response to strengthened FDA warning about cardiovascular risks of NSAIDs</p> <ul style="list-style-type: none"> • Decided not to prescribe etodolac or diclofenac in patients with high cardiovascular risk <p>Clarified prescribing for female patients of child-bearing age who decline to use contraception</p> <ul style="list-style-type: none"> • In non-opioid arm, decided to limit options to those safer in pregnancy • In opioid arm, decided to use lower dosages and instruct patient to contact study ASAP and not abruptly stop opioids if she becomes pregnant. If a patient becomes pregnant while on opioids, would initiate a very slow taper and discontinue opioids
October 2015	<p>Clarified NSAID use in patients with higher cardiovascular risk</p> <ul style="list-style-type: none"> • Document discussion of cardiovascular risks with patient • Allow patient to make informed decision about continued use of NSAIDs
May 2016	<p>Revised non-opioid intervention approach</p> <ul style="list-style-type: none"> • Added topical diclofenac due to its addition to VA formulary • Decided PPIs not needed when topical diclofenac is prescribed • Decided to check creatinine with topical diclofenac as with oral NSAIDs • Decided to recheck AST & ALT within 3 months of starting oral diclofenac and at end of study if oral diclofenac continuation is recommended

PROTOCOL: Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE)
PRINCIPAL INVESTIGATOR: Erin E. Krebs, MD, MPH

BACKGROUND:

Chronic musculoskeletal pain conditions are among the most common problems seen in primary care. As the importance of these conditions for the health of individuals and society has been increasingly recognized, use of long-term opioid therapy for chronic musculoskeletal pain has grown exponentially.^{1,2} Unfortunately, research has not kept pace with this change in opioid prescribing practice.

The balance of benefits and risks for patients receiving opioids for chronic pain is currently unclear. Available evidence for effects of opioid treatment on chronic pain is primarily from short-term placebo-controlled trials with limited applicability to clinical practice.^{3,4} Guidelines support the use of opioid therapy when other treatments have not improved pain intensity and function, but these recommendations are based primarily on expert opinion due to limitations in the quantity and quality of evidence.^{5,6}

The long-term medical safety of opioids is poorly described in the literature. Clinical trials of opioids have been designed to primarily assess short-term side effects, such as constipation. Preliminary investigations suggest that long-term opioid therapy may adversely affect pain sensitivity, endocrine function, fall risk, and sleep, but the incidence and severity of these potential effects have not been well-quantified.⁷⁻⁹ Additionally, despite widespread concerns about opioid misuse and iatrogenic addiction, the magnitude of these risks is currently unknown. Estimates of 12-43% for misuse and 3% for addiction among patients receiving opioids are based on research with important methodological limitations.¹⁰

As a result of these uncertainties, the proper place of opioids in chronic pain is controversial. Some experts argue for a reduced role, pending evidence of opioids' long-term effectiveness and safety; whereas others argue for expanded use of strong opioids, such as morphine, as important weapons in the fight against chronic pain. Primary care clinicians are caught in a double-bind—concerned that they may cause more harm than benefit, but not wanting to under-treat pain.

We propose to fill a critical gap in the evidence by conducting a pragmatic randomized trial comparing two clinically relevant prescribing strategies—opioid-intensive versus opioid-avoidant—for chronic musculoskeletal pain. The **Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE)** trial will evaluate multiple patient-centered pain and safety outcomes over 12 months. It will compare two prescribing strategies that are both flexible algorithms, but differ strongly in their emphasis; the opioid-intensive strategy will use strong opioids early in treatment, whereas the opioid-avoidant strategy will optimize non-opioid medications while delaying and minimizing opioid use. Participants will be Veterans seen in primary care for chronic back or lower-extremity arthritis pain who have moderate-severe pain refractory to daily analgesics.

SPECIFIC AIMS AND HYPOTHESES

Aim 1: To compare 12-month effects of opioid-intensive and opioid-avoidant prescribing strategies on pain-related function and pain intensity.

Hypothesis 1: The opioid-intensive strategy will improve pain-related function and pain intensity more than the opioid-avoidant strategy.

Aim 2: To compare harms of opioid-intensive and opioid-avoidant prescribing strategies over 12 months.

Hypothesis 2: The opioid-intensive strategy will cause more adverse medication-related symptoms, more clinically important adverse events, and greater decrements in physical and cognitive performance than the opioid-avoidant strategy.

Aim 3: To compare effects of opioid-intensive and opioid-avoidant prescribing strategies on secondary outcomes, including health-related quality of life, pain sensitivity, and aberrant drug-related behaviors.

Aim 4: To elicit participants' perceptions of their response to the intervention and of the value of intervention components.

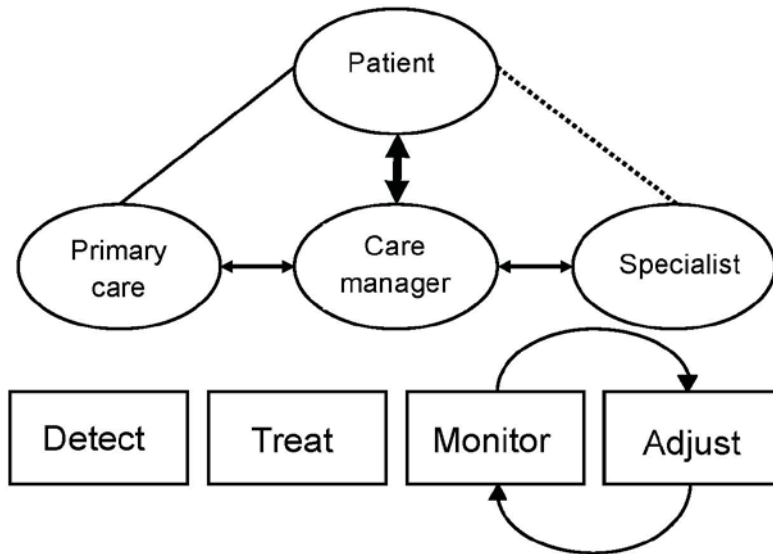
RESEARCH DESIGN AND METHODS

A. Conceptual model

As noted previously, chronic pain management is often complex and time-consuming. Many Veterans with chronic pain are dissatisfied with pain management and many VA primary care providers feel unsupported in their efforts to treat pain. The SPACE trial will compare two different analgesic prescribing strategies, both delivered through an intervention model that is designed to address key barriers to effective pain treatment in primary care. The SPACE intervention design draws on the Three Component Model (TCM), which was initially developed and validated by Roudebush (Indianapolis) VA Co-investigator Dr. Kroenke and colleagues in a multisite depression implementation trial.¹¹ The TCM was designed to provide a structured approach to depression interventions, addressing the main barriers to effective depression care while maintaining feasibility in community practices. The barriers that it was designed to address are equally applicable in pain care—primary care time pressures, competing demands of acute concerns and medical conditions, suboptimal access to specialty care, and lack of structured reassessment and action in response to failure of interventions that are undertaken. PI Dr. Erin Krebs, previously of the Roudebush (Indianapolis) VA and colleagues have successfully used the TCM as the basis for two trials focused on management of pain symptoms, INCPAD (an NCI-funded trial involving cancer patients with pain or depression)¹² and SCOPE. By enhancing primary care and creating a bridge to specialty consultation, the TCM complements the VHA stepped care model of pain care described in the current VHA Pain Management Directive.¹³

The TCM is compatible with the Chronic Care Model, but is focused on the relationship among three care providers collaborating through structured communication to optimize symptom care processes. The three components of the TCM are primary care, care management, and enhanced specialty support. Figure 1 shows the relationships among the three types of providers and the central role of the care manager. In SPACE, care management will be delivered by a clinical pharmacist care manager and specialty supervision will be provided by clinician investigators. The four key process steps addressed by the TCM are symptom detection, treatment initiation, monitoring of response and adverse effects, and adjustment of therapy when needed. Within the VA, the first step (symptom detection) has been widely implemented through the Pain as the Fifth Vital Sign Initiative. Participants in SPACE will have already had treatment initiated, but will not have experienced a meaningful response, so SPACE will focus on the monitoring and treatment adjustment processes, which will occur as a series of structured treatment trials. Use of measurement tools for interval reassessment is a key feature of the TCM that will be fully integrated into the SPACE interventions.

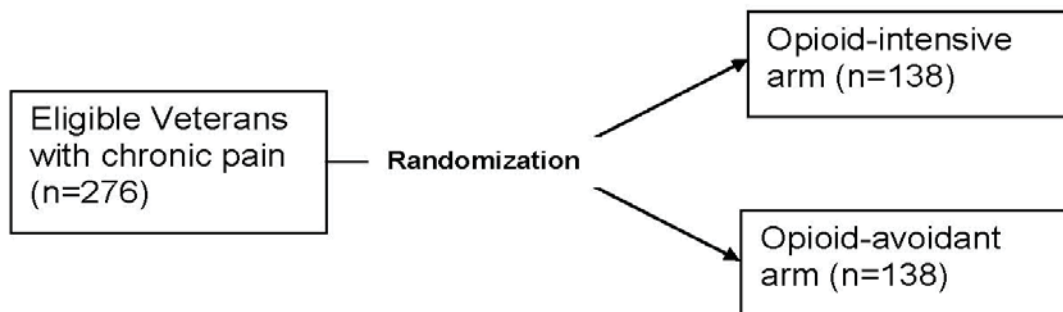
Figure 1: Three Component Model (TCM)



B. Study design overview

SPACE is a pragmatic randomized clinical trial designed to compare the effectiveness at 12 months of two clinically-relevant prescribing strategies delivered within a care management model for chronic musculoskeletal pain. Rather than comparing simple uniform treatments, this study will compare two flexible prescribing algorithms that can each be tailored to individual patient preferences and responses. Patients will be assigned to either 1) the opioid-avoidant arm, which emphasizes non-opioid medications from several drug classes, or 2) the opioid-intensive arm, which emphasizes early use of strong opioid analgesics. SPACE will randomize 276 Veterans with chronic musculoskeletal pain of at least moderate severity to either the opioid-avoidant (n=138) or the opioid-intensive (n=138) arm (see Figure 2). In both arms, treatments will be titrated, added, or rotated as needed to achieve improvement in pain. The intervention structure and data collection protocol will be the same for both arms; only the prescribing strategy assignment will differ between them.

Figure 2: SPACE Study Design



C. Recruitment

C1. Inclusion criteria

Veterans will be eligible for participation if they have chronic back or lower extremity osteoarthritis pain with moderate-severe intensity and interference with function despite analgesic therapy. Inclusion criteria are further defined as follows:

(a) *Chronic back or lower extremity osteoarthritis pain*: For this study, we define chronic pain as pain that is present nearly every day for at least 6 months. A standard definition of chronic pain is not agreed upon, but most studies have used 3-6 months as the required duration.¹⁴ Patients with a primary pain complaint of back pain or hip or knee arthritis pain are eligible. These two types of pain account for the majority of pain complaints and long-term opioid therapy.¹⁵ Patients with additional pain locations will not be excluded unless they have a primary location other than back, hip, or knee or meet criteria for fibromyalgia.

(b) *Moderate-severe intensity and interference with function*: Eligible patients will have both moderate-severe pain intensity nearly every day, defined using standard cutoffs as Brief Pain Inventory (BPI) average pain item ≥ 5 (on a scale of 0-10), and interference with function, as defined by BPI interference score ≥ 5 .^{16,17}

(c) *Despite analgesic therapy*: To ensure that potential participants are appropriate for opioid therapy, we will require that their pain has persisted at a moderate-severe level despite analgesic use at least nearly every day for the past 6 months. Veterans already receiving current chronic opioid therapy will be excluded (see C2 below).

C2. Exclusion criteria

As a pragmatic clinical trial, this study will enroll a generalizable sample of primary care patients who would be considered eligible for either opioid or non-opioid analgesic therapy. We have therefore kept exclusion criteria to the minimum necessary to ensure both patient safety and internal validity. Veterans who meet any of the following exclusion criteria that may interfere with outcome assessment will be ineligible: a) schizophrenia, bipolar disorder, or other psychosis; b) moderately severe cognitive impairment, *defined as ≥ 2 errors on a brief cognitive screener*;¹⁸ c) anticipated back, knee, or hip surgery within 12 months; and d) anticipated life expectancy of less than 12 months. We will also exclude patients receiving current chronic opioid therapy and those with absolute contraindications to either prescribing strategy.

For exclusion purposes, we define current chronic opioid therapy as any long-acting opioid (i.e., methadone, transdermal fentanyl, or any sustained-release opioid) dispensed in the past 3 months or any prescription for ≥ 60 tablets/capsules of short-acting schedule 2 or 3 opioids dispensed in the past 3 months. Under this definition, patients who received a small number of short-acting opioids per month, but less than required to use them on a daily round-the-clock basis, would be eligible. Patients receiving current chronic opioid therapy will be excluded for two main reasons. First, whether to discontinue or rotate/escalate opioid therapy in patients without an adequate response to opioids is a different research question from those addressed by this study. Second, insufficient “washout” of preexisting opioid therapy could confound study results because chronic opioid therapy can induce physical dependence and because discontinuation of opioids may lead to changes in pain sensitivity of uncertain duration.

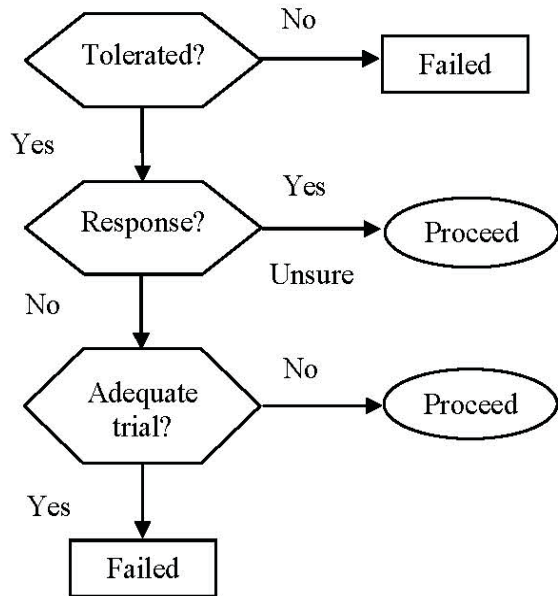
Finally, because participants should be considered eligible in clinical practice for either opioid or non-opioid analgesic therapy, patients with contraindications to all drugs in either arm will be excluded. In general, contraindications for specific medications include known allergy, previous serious adverse effect, or failure of a previous adequate trial of that medication. Specifically, in the opioid-avoidant arm, a patient who previously failed adequate trials of all three drug class steps would meet exclusion criteria; in the opioid-intensive arm, a patient who previously failed high-dose sustained-release opioid therapy would meet exclusion criteria.

To determine adequacy of prior medication trials, the pharmacist care manager will conduct a medication history as described in Section E1. For each drug used, patients will be queried about adverse effects, pain response, and dose/duration of use. We will consider a patient to have “failed” a drug if they did not tolerate it or did not respond to an adequate trial. Adequacy of a drug trial is defined by both dose and duration of use. Figure 3 includes a flow chart for this assessment and a preliminary

table of dose/duration specifications for key drugs; these specifications will be expanded and finalized by the study team during the start-up phase of the trial.

For opioid therapy, additional contraindications include those outlined by VA/DoD clinical practice guidelines,⁶ as follows: a) acute psychiatric instability, defined as current uncontrolled severe depression, severe PTSD, or suicidal ideation; b) substance use disorder not in remission or treatment; and c) documented or suspected diversion of controlled substances.

Figure 3: Determination of an adequate analgesic drug trial



Preliminary adequate trial specifications

Prior medication	Daily dose	Duration
Acetaminophen	3000 mg	2 weeks
Naproxen	1000 mg	2 weeks
Ibuprofen	1800 mg	2 weeks
Tramadol	300 mg	2 weeks
Gabapentin	2700 mg	4 weeks
Amitriptyline	75 mg	4 weeks
“Low dose” opioids	4 tablets*	2 weeks
“High dose” opioids	100 MEq mg	2 weeks

*Combinations of a “weak” opioid with acetaminophen (e.g., codeine/acetaminophen)

C3. Identifying potential participants

Primary care providers (PCPs) will be informed of the study and asked to provide written consent to approach their patients for participation. The Minneapolis VA has 47 full-time equivalent primary care physicians. We have an excellent track record of recruiting PCPs in this manner; in previous trials at the Roudebush VA, >90% of PCPs have consented.

The primary enrollment method will be a mail and phone strategy as used in our trials conducted at the Roudebush VA.¹⁹ Potentially eligible patients of participating PCPs will be identified through local VistA searches, using the criteria in Table 1. Searches will be updated every month during the enrollment period. Potentially eligible Veterans will be mailed a recruitment letter describing the study and co-signed by study Principal Investigator Dr. Krebs and their PCP. Potential participants will then be contacted by phone within a week after receipt of the letter to determine interest in participating and to assess eligibility. If the Veteran is eligible and interested in participating, an appointment will be scheduled for the informed consent process. After participants provide written informed consent and authorization, the baseline interview will be conducted.

Table 1. Search Criteria to Identify Potential Study Participants

Criterion	Search variable
Pain	1) 715xx, 721.xx, 722.xx, 724.xx <u>and</u> 2) pain score on most recent visit ≥ 5

Visit	Primary care visit in past 12 months
No chronic opioids	In the past 3 months... 1) No fentanyl patch, methadone, morphine SR, oxycodone SR dispensed <u>and</u> 2) <60 short-acting opioid pills dispensed for 30 days

If enrollment falls below targets, a second method of enrollment will be in-clinic contact of potential subjects by cross-referencing of the potentially eligible list with the appointment schedule for each participating PCP.

C4. Inclusion of women and minorities

This study will be performed at the Minneapolis VAMC, where we expect approximately 7-10% of the potentially eligible population to be women. Eligible women and racial/ethnic minorities will be encouraged to enroll. This study will not be powered for subgroup analyses with women or minority participants, but we will examine results for evidence of trends that can be prospectively evaluated in a future multisite trial. Gender and race/ethnicity will be considered in all multivariable analyses. Additionally, the purposive sampling technique we will use for the qualitative evaluation will specifically “oversample” female and minority participants in order to adequately represent their views.

D. Randomization

After providing informed consent and completing the baseline assessment, participants will be randomized to the opioid-intensive arm (n=138) or the opioid-avoidant (n=138) arm. Randomization will be stratified by primary pain location (back or hip/knee) to assure balanced numbers of participants with LBP or OA. Randomization will occur in randomly varying block sizes of 2 and 4.

D1. Masking and allocation concealment

Participants will not be masked to treatment arm assignment due to the complexity of the medication prescribing strategies. The pharmacist care manager and supervising clinical investigators who implement the interventions will also be aware of treatment assignment. To maintain allocation concealment, randomization will be conducted by the pharmacist care manager at the first treatment visit, using sealed envelopes prepared by the statistician. Outcome assessors will be masked to treatment assignment. The masking of outcome assessors and the structured nature of outcome measures are expected to minimize potential biased ascertainment.

E. Interventions

E1. Intervention structure

A clinical pharmacist care manager will be the central intervention provider for both arms. Clinical pharmacists have an established role in Minneapolis VA primary care clinics that includes protocol-driven adjustment of medication therapy. Clinical pharmacists assigned to each primary care clinic can currently be consulted to see patients with difficult to control hypertension or hyperlipidemia. They adjust medications, monitor response, and return disease management back to the primary care provider once blood pressure or lipid medications are optimized. This program has been both well-received by primary care providers and associated with improvement in outcomes.²⁰ The SPACE intervention protocol echoes this familiar and successful program.

Participants will see the pharmacist care manager in a study clinic, with the first intervention visit scheduled as soon as possible after study enrollment. At this visit, the care manager will obtain a detailed history of current and past pain medications. The medication history will include review of current and past medications, including examination of patients’ medication packages they will bring to the visit and CPRS medication lists. Information from these sources will be supplemented by review of a checklist of analgesic and adjuvant medications, including photographs of drugs to stimulate patient

recall. The care manager will confirm eligibility as described in Sections C, randomize the participant as described in Section D, and recommend initial medication adjustment according to the prescribing strategy for the assigned treatment arm.

We expect that most adjustments in pain medications will occur in the beginning of the study period for most patients, so intervention visits will be scheduled at baseline and approximately monthly for the following two visits. Additional visits will be scheduled according to individual participants' needs during the remainder of the 12 month intervention period, with a maximum of 6 months between visits for participants who achieve adequate pain control on a stable medication regimen. Because the extent of care manager contact may differ among patients over the course of the trial, we will track these contacts and examine between-group differences in care manager contact as a potential confounder. Before and between intervention clinic visits, patients will have their symptoms reassessed using automated symptom monitoring (see Section F).

Case review meetings with the pharmacist care manager and supervising clinician investigators will be held each week to review progress with pain management, adverse effects, and any clinical problems. Clinical pharmacists are able to write prescriptions for non-scheduled medications. A physician investigator will sign paper prescriptions for DEA scheduled medications (i.e., opioids). All study medications will be dispensed through the Minneapolis VA research pharmacy and mailed to participants; from the participants' perspective, this dispensing process will not differ from the usual non-research medication dispensing experience.

The primary method of communicating with primary care about routine patient progress and pain treatment decisions will be care management notes entered into CPRS; this is consistent with usual consultant practice at our VAMC. If indicated by emergent adherence or safety issues (e.g., repeated attempts by a participant to receive pain medication outside of the study, important adverse effects), a care manager or investigator will communicate directly with the patient's primary care provider. At the end of the trial period, we will provide primary care providers with a synopsis of each patient's individual response to therapy, including change in pain and function and any adverse effects. A plan for continuation or discontinuation of study therapy will be developed for each patient on an individual basis. The clinical pharmacist will facilitate tapering of opioids at the end of the study if, based on individual patient outcomes, discontinuation of study opioids is determined to be the appropriate course.

F. Automated symptom monitoring

Interval reassessment of pain, adverse effects, and adherence will be done by automated symptom monitoring, through interactive voice recorded (IVR) phone calls. Automated symptom monitoring will be scheduled to occur prior to in-person study clinic visits and at the time of medication refill or renewal. It can also be scheduled at interval time points as customized by the care manager, such as 1-2 weeks after a medication change. The automated symptom monitoring assessment will include the following abbreviated measures: (a) the 3-item PEG, a brief measure of pain intensity and interference that is responsive to change;^{21,22} (b) a patient global impression of change rating;²³ and (c) the PHQ-4, which includes the depression screening items of the widely used PHQ-2 plus two anxiety screening items.²⁴ Also included will be single questions about medication underuse, overuse, and side effects, as well as the option to send a request for contact by the care manager. Participants who do not complete their scheduled automated assessments will receive a reminder; if this fails, they will have the option of completing a paper version of the assessment at the time of their next visit.

Automated symptom monitoring by IVR will be used solely as a clinical tool for the pharmacist care manager and supervising clinician investigators to monitor and adjust therapy. It will not be used to assess research outcomes. The Minneapolis VA has an existing contract with Audiocare for clinical and research IVR services. Appropriate VA data security, information privacy, and research oversight bodies have approved IVR use in prior studies.

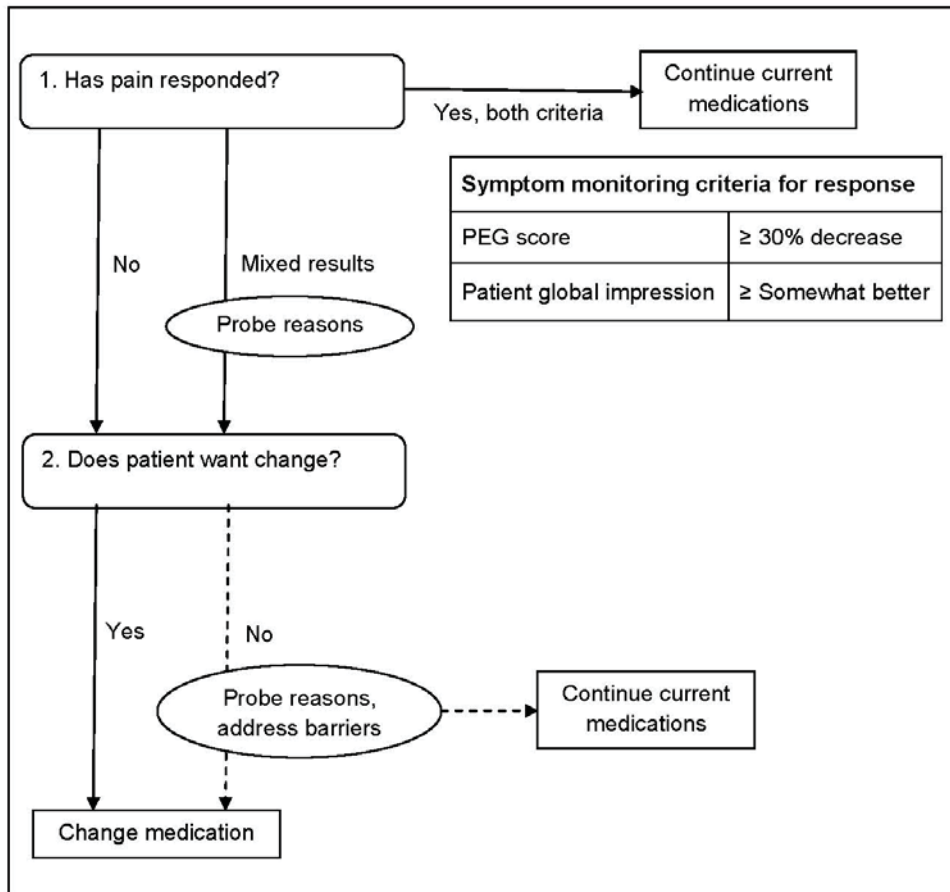
G. Analgesic prescribing strategies

The analgesic prescribing strategies in this proposal were developed based on evidence-based recommendations from published disease and drug class-specific guidelines,^{5;6;25;26;27} systematic reviews,^{3;4;28-30} and our own published reviews^{31;32} and refined through our experience with algorithm-based pain medication adjustment in the clinical trials at the Roudebush VA. Each medication has demonstrated efficacy for relevant indications from randomized clinical trials and, in most cases, from meta-analyses or systematic reviews of multiple RCTs. Direct comparative data are not available for most medications, so sequencing is based on other factors, such as safety, tolerability, and VA formulary availability. As is the case with depression, regular monitoring and adjustment of pain therapy is likely as important in achieving good outcomes as the specific initial treatment chosen.³³ Both prescribing strategies will be operationalized as a series of individual medication trials undertaken by the patient and pharmacist care manager using a structured shared decision-making approach.

Patients will enter the prescribing strategies at different levels, depending on their baseline medications and past medication history. Their baseline medications may be discontinued, adjusted to achieve an adequate therapeutic trial, or continued with the addition of adjunctive drugs, depending on their individual history of medication use (including dosing, scheduling, and adherence), therapeutic response, and adverse effects. In general, each level in each step of the prescribing strategies will be tried before moving to the next higher step. Importantly, both the opioid-intensive and opioid-avoidant prescribing strategies are titrated to clinical response rather than a specific type or dose of treatment. This pragmatic treat-to-target approach more closely mirrors real-world practice, which tailors evidence-based treatments to patient-specific outcomes.^{12;34;35}

Decisions to change pain medications must be made in a shared process because, unlike assessment of conditions that are evaluated independent of patient report (e.g., hypertension), pain control is inherently subjective. Decisions about whether to continue a current medication or change to another drug or dose are necessarily influenced by factors unique to the individual patient with pain, such as internal weighing of pain and medication effects on valued roles and activities, beliefs and values about pain and pain medications, and personal coping styles. SPACE will use a structured decision-making approach to consider patient preferences along with results of symptom monitoring. The two main considerations included in the algorithm for medication change decisions (Figure 4) are the following: 1) presence of pain response, defined as improvement in both PEG score and patient global impression of change, and 2) whether the patient desires change in medications.

Figure 4: Algorithm for medication change decisions



G1. Opioid-intensive prescribing strategy

Evidence for relative effectiveness of various opioid regimens, including different drugs and dosing schedules, is extremely limited;³⁶ therefore, opioid initiation and adjustment will be guided by VA/DoD guideline-concordant principles, applied in a personalized manner.⁶ Figure 5 outlines principles of opioid adjustment and stepped medication options.

Opioid medications will be titrated gradually, with frequent reassessment, until treatment goals are met, dosing is limited by adverse effects, or a morphine equivalent (MEq) daily dose of 200 mg is reached. The issue of opioid dosing limits is highly controversial and no well-accepted upper dosing limit has been established; however, evidence for use of high-dose opioids is limited and reports suggest a positive relationship between dose and serious adverse events.³⁷ Current VA/DoD guidelines recommend dosing based on patient need, not on predetermined maximal dose.⁶ In contrast, opioid prescribing guidelines from a Washington State interagency group recommend specialty consultation for doses >120 mg/day.³⁸ Given these data and remaining uncertainties, we will not increase doses beyond 200 MEq mg/day in this study. Participants reaching this limit may be rotated to another opioid, which can allow a decrease in the total daily dose.

Figure 5: Opioid-intensive Prescribing Strategy

Principles for initiation

- Start with a low dose of one Step 1 opioid medication.
- Consider starting with a short-acting opioid if pain fluctuates during the day or if patient is at higher risk for adverse effects.
- Consider starting with a long-acting opioid on a defined schedule if pain is continuous.

Principles for adjustment

- Adjust one medication at a time.
- Increase daily opioid dose in increments of 25-100% at a time.
- Increase dose no more often than once a week. Assess pain & function after each change.
- Increase dose more gradually for patients ≥ 65 years old, with frailty, or with hepatic, cardiac, pulmonary, or renal dysfunction.
- Consider switching to a long-acting opioid if no response to short-acting opioids.
- Consider adding a short-acting opioid for breakthrough pain during the titration phase.
- Consider rotating from one opioid to another if treatment goals are not met, side effects are bothersome, or dose is approaching maximum of 200 morphine-equivalent mg/day.
- For opioid rotation, follow conversion tables from VA/DoD opioid management guidelines.
- For methadone titration, follow methadone dosing recommendations from VA/DoD opioid management guidelines.

Step 1: First-line opioids

- Short-acting opioids (hydrocodone, morphine IR, oxycodone IR)
- Morphine SR

Step 2: Second-line long-acting opioids

- Methadone

Add on for breakthrough

- Morphine IR
- Oxycodone IR

Step 3: Non-formulary long-acting opioids

- Oxycodone SR, transdermal fentanyl

G2. Opioid-avoidant prescribing strategy

As in the opioid-intensive arm, medication initiation and adjustment in the opioid-avoidant arm will be guided by general principles applied in a personalized treat-to-target manner. Figure 6 outlines the opioid-avoidant principles and stepped medication options. Adjuvant medications (designated Steps A and B) are included as analgesia-enhancing steps that may occur in parallel with prescribing of analgesics in Steps 1-3. Tramadol, included in Step 2, is a centrally acting analgesic that affects mu opioid receptors, as well as serotonin and norepinephrine reuptake.²⁸ Tramadol is not a DEA controlled substance due to its limited abuse potential. Some patients in the opioid-avoidant arm will advance to low-dose therapy with typical opioids (Step 3), but the nature of the prescribing strategies will create a clear separation between the arms in the incidence and intensity of opioid use.

Figure 6: Opioid-avoidant Prescribing Strategy

Principles for adjustment

- Adjust one medication at a time.
- Increase dose no more often than once a week. Assess pain & function after each change.
- Consider adding adjuvants if appropriate and analgesics are only partially effective.
- For patients receiving daily Step 1 or 2 medications, consider providing a small amount of a higher Step analgesic for breakthrough or exacerbation pain.

Step 1: Simple analgesics

- Acetaminophen
- Naproxen
- Second-line NSAIDs (salsalate, etodolac, ibuprofen, diclofenac)

Step 2: Tramadol

- Consider concurrent acetaminophen dosed with tramadol TID-QID

Step 3: Low-dose schedule III opioids

- Codeine/acetaminophen
- Hydrocodone/acetaminophen

Adjuvant Step A

If painful area is limited in size

- Capsaicin 0.025/0.075% cream

Adjuvant Step B

If pain has neuropathic aspects

- Amitriptyline, nortriptyline
- Gabapentin

H Medication safety considerations

Treatment agreements are widely advocated for use among patients receiving opioid medications, although evidence for their effectiveness in preventing opioid misuse is limited.³⁹ VA/DoD guidelines recommend reviewing a written Opioid Pain Care Agreement before initiating opioid therapy.⁶ In the proposed trial, a Pain Care Agreement will be employed in both intervention arms (regardless of medication type prescribed) as a way to structure medication education and clarify roles and responsibilities. At the time of study enrollment, the SPACE Pain Care Agreement will be entered into the patient's CPRS medical record and copies will be provided to the patient and his/her primary care provider. Violations of the agreement will be handled according to the nature of the behavior, as described in Section J.

At each intervention visit, use of non-study medications, over-the-counter medications, and herbal therapies or supplements will be evaluated, along with risk of drug interactions. Participants will be informed of potential interactions and study therapy will be adjusted as needed to avoid or minimize the likelihood of adverse drug interactions and maximize therapeutic response. A number of medication or class-specific safety rules will also be employed, including but not limited to the following: 1) Acetaminophen will be limited to ≤ 2 gm/day in liver disease or regular alcohol use (≥ 3 drinks per day or ≥ 5 drinks episodically) and ≤ 4 gm/day in other patients. 2) Patients considered for an NSAID must have had a creatinine within 6 months of initiation. Patients with estimated GFR < 60 , heart failure, peptic ulcer disease, or liver failure will not be started on an NSAID. Patients initiating an NSAID who are older than 65, have diabetes, or use a diuretic will have a follow-up creatinine within 4-8 weeks. Gastrointestinal prophylaxis will be prescribed in concordance with current guidelines.⁴⁰ 3) Tramadol will not be used in patients with a history of seizures. 4) Patients with a history of heart disease, arrhythmia, or syncope will not be started on methadone. Patients considered for methadone must have had an electrocardiogram (ECG) within 3 months. If the baseline QTc interval is > 450 ms, methadone will not be started. Patients receiving methadone will receive a follow-up ECG 3-6 weeks

after starting therapy; if the follow-up QTc is >450 ms and <500 ms, the potential risks and benefits of therapy will be reevaluated with the patient and the ECG will be monitored at least every 2 months. If any follow-up QTc is >500 ms, methadone will be discontinued or tapered.⁴¹

The American Geriatrics Society (AGS) recently published updated guidelines for pain treatment in patients who are frail or ≥ 75 years old.⁴² For older adults, as well as participants with higher risk for adverse effects (e.g., those with chronic medical conditions), we will follow safety recommendations outlined in the AGS guidelines as well as the classic geriatrics maxim to “start low, go slow.” Examples of specific safety rules that will be employed include, but are not limited to, the following: 1) The lowest possible dose of a given drug will be used as the starting dose; 2) Nortriptyline will be titrated to a maximum dose of 50 mg; amitriptyline will not be used; 3) Tramadol will be titrated to a maximum dose of 300 mg; 4) An immediate-release opioid will be used prior to any long-acting opioid to determine the appropriate starting dose; 5) NSAIDs with high cyclooxygenase-2 inhibitor selectivity (e.g., diclofenac) will not be used. All participants will receive closer monitoring than is available in usual practice, with reassessment of pain and adverse effects after each medication change, and dose adjustments no more often than once a week.

I. Clinical management of adverse effects (AEs)

Reports of side effects from automated symptom monitoring (Section F) will be followed up by the pharmacist care manager. In response to patient reports of adverse effects (AE), medications may be adjusted or clinical strategies may be employed to address ameliorable or preventable minor AEs (e.g., itching). Recommendations for prevention of constipation will be provided to all participants in both study arms at the outset. Important AEs (e.g., rectal bleeding) will also be evaluated by a study physician and reported to the patient’s primary care provider. Potentially urgent AEs (e.g., chest pain) will be referred for immediate evaluation in the medicine clinic or emergency department.

Patients with mood symptoms will be further evaluated with the PHQ-9 for depression or GAD-7 for anxiety.^{43;44} Clinically significant new or worsening psychiatric symptoms will be reported to the primary care provider and patients will be offered referral to their primary care team psychologist. Veterans who endorse thoughts of self-harm on item 9 of the PHQ-9 depression scale will be assessed with a suicide risk algorithm.

J. Clinical monitoring of adherence

Problems with medication overuse or underuse have many potential causes, including those related to the therapy (e.g., inadequate efficacy, side effects) and those related to patient (e.g., concerns about medication). When medication adherence issues are identified, they will be evaluated and addressed by the study care team on an individual basis with the goals of improving pain and tolerability of pain medications.

Aberrant drug-related behaviors (ADRB) are a particular class of nonadherence behaviors that have been associated with opioid misuse and substance use disorders. Although ADRB are often discussed in relation to opioid analgesic therapy, they may occur in any patient with pain. Indeed, ADRB may represent “pseudo-addiction” in the context of pain under-treatment, which may be more likely to occur among patients receiving only non-opioids or low-dose opioids. For these reasons, the clinical response to ADRB will be determined by the nature of the observed behaviors, rather than the medication prescribed or the study arm assigned.

A validated checklist of potentially concerning ADRB will be completed by the care manager at each visit for participants in both arms.⁴⁵ Any emerging pattern of ADRB will be reviewed at weekly case meetings and the study team will prescribe an individual monitoring plan to aid in diagnosing and ameliorating the behavior. This plan will be reassessed at each visit and may include any combination of the following actions: a) medication adjustment; b) more frequent study visits; c) adherence counseling or education; d) review of state prescription monitoring database to identify duplicate or unreported external opioid prescriptions; e) referral for evaluation by a mental health or addiction

clinician; f) shorter prescription renewal intervals; g) urine drug testing; and h) pill counts. Serious ADRB, such as illicit drug use or potential diversion of prescribed medication, may result in medication changes, including tapering or discontinuation of opioids. These behaviors will not be considered reasons for withdrawal from the trial and all participants will be evaluated in their assigned arm.

K. Data Collection

Study measures include both patient-reported outcomes that will be collected in interviews at baseline and 3, 6, 9, and 12 months and test-based outcomes that will be completed in person at baseline, 6, and 12 months. Interviews will require approximately 50 minutes at 0, 6, and 12 months and approximately 15 minutes at 3 and 9 months. In-person outcome assessment visits will require 50-60 minutes. A small incentive (\$20) will be provided for each outcome assessment call and visit. Incentives of this magnitude offset costs of participation and are in the standard range used in our previous VA and non-VA effectiveness trials. No incentives will be provided for study clinical visits nor for automated symptom monitoring, which is conducted for clinical intervention purposes.

Patient-reported outcome measures and timing of administration are displayed in Table 2 and described in Section K1. Although participants will be asked to complete a substantial battery of patient-reported measures in this proposed study, we believe this outcome assessment protocol is both appropriately comprehensive and reasonable in terms of respondent burden. Outcome assessment protocols of similar length have been well tolerated in multiple symptom management trials involving thousands of patients with depression or pain.^{12,34,46} Indeed, many participants in these trials have reported that they appreciated the sustained attention to their symptoms and perceived benefit from therapeutic disclosure.

Table 2: Patient-reported Outcome Assessment Protocol

Domain	No	Measure	Items*	Schedule				
				0 mo	3 mo	6 mo	9 mo	12 mo
Pain	1	Brief Pain Inventory	11	X	X	X	X	X
	2	Roland Disability-short form	11	X		X		X
	3	Global Rating of Change	1		X	X	X	X
Health-related QOL	4	SF-12	12	X	X	X	X	X
Adverse effects	5	Symptom checklist	15	X	X	X	X	X
Fatigue & sleep	6	Multidimensional Fatigue Inventory	20	X		X		X
	7	Athens Insomnia Scale	5	X		X		X
Headaches	8	Headache Impact Test	6	X		X		X
Sexual function	9	Arizona Sexual Experience	5	X		X		X
Mental health	10	PHQ-9	9	X		X		X
	11	GAD-7	7	X		X		X
	12	Primary Care-PTSD	4	X		X		X
Substance use	13	AUDIT	10(3)	X		X		X
	14	Drug use & smoking items	11(5)	X		X		X
Medication beliefs	15	Medication Beliefs Questionnaire	5	X				X
Expectations	16	Treatment expectation items	4	X	X			
Co-interventions	17	Treatment checklist	5	X	X	X	X	X

QOL= quality of life; PTSD = Posttraumatic Stress Disorder

*Items completed for repeat assessment are in parentheses when they differ from those completed at baseline.

K1. Description of patient-reported measures

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines recommend assessment of multiple core outcome domains in pain clinical trials, including pain intensity, function, patient ratings of improvement, and symptoms and adverse events.⁴⁷ We will assess each of these *pain outcome domains* with validated patient-reported measures.

1. The Brief Pain Inventory (BPI) is a multidimensional measure that includes two scales, which we will use as the primary measures of pain intensity and pain-related function. The BPI severity score is the average of four 0-10 items assessing current, least, worst, and average pain intensity in the past week. The BPI interference score is the average of seven 0-10 ratings of interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The BPI was originally developed for use in cancer-related pain, but has been validated for use in numerous other populations, including primary care patients with non-cancer chronic pain.^{47;48;49} IMMPACT has recommended the BPI as a core outcome measure for chronic pain clinical trials. We have used the BPI successfully as the primary pain outcome measure in recent and ongoing trials at the Roudebush VA.

2. The Roland Disability Scale is a pain-specific measure of physical function that was originally validated in back pain.⁵⁰ An 11-item short form that was developed and validated among diverse chronic pain patients will be used as a secondary measure of pain-related function.⁵¹

3. A 7-grade patient-reported global impression of change rating will assess patients' views of overall improvement or worsening in pain.⁵²

4. The Medical Outcomes Study Short Form-12 (SF-12) is a well-validated measure of health-related quality of life that will be used as a primary measure of general mental and physical function.⁵³

We will assess *adverse effects* with an inventory of medication-related symptoms as well as targeted assessment of key adverse effect domains: fatigue, sleep, headache, and sexual function.

5. A validated adverse effects Symptom Checklist⁵⁴ will assess the number and severity of common symptoms and participants' beliefs about whether or not they are medication-related. In addition to the ten common symptoms included in the original checklist (problems with sleep, changes in mood, gastrointestinal problems, dizziness and problems with balance, headache, fatigue, muscular aches, incontinence, sexual problems, and rash or itching), we added the following symptoms, which represent five of the most common patient-reported side effects of analgesic medications: memory problems, dry mouth, trouble concentrating, sweating, and weight gain.⁵⁵

6. The Multidimensional Fatigue Inventory has been validated among adults with chronic illness, chronic fatigue syndrome, and cancer, as well as among healthy adults.⁵⁶

7. The Athens Insomnia Scale-5 item version is based on ICD-10 criteria and has been recommended by the OMERACT group for use in clinical trials on the basis of both its feasibility and psychometric properties.⁵⁷

8. The Headache Impact Test is a brief validated measure of headache severity.⁵⁸

9. The Arizona Sexual Experience (ASEX) scale assesses 5 domains of sexual function in men and women.⁵⁹

Mental health and substance use disorders are commonly comorbid with chronic pain and can affect outcomes of pain treatment. These domains will be assessed with several brief measures.

10. The Patient Health Questionnaire (PHQ)-9 is a well validated brief measure of depression severity that is based on DSM criteria for major depression.⁴³
11. The General Anxiety Disorders questionnaire (GAD-7) has been validated as an anxiety screening and severity measure in primary care.⁴⁴
12. The Primary Care Post-traumatic Stress Disorder (PC-PTSD) Screen is a screening test for PTSD that was developed and validated in VA primary care.⁶⁰
13. The AUDIT questionnaire is a well-established assessment tool for alcohol use disorders that accurately identifies primary care patients with at-risk drinking.⁶¹ The full AUDIT will be used at baseline and the brief 3-item AUDIT-C will be used at follow-up.
14. To assess past and current drug use, we will use a single item drug use screener that predicts drug use disorders in primary care, plus 6 history items we developed for a previous study.⁶² Four questions from the National Survey on Drug Use and Health assess past and current smoking.⁶³
- Finally, we will include *additional secondary measures* that that may help explain response to therapy.
15. The Medication Beliefs Questionnaire⁶⁴ assesses beliefs that may mediate opioid misuse.
16. Treatment expectation questions adapted from prior pain trials will be asked at baseline (prior to intervention group assignment) and the first follow-up assessment (after group assignment).⁶⁵
17. Participants will be asked to report prior pain treatment history at baseline and to report co-interventions at each outcome assessment, including new medications, pain-related procedures, and physical and psychological therapies.

K2. Description of test-based measures

At 0, 6, and 12 months, participants will undergo an in-person assessment of domains that cannot be adequately captured with self-reported measures. A research assistant will administer tests of pain sensitivity, physical performance, and cognitive function.

Painful conditions are associated with risk of falling among both middle-aged and older patients; this risk may be exacerbated by medications with psychomotor effects. We will test 3 physical performance factors that may be especially important in determining risk for falls—balance, lower extremity strength, and gait speed. The Fullerton Advanced Balance scale is a 10-item test that evaluates multiple dimensions of balance in independent adults. It was designed to be more challenging than balance measures developed for frail elderly persons and has been validated as a predictor of falls risk among middle-aged and older adults with chronic pain.^{66,67} Participants will also complete the Chair Stand test, a brief assessment of lower extremity strength. The Chair Stand measure assessed healthy adults' (age 20-85) time to stand from a seated position ten times, but subsequent studies found substantial floor effects among older adults and arthritis patients, who were often unable to complete ten stands. In our population of patients with functional limitations due to back and lower-extremity arthritis pain, we will use a modified version that counts the number of stands completed in 30 seconds.⁶⁸ Gait speed tests are commonly used as performance measures in osteoarthritis.⁶⁹ We will use a timed 8-meter walk protocol that has been shown to reliably assess normal and fast-paced walking speeds among moderately-impaired osteoarthritis patients.⁷⁰

Cognitive function will be assessed with a brief battery of tests, the Indiana University Telephone-Based Assessment of Neuropsychological Status (IU-TBANS), which includes four standard clinical instruments covering the following domains: attention, learning and recall, information processing speed, and verbal fluency.⁷¹ This test battery was developed as a sensitive measure of subtle cognitive dysfunction among community-dwelling cancer survivors (at least one year post-treatment) so we

believe it will be sensitive to small deficits in cognitive function among patients with pain. IU-TBANS has been validated in both telephone and in-person forms and can be completed in 15-20 minutes.

Participants will also have blood collected by VA clinical staff according to their routine procedures. Urine for drug testing will be collected at 0, 6, and 12 months. All participants will have total testosterone measured at 0 and 12 months; women will also have estradiol measured at 0 and 12 months.⁸ We will assess *pain sensitivity* at baseline and follow-up visits with the Cold Pressor task, a method that has been used in clinical research with adults and children since the 1960s and is the most sensitive measure of opioid-associated pain hypersensitivity.^{7,72} Following recommended protocols for testing, participants will submerge their non-dominant hand up to the wrist in 1° C water continuously circulated by a commercial cooling bath.⁷² They will be asked to keep their hand submerged until it becomes too uncomfortable to continue, at which time they are instructed to withdraw it from the water. Pain threshold is time until the stimulus is first perceived as painful; pain tolerance is time until withdrawal of the hand.

K3. Description of additional measures

Adverse events will be ascertained using a combination of patient report and medical record review. Participants will also be asked to report occurrence of any falls, hospitalizations, or emergency visits at each outcome assessment call.

Additionally, falls will be assessed using a prospective calendar and postcard monitoring protocol.⁷³ Participants will track falls on monthly falls calendars and will be asked to complete a postcard and mail it to the research team if a fall occurs. When postcards are received, a research assistant will follow-up with a phone call to obtain information about the cause and outcome of the fall. To ensure no falls are missed, the calendars will be collected every three months and outcome assessors will follow-up on any additional falls recorded on the calendars but not previously reported by postcard. This method of fall ascertainment is consistent with recommendations based on a systematic review of fall outcome assessment.⁷³

Hospitalizations and emergency visits will be identified and confirmed using medical record review at the end of the study. VA hospitalizations and emergency visits will be ascertained using complete data available in VistA; non-VA hospitalizations and emergency visits will be ascertained from patient report and confirmed by medical records. These events will be considered as adverse outcomes regardless of where they occurred. To determine whether the events were analgesic-related, two physicians who are masked to study arm assignment will review records of emergency visits and hospital admissions. The World Health Organization system for standardized case causality assessment will be used to determine whether the relationship between an event and analgesic use is probable or greater.⁷⁴ Initial reviews will be conducted independently to allow for calculation of inter-rater reliability. Subsequently, reviewers will meet and attempt to reach consensus; if the two reviewers disagree and cannot reach consensus, a third reviewer will break the tie.

No single measure is adequately predictive or diagnostic of opioid misuse,⁵ so data from patients, clinicians, records, and laboratory tests will be used to assess the occurrence of behaviors suggestive of opioid misuse or addiction. In addition to previously described measures, patient-reported substance use history⁷⁵ will be evaluated at baseline. The Addiction Behavior Checklist (ABC) will be completed by the clinical pharmacist at each intervention visit. The ABC was developed within a VA chronic pain setting to provide a brief measure for longitudinal clinician assessment of ADRB.⁴⁵ Urine drug testing will be obtained at 0, 6, and 12 months as part of outcome assessments for all participants. Additionally, medical record reviews will be completed at the end of the study. Research assistants trained in chart abstraction will review the electronic medical record over the 12 month study period for documented ADRB and evidence of potential opioid misuse.

L. Prevention of missing data

In pain clinical studies, dropouts often occur due to intervention-related factors (e.g., adverse effects, lack of treatment efficacy) and missing data can pose a substantial threat to internal validity. SPACE has several design features meant to enhance participant retention and reduce missing data.⁷⁶ First, the interventions are flexible treat-to-target prescribing strategies that allow tailoring to each patient's needs. Medications will be adjusted individually, reducing dropouts due to lack of efficacy or intolerance. Second, both study arms are active interventions, which should reduce differential dropout that can occur among patients assigned to a control arm. Third, all randomized participants will be strongly encouraged to complete all outcome assessments, whether or not they continue in the intervention. Fourth, to reinforce participants' sense of commitment to the study, we will send a quarterly SPACE newsletter to participants including tips on pain self-management and positive news from pain research. Finally, if participants are at risk of dropping out due to assessment burden, they will be given the option of completing a minimum core assessment comprising primary pain (i.e., BPI) and adverse effect (e.g., symptom checklist) measures.

M. Qualitative recruitment and data collection

We will recruit four subgroups of SPACE participants for qualitative interviews—those who respond to pain treatment and non-responders from each of the two arms. Within each of the subgroups, we will purposefully sample participants with a broad range of intervention adherence behavior (e.g., number of completed care manager contacts).⁷⁷ Experience with conduct of the trial will inform our sampling strategy; for example, we may identify patterns of non-adherence that merit further exploration. During the initial consent process for the SPACE trial, all participants will be asked for permission to contact them after intervention completion. The data analyst will provide names of potential participants for the qualitative phase and the study coordinator will contact them within four weeks of completing the SPACE trial.

Throughout data collection and analysis, the research team will remain masked to participants' responder and adherence status. We will use individual semi-structured interviews to address our qualitative aims. Development of the semi-structured interview guide will be informed by the collaborative management framework and TCM as well as questions that arise during the conduct and analysis of the main SPACE trial. Based on experience with the main trial, questions will be further developed, revised, and piloted prior to the beginning of the qualitative phase. The project coordinator, will conduct interviews in a private VA office within 2 months of each participant's trial completion. Interviews will be digitally audio-recorded and transcribed for analysis as they become available. We will continue to conduct interviews with patients until theoretical saturation is reached. Based on our experience and recommendations for sampling subgroups,⁷⁷ we expect to conduct up to 10 interviews for each group (responders and non-responders in each study arm), for a total of 40 participant interviews.

N. DISSEMINATION PLAN

Results of the SPACE trial will be interpreted not in isolation, but in the context of results from complementary VA-funded pain clinical trials designed to address different gaps in our knowledge of chronic pain management. Together, these distinct but complementary studies will provide necessary data for clinicians and policy-makers working to improve VA pain care.

The primary knowledge gap SPACE addresses is the long-term benefit of an opioid-intensive prescribing strategy compared with an opioid-avoidant strategy. Information about the magnitude of benefit, along with additional information about the likelihood of harm, is necessary for providers to make the best decisions with individual patients about their pain treatment options. Meanwhile, results of complementary studies, including SCOPE and ESCAPE at the Roudebush VA, will inform VA on how to address provider and structural barriers to pain care.

To disseminate pain research findings, we will take full advantage of the robust pain care infrastructure that exists within the VA. The National Pain Management Strategy Coordinating Committee is an

important channel for disseminating findings to VA providers, administrators, and policy makers. Dr. Bair serves on this committee and will facilitate reporting of findings in the form of reports and presentations at their meetings. Findings will be further disseminated through VISN Pain Points of Contact, the Office of Quality and Performance, and VA Center for Medication Safety. We will also present to the large clinically-oriented audience of the VA pain list-serve and monthly national VA pain educational teleconferences.

Findings will be disseminated to our research audiences through scientific presentations and publications, HSR&D cyber seminars, and presentations to VA and non-VA interest groups. Principal Investigator Dr. Krebs and Co-Investigator Dr. Bair are both active members of the VA Pain Research Working Group and Society of General Internal Medicine (SGIM) Pain Interest Group. Both groups have active list-serves and annual face-to-face meetings. The VA Pain Research Working Group has monthly telephone conferences to promote coordination and dissemination of VA-relevant pain research. In addition, we will disseminate study findings to the Substance Use Disorder and Polytrauma QUERIs and the HSR&D Center for Information Dissemination and Education Resources (CIDER).

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C7. Analysis Plan

C7a. Sample size estimates

Sample size is calculated based on estimated effects on the primary outcome measure, the BPI Interference score. A between-group treatment difference of 1 point in the BPI Interference score represents a minimum meaningful intervention effect.¹⁰⁸ For our calculations, we assume the standard deviation (SD) of the BPI Interference score in both arms will be 2.7, based on the intervention arm of the SCAMP trial.⁵² A sample size of 115 in each arm is estimated to provide 80% power to detect a 1-point difference in the mean BPI Interference score between groups, assuming 2-sided alpha of 0.05. Based on our prior studies, we anticipate a dropout rate of 8-12%; allowing for a conservative estimate of 20% attrition, we will aim for 138 participants in each arm. This sample size will also provide 86% power to detect a 1-point difference in the BPI Severity score and 94% power to detect a 3-point difference in the Roland disability score. Contamination effects related to primary care assignment are expected to be minimal because primary care providers will not be directly involved in the study interventions.

We will examine response rate as a secondary measure of effectiveness. The standard definition of response to chronic pain treatment is a 30% improvement.¹⁰⁸ For this study, we define pain response as a 30% difference from baseline in the BPI Severity score and functional response as a 30% difference in the BPI Interference score. Our power to detect a 20% difference in response rate (0.25 vs. 0.45) is 0.86. This analysis will also allow us to calculate numbers-needed-to-treat (NNT) and harm (NNH).

C7b. Primary analyses

We will use an intent-to-treat analysis approach, including all participants in the arm to which they were originally assigned. Preliminary analyses will compare baseline characteristics and potential confounding variables between the two treatment arms. Any imbalance in a measure will lead to additional analyses, as described in C7c. Medication use at the end of the trial in each arm will be presented in a descriptive table, including numbers using each drug and mean daily dose. For opioids, doses will be described as morphine-equivalent mg per day; for non-opioids, doses will be described both as the actual daily dose and, as a standardized value to facilitate comparisons between drugs, as percent of the maximum daily dose.¹⁰⁹

Aim 1: To compare 12-month effects of opioid-intensive and opioid-avoidant prescribing strategies on pain-related function and pain intensity.

The primary outcome is BPI Interference score measured at 12 months. Consistent with recommendations for pain clinical trials, we will assess group differences on additional core pain-related domains as described in Section C6b. Preliminary analyses will use intent-to-treat analyses to compare mean scores on primary and secondary pain measures between groups at 12 months (with last observation carried forward for missing data) and at each time point. These will be based on analysis of variance (ANCOVA), which controls for the baseline score as a covariate. For analyses of the primary outcome, all repeated measurements of BPI Interference score will be fitted in a mixed model for repeated measures (MMRM)¹¹¹ as a function of the group assignment, while controlling for time points and baseline values of the outcome as fixed effects, with patients as random effects. Between-group differences at month 12 will be estimated and tested using an appropriate contrast as the primary test of intervention effect. BPI Severity score and other pain-related outcomes will be similarly analyzed, using appropriate simple two-group comparisons at month 12 as preliminary analysis. Where the secondary outcome variable has a non-normal distribution, an appropriate link function will be chosen for the

outcome in the mixed model, for a generalized MMRM. In particular, we will compare response rates for pain-related function and pain intensity between arms at 12 months using chi-square tests as preliminary analyses, followed by a generalized MMRM with a logit link for the binomial outcomes. If our findings are robust, we expect findings on the each of the secondary pain measures to be consistent with findings on the primary outcomes and the preliminary comparisons to agree with results from the mixed models.

C7c. Handling missing data and potential confounding

Although we expect a low rate of missing data, especially in the primary outcomes, reasons for missing data (dropouts and missing observations) will be documented and reported, and the observed outcomes at time points prior to dropout will be compared between groups. As long as the missingness depends only on the observed data but not the unobserved missing data, the missing at random assumption in the MMRM is met. Imputation of missing primary outcomes based on last-observation carried forward is only used for the preliminary analyses. To evaluate the robustness of our primary findings based on the mixed models, we will perform sensitivity analyses using different imputation strategies for missing data, including last observation carried forward for all outcomes and predicted values for the primary outcomes from multiple regression on observed data. We will not have enough missing data to fit complex models that assume certain missing data models, especially when the assumptions cannot be checked.

If potential confounding variables (e.g., prior failed analgesic trials, prior pain treatments, treatment expectations, co-interventions) are not balanced between groups, we will conduct additional analyses to evaluate whether findings may be due at least in part to these imbalances. We will adjust for potential confounders by adding them as covariates in models. Second, we will evaluate potential effects of interactions between confounders and treatment group by adding relevant interaction terms to the models.

Treatment groups may differ in the mean number of care manager contacts during the course of the trial, but we expect the number of contacts will overlap substantially between groups. We will conduct sensitivity analyses to examine effects of care manager contacts; specifically, the number of contacts will be added to models as a covariate. If between-group differences in outcomes are eliminated or attenuated after this adjustment, it would suggest that intervention effects are, at least in part, explained by non-specific care manager effects.

C7d. Secondary Analyses

Aim 2: To compare harms of opioid-intensive and opioid-avoidant prescribing strategies over 12 months.

Analyses of harms will be conducted to better understand the risk of harms between treatment groups and, secondarily, as associated with the specific drug or opioid dose received. We will assess potential medication-related harms in three domains: 1) patient-reported adverse symptoms; 2) adverse events; and 3) adverse effects on physical and cognitive performance. Given the limited available evidence for long-term opioid safety, we aim to assess the harms domain as comprehensively as possible; therefore, our assessment of potential adverse effects is broad and exploratory at the risk of finding spurious associations. No adjustment is made for multiple testing because we want our analyses to be sensitive to any potential harm signals. Findings from these analyses will be reported cautiously as needing prospective evaluation in future research.

Patient-reported adverse symptoms: The primary patient-reported symptom outcome is the number of symptoms (range 0-15) reported on the Symptom Checklist. Using repeated measures with four follow-up time points and assuming SD=4 and $r=0.5$, our power is 87% to detect a between-group difference of 1.0 symptom (from 2.5 to 3.5).⁸⁷ As a secondary outcome, we will examine the number of symptoms causing “a lot” of bother (range 0-15). Between-group differences will be tested using MMRM. If the distribution is non-normal, an appropriate link function will be used. We will secondarily explore the risk of events as functions of drug class and, in the subset of those receiving opioids, opioid dose (in daily morphine equivalents); these factors will be added to the models as time varying covariates within 60-day exposure windows preceding each follow-up time point. For this analysis, medications received by the participant will be included as exposures regardless of their source. The same approach (generalized MMRM to test between-group differences followed by the addition of time varying drug class and opioid dose to test their effects on the outcome) will be used to analyze the other harm outcomes using appropriate link functions for their respective distributions.

Power estimates for secondary patient-reported adverse symptom measures are presented in Table 4. In general, 115 subjects per group will yield 80% power to detect between-group differences >0.375 SD. If the 12-month outcome is correlated with its baseline measure with $r=0.5$, the detectable difference drops to 0.28 SD.

Table 4: Power Estimates for Secondary Patient-Reported Harm Measures

Measure	Estimated power*	Clinical context
Multidimensional Fatigue Inventory	81% to detect 6 points (60 vs. 66, SD=16)	MCID in rheumatoid arthritis = 16.6 points. ¹¹²
Athens Insomnia Scale	87% to detect 2 points (5 vs. 7, SD=4.9)	Difference between persons with and without insomnia = 8.8 points ¹¹³
Headache Impact Test	88% to detect 2.5 points (50 vs. 50.5, SD=6)	Difference between mild and moderate headache severity = 7 points ⁹⁰
Arizona Sexual Experience	88% to detect 2 points (11 vs. 13, SD=4.8)	Difference between male patients and controls = 6.3 ⁹¹

*Estimated power to detect a between-group difference, assuming $n=115$ per group and 2-sided $\alpha=0.05$.

Adverse events: The adverse event outcomes are 1) falls and 2) analgesic-related hospitalization or emergency department (ED) visit. Because the risk of misclassification exists with all methods of adverse event causality assessment,¹¹⁴ we will examine all-cause events in sensitivity analyses. Adverse events will be evaluated in 30-day intervals during the study period. We will test the between-group differences using generalized MMRM as described above, with a logit link for the binary outcomes and a log link for the number of events. The number of expected events is difficult to estimate with precision. A longitudinal study estimated annual fall rates in a relatively healthy and affluent community population to be 21% for middle-aged (46-65 years) and 35% for older (>65 years) adults;¹¹⁵ whereas a study of predominantly middle-aged fibromyalgia patients found a fall rate of 41%.⁹⁸ Assuming the event occurs in 20% of patients in the group with the lower event rate, we have 80% power to detect a 15% increase in proportion of patients with events in the other group using two-sided tests at 5% significance. A recent study found 12-month ED visit rates of 24-28% among patients receiving

opioids¹¹⁶ and another reported adverse effect-related hospitalization rates of 100-105 per 1000 for patients on non-opioids and 155 for those on opioids.¹¹⁷ Assuming 15% of patients in the opioid-avoidant group have a hospitalization or ED visit, we have >80% power to detect a 15% increase in proportion of patients with events in the opioid-intensive group. Using data from multiple intervals and basing analyses on event counts (instead of presence/absence) will allow us to detect smaller effect sizes.

Physical and cognitive performance: The primary outcome in this domain is the Fullerton advanced balance scale total score. A prior study of fibromyalgia patients found that the Fullerton scale differentiated between fallers (mean=29.8, SD=7.1) and non-fallers (mean=33.1, SD=5.5). Using two follow-up time points and assuming SD=7 and $r=0.5$, we have 86% power to detect a between-group difference of 2.0 (from 30 to 32).⁹⁸

Aim 3: To compare effects of opioid-intensive and opioid-avoidant prescribing strategies on secondary outcomes, including health-related quality of life, pain sensitivity, and aberrant drug-related behaviors.

Health related quality of life: The approach described above (generalized MMRM to test between-group differences followed by the addition of time varying drug class and opioid dose to test their effects on the outcome) will be used to analyze SF-12 data. We estimate 81% power to detect a 3-point difference in the Physical Component Score (PCS-12).¹¹⁸

Pain sensitivity: Pain threshold and tolerance at 12 months will be compared between study arms using linear models, with outcomes transformed to normality if necessary. Covariates will then be added to determine whether pain sensitivity after 12 months of treatment is affected by the drug class and opioid dose, controlling for baseline pain sensitivity. We will also use generalized linear models to test whether pain sensitivity at baseline predicts the number and distribution of patient-reported pain symptoms or headache severity.

Aberrant drug-related behavior: Data from patient, clinician, and chart-review sources will be categorized according to nature and severity into the following 3 groups: 1) serious ADRB, meaning documentation of prescription drug diversion, buying prescription drug from illicit sources, or simultaneously obtaining controlled substances for the same condition from multiple prescribers; 2) minor ADRB, including behaviors other than those included under serious ADRB; and 3) substance-related ADRB, including documented alcohol disorders or illicit drug use, health or legal consequences of alcohol or illicit drug use, or any urine drug screen positive for an illicit drug or non-prescribed controlled medication (e.g., opioid or benzodiazepine). Using ordinal logistic regression, we will compare rates of misuse between arms; secondarily, we will examine predictors of misuse.