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Design of a Multicenter Randomized Controlled Trial comparing the effectiveness of shared decision making versus motivational interviewing plus cognitive behavioral therapy for voluntary opioid tapering: The INSPIRE study protocol

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ABSTRACT

Background: This paper describes the design and protocol of a pragmatic, randomized trial to evaluate the comparative effectiveness of shared decision making versus motivational interviewing plus cognitive behavioral therapy for chronic pain for the voluntary tapering of opioid dose in adults with chronic noncancer pain. Integrated Services for Pain: Interventions to Reduce Pain Effectively (INSPIRE) is a multicenter, randomized trial conducted at three academic health centers in the southeastern United States. Participants are adults receiving long-term opioid therapy of at least 20 morphine milligram equivalents daily for chronic noncancer pain.

Methods: Participants were randomized to either the shared decision-making intervention or the motivational interviewing session and cognitive behavioral therapy for chronic pain intervention. All participants also received guideline-concordant care supporting opioid pharmacotherapy. The primary outcome was change from baseline in average daily prescribed opioid dose at 12 months, using prescribing data from electronic health records. Secondary outcomes were Patient-Reported Outcomes Measurement Information System Pain Interference and Physical Function at 12 months.

Conclusion: This trial evaluates the comparative effectiveness of shared decision making versus motivational interviewing plus cognitive behavioral therapy for chronic pain for the voluntary tapering of opioid dose in adults with chronic noncancer pain. Results from this study can guide clinicians, researchers, and policymakers as they seek to reduce opioid prescribing and improve management of chronic pain.

Clinical trials registration: ClinicalTrials.gov Identifier: NCT03454555 (https://clinicaltrials.gov/ct2/show/record/NCT03454555). Participant enrollment began on June 26, 2019.

1. Introduction

About 20% of Americans suffer from chronic noncancer pain (CNCP), and 8% have "high-impact" pain causing significant morbidity [1,2]. Traditionally, clinicians have used pharmacotherapeutic approaches, generally nonsteroidal anti-inflammatory agents and opioids, to treat CNCP. However, the efficacy of long-term opioid therapy (LTOT) has faced increased scrutiny. Systematic reviews of opioids and one randomized clinical trial found that opioid therapy is non-superior to nonopioid therapy for CNCP and is associated with greater health risks,

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including fractures, falls, and endocrinological adverse events, such as testosterone deficiency [3–5].

Because of the potential risk and often lack of benefit associated with LTOT, effective interventions are needed to taper individuals off opioids or reduce their dose, while maintaining appropriate access for patients who may benefit from LTOT. The 2022 Centers for Disease Control and Prevention (CDC) Clinical Practice Guideline for Prescribing emphasizes that clinicians should periodically re-evaluate the risk-benefit ratio for LTOT. The CDC Guideline alludes to a shared decision-making (SDM) approach by emphasizing that when possible, the clinician and patient should collaboratively make the decision to taper, and non-pharmacologic and nonopioid treatments should be used [6]. However, decisions by some clinicians to terminate patients' opioids have sometimes been made arbitrarily and implemented inappropriately [7]. Opioid tapering is sometimes associated with mental health crises and overdose, particularly when the taper is done rapidly [7,8]. A recent systematic review found that the best approach for tapering individuals off LTOT is unclear [9]. Pain management approaches, such as cognitive behavioral therapy and mindfulness, "probably" reduce opioid dose moderately, compared to treatment as usual, and "might" effectively substitute for opioids; but overall, the quality of the evidence is low [9].

Integrated Services for Pain: Interventions to Reduce Pain Effectively (INSPIRE) is a pragmatic randomized controlled trial (RCT) to compare the effectiveness of a patient-clinician SDM approach for voluntary tapering and enhanced pain functioning versus individual motivational interviewing plus a group-based, cognitive behavioral therapy for chronic pain (CBT-CP) program (MI + CBT) in adults with CNCP. SDM and MI + CBT-CP can both be used in treating a wide range of CNCP disorders, including the most common, such as spinal pain, arthritides, and neuropathies. Both strategies include components for enhancing motivation and addressing the physical and psychological aspects of pain. Neither approach is directive; both support patient choice, and both are behavioral interventions. SDM involves a clinician and a patient collaborating to make optimal health care decisions for the patient [10–13] using evidence-based information about available options, the patient's values and preferences, and the clinician's knowledge and experience. Central to the practice of SDM is the two-way exchange of information between a clinician and patient. SDM has been shown to enhance patient satisfaction and trust in medical care across a variety of disorders including cancer, diabetes, and treatment for mental health conditions unrelated to pain [14,15]. Yet effects of SDM on pain-related functioning [16,17] and clinical outcomes, including LTOT are unclear [14,16–18]. A recent, prospective study of U.S. veterans treated with opioids suggested that SDM can lessen misuse through fostering trust between clinicians and patients [19], lending support for SDM as a promising tool for addressing CNCP.

MI is a patient-centered, evidence-based, goal-oriented counseling technique used to enhance an individual's intrinsic motivation for behavioral change [20]. MI has been studied most extensively in substance use disorder treatment and is effective for a wide range of clinical issues for which patient motivation is important, such as lifestyle interventions to manage obesity [21] and type 2 diabetes mellitus [22]. MI has been used to help patients engage in CBT-CP [23], a well-established intervention for chronic pain that is recommended by pain guidelines [23–29]. CBT-CP aims to identify, challenge, and change maladaptive thoughts, emotions, and behaviors centered on patients' chronic pain and replace them with more adaptive ones [25]. CBT-CP also teaches coping skills and relaxation training. By doing so, CBT-CP helps patients improve their affective state, engage in more positive behaviors, and manage their pain to foster improved functioning.

Although SDM and CBT are behavioral interventions, they each differ in many ways: content covered, training of those delivering the intervention (medical vs. behavioral health), timing, and format (individual SDM vs. group CBT). SDM focuses on clinician-patient collaboration to make optimal health care decisions for the patient using evidence-based information about available options, the patient's values and preferences, and the clinician's knowledge and experience. CBT focuses on enhancing cognitive restructuring, coping skills, and relaxation techniques.

The primary objective of INSPIRE is to assess whether the interventions result in opioid dose reduction and to compare their effectiveness at 12 months. Secondary objectives are to examine the impact of the interventions on physical function and pain interference with the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference and PROMIS Physical Function.

2. Methods

2.1. Trial design and setting

The study included people with chronic pain on LTOT from 17 primary care, internal medicine, pain management, and rheumatology clinics in three health systems: Duke University, Durham, NC; the University of North Carolina (UNC), Chapel Hill, NC; and Vanderbilt University Medical Center (VUMC), Nashville, TN. RTI International is the coordinating center.

The protocol design was guided by input from a Stakeholder Advisory Committee that includes patients, patient education, and advocacy organizations, clinicians, and subject matter experts. Approval for the study was received from UNC's Institutional Review Board (IRB), which serves as the reviewing IRB for all sites, and informed consent was obtained from all participants. The trial has a Data and Safety Monitoring Board.

2.2. Study participants and eligibility

Eligibility criteria are shown in Table 1.

The original inclusion criteria were most recent prescription average daily opioid dose ≥40 morphine milligram equivalents (MMEs), receiving care at one of the participating clinics from a participating clinician with a scheduled visit within the next 90 days, and aged 18 to 75 years. Because of enrollment challenges, we made three modifications in late 2019 to the inclusion criteria to increase the recruitment pool: 1) increased the maximum age limit from 75 to 85 years, 2) decreased the minimum MME from ≥40 MME to ≥20 MME, and 3) removed the criterion that the patient must have a visit scheduled within the next 90 days.

Exclusion criteria included receiving opioids for cancer pain or for maintenance treatment of an opioid use disorder, currently receiving CBT, active suicidal ideation, suicide attempt within the past 3 years, or other reason at the discretion of the investigator. We included the discretionary exclusion criterion to allow institutions to handle rare

Table 1
Inclusion and Exclusion Criteria for Adults Receiving Long-Term Opioid Therapy for Chronic Noncancer Pain.

Inclusion criteria
• Aged 18 to 85 years
• Chronic noncancer pain
• Average daily dose of at least 20 morphine milligram equivalents for chronic noncancer pain according to most recent prescription
• Receiving care at a participating clinic from a participating clinician as evidenced by at least one in-person visit within the past 12 months
Exclusion criteria
• Opioid use is for cancer pain
• Opioid use is for maintenance treatment of an opioid use disorder
• Suicide attempt within the past 3 years
• Active suicidal ideation
• Currently receiving cognitive behavioral therapy
• Non-English speaking
• Other reason at the discretion of the investigator (e.g., cognitive impairment, behavioral disturbance)

cases in which patients would clearly be inappropriate for the study, such as behavioral disturbances or cognitive impairment. It is difficult to anticipate the rare, often unique types of situation in which a patient may not be fit for the intervention and to develop specific exclusion criteria for each hypothetical instance.

Study staff informed patients that they would not have to decrease or discontinue their opioids to participate in the study; the decision to taper or discontinue opioids was voluntary (unless a clinician had concerns regarding misuse or an excessively high MME independent of any risk of misuse). Although the inclusion criteria stated that the opioid prescription needed to be for treatment of chronic noncancer pain, there were no specific inclusion criteria for the duration of opioid use.

3. Recruitment

Site staff queried electronic health records (EHRs) to identify potentially eligible participants and reviewed EHRs manually to calculate MME using standard conversion ratios [25]. Recruitment began June 26, 2019, and ended March 31, 2022. Although recruitment paused from March 2020 to August 2020 due to the COVID-19 pandemic, clinical care in the intervention continued. Participants were recruited by mail, email, and phone and in participating clinics by research coordinators and clinicians who explained the study and assessed interest. Staff conducted screening in person before COVID-19 and in person or remotely after its onset. After screening, staff asked eligible participants to provide informed consent to participate in the study (see Supplemental File 1 for model informed consent form). Participants subsequently completed the baseline questionnaire. Participants were enrolled and then randomized to one of two intervention arms (Fig. 1).

3.1. Allocation

Participants were randomized to SDM or MI + CBT-CP in a 1:1 ratio using permuted blocks of size 4 or 6, stratified by study center. Study staff assigned participants to a treatment arm using the randomization tool in REDCap. The participant's assignment to an intervention arm was not revealed until after the baseline questionnaire was completed. Because of the nature of the interventions, it was not possible to blind participants or clinicians to intervention arm assignment.

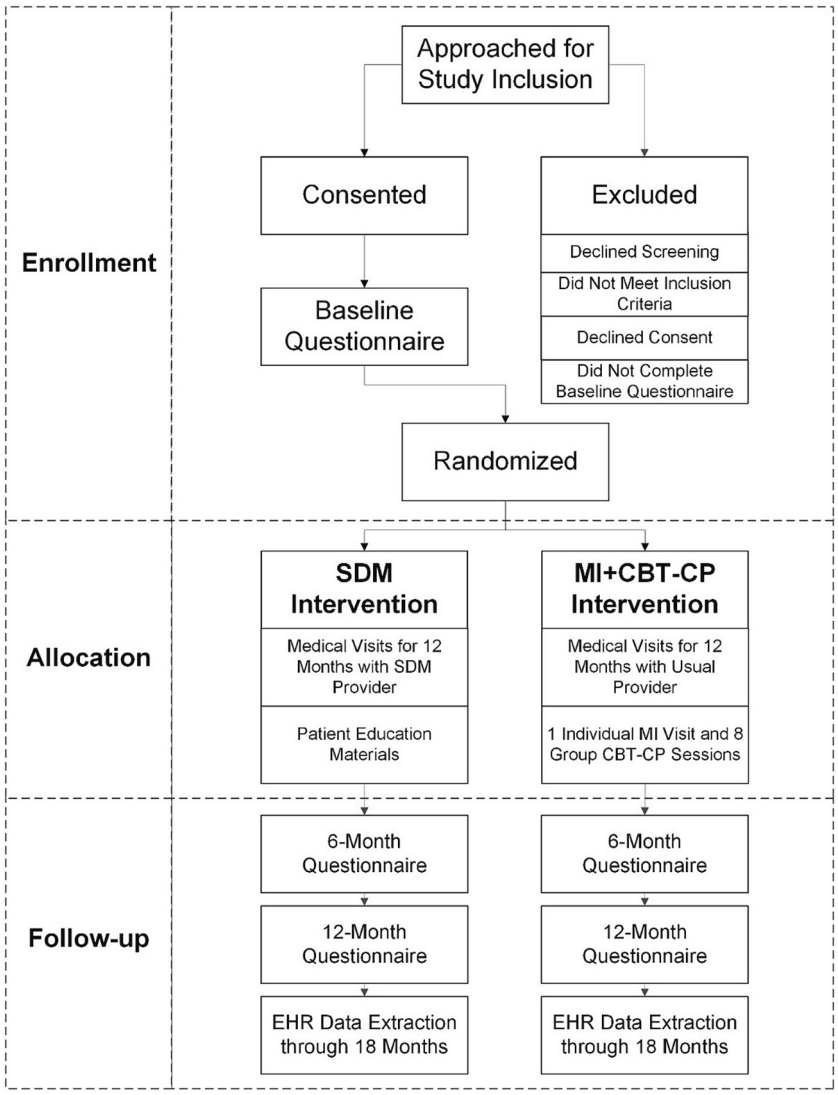

Fig. 1. Study flow diagram.
Note: Flowchart depicting process for participant selection, randomization, and data collection for the study. CBT-CP = cognitive behavioral therapy for chronic pain; EHR = electronic health record; MI = motivational interviewing; SDM = shared decision making.

3.2. Intervention arms and participation

Before the onset of COVID-19, all SDM, guideline-concordant care (GCC), MI, and CBT-CP visits were in person. The onset of the pandemic occurred early in the intervention, and the clinical sites initially required that all behavioral health sessions, (i.e., MI and CBT-CP) be conducted virtually (videoconferencing or phone). We observed that virtual sessions improved participant willingness and ability to attend the intervention, so when the clinics lifted this requirement, we chose to continue conducting sessions virtually. The same requirement did not apply to visits for physical health issues (i.e., visits for chronic pain), and providers could see the patient in person or virtually. If the participant was a no-show for an intervention visit, standard clinic procedures were used for follow-up. Participants could discontinue the intervention at any time.

3.2.1. Guideline-concordant care

During the intervention period, individuals in both arms continued to receive standard GCC for opioid pharmacotherapy [6]. GCC included patient risk assessment (including screening for substance use disorders and mental health disorders), periodic assessment of the state prescription drug monitoring program, pain monitoring with self-reported pain scores (0−10) at each visit, urine drug screens, urine pregnancy testing for women with childbearing potential, assessment of adverse drug events, and patient education and goal setting. Clinicians providing GCC completed state training requirements for opioid prescribing. For SDM participants, GCC was included in SDM visits, although for MI + CBT-CP participants, GCC was provided in regular pain care visits.

3.2.2. Shared decision making

We used the AHRQ (Agency for Healthcare Research and Quality) SHARE approach as a core component of the SDM intervention [30]. This approach involves five steps that clinicians use to implement SDM: **S**eeking patient participation, **H**elping them explore treatment options, **A**ssessing patient values and preferences, **R**eaching a treatment decision, and re**E**valuation after a decision has been made. In INSPIRE, using this approach involved exploring and comparing the benefits and risks of pain management options through meaningful dialogue centered on what matters most to the patient [15].

SDM interventions use decision aids or conversational aids to educate the patient and encourage thoughtful consideration of alternative treatment strategies, with the goal of promoting more meaningful conversations between patients and clinicians. Decision aids improve knowledge of treatment options, help patients feel better informed, promote more accurate expectations of benefits and harms, and increase participation in decision making [30–32]. Decision aids for INSPIRE included multiple educational materials on pain management, opioids, and SDM and a link to a short video on pain management (Table 2). SDM participants received an electronic and physical packet of these materials after enrollment and were encouraged to review them before their next pain care visit.

For training, INSPIRE SDM clinicians completed a 20-min, web-based introduction to the INSPIRE study and SDM. This introduction was followed by 2 to 3 h of independent study focused on the following seven modules developed by AHRQ for SDM training:

1. Essential Steps of SDM
2. Expanded Reference Guide with Sample Conversation Starters
3. Overcoming Communication Barriers with Your Patients
4. Health Literacy and SDM
5. Communicating Numbers to Your Patients
6. Using the Teach-Back Technique
7. Taking Steps Toward Cultural Competence [32]

Clinicians also reviewed the packet given to participants.

Finally, clinicians attended a 1-h live session covering the goals of the INSPIRE study, recruitment, safety issues, SDM, differences between SDM and GCC, and documentation requirements. To demonstrate competency, clinicians responded to knowledge questions after the training and participated in roleplays. Clinicians received continuing medical education credits.

To provide structure to SDM delivery, clinicians received guidance suggesting an order and timing for offering the SDM content. We suggested that clinicians first introduce basic information found in the educational video before moving on to more in-depth information about opioid risks and alternative treatments. We also guided SDM clinicians to raise the topic of potential opioid reduction within 6 months of the intervention. Given the study's pragmatic design, SDM clinicians applied this guidance as they deemed practical and medically appropriate.

Only clinicians who completed the SDM training could provide the SDM intervention. If a participant's prescribing clinician was not trained in SDM, we asked the participant to switch to an SDM-trained clinician for their pain-related care for the 12-month intervention period. They could continue seeing their current clinician for care not related to chronic pain. We informed potential participants of this before enrollment. If they did not wish to switch clinicians, they could decline to participate and were not randomized.

Participants in the SDM arm received their regular pain care visits with a designated SDM-trained clinician over a 12-month period. SDM intervention participants scheduled pain visits as often as needed for pain management (typically quarterly). The first SDM visit usually occurred 1 to 3 months after enrollment. SDM visits incorporated GCC, such as discussions about opioid risks and alternative treatments. SDM intervention visits were distinct from nonintervention visits (i.e., GCC-only visits): SDM visits utilized decision aids in the SDM packet for education, and as a catalyst for discussions on patient values, goals, and preferences, using SDM techniques. Because only SDM participants received the SDM packet, we minimized the threat of MI + CBT-CP participants being exposed to the SDM intervention. The differences between GCC and SDM are summarized in Table 3. To monitor adherence, study coordinators completed a case report form indicating when the participant's first SDM visit occurred. SDM clinicians documented

Table 2
Elements Differentiating Shared Decision Making and Guideline-Concordant Care.

Component	SDM + GCC	GCC Only
Patient Education		
*Patient receipt of educational materials†	++	
Patient-clinician interactions		
Discussion of alternative nonopioid pain treatments	++	++
Discussion of risks and benefits of opioid treatment	++	++
Discussion of opioid tapering	++	+
*Discussion of patient preferences, values, and goals	++	+
*Discussion of information in decision aids†	++	
Clinician Assessments		
Clinician assessed pain and function within last 6 months	++	++
Clinician performed risk assessment	++	++
Clinician checked PDMP within the last 6 months	++	++
Clinician requested a urine drug screen in the last 12 months	++	++

Notes: Table depicting differences between shared decision making (SDM) (Arm 1) and guideline-concordant care (GCC). GCC was part of Arm 2. PDMP = Prescription Drug Monitoring Program. ++ denotes greater intensity; + denotes a lesser intensity; blank denotes not conducted; * denotes key differences between the interventions; † Education materials: Prescription Opioids: What You Need to Know (Centers for Disease Control and Prevention); Taking Opioid Medicine for Chronic Pain: Talk to Your Doctor About What's Right for You (RTI); Preparing for Your Health Care Visit (American Chronic Pain Association); Non-Opioid Options for Managing Chronic Pain (Harvard Medical School); A Car with Four Flat Tires (American Chronic Pain Association).

Table 3
Outcome measures.

Primary Outcome	Change in MME from baseline to 6, 12 (primary), and 18 months
Secondary Outcomes†	PROMIS Short Form v1.0 - Pain Interference 8a PROMIS Short Form v1.0 - Physical Function 8a
Other Outcomes†	PROMIS Scale v1.0 - Pain Intensity 3a PROMIS Short Form v1.0 - Anxiety 4a PROMIS Short Form v1.0 - Depression 4a BPI Pain Severity subscale BPI Pain Interference subscale Self-reported intent to taper Self-reported relative opioid use (higher than baseline, lower than baseline, no longer taking opioids)
Covariates	Demographics (age, sex assigned at birth, race, ethnicity) Health Literacy Skills Instrument Patient-Centered Communication in Cancer Care Health insurance type Chronic noncancer pain conditions (ICD-10) Charlson Comorbidity Index (ICD-10) Body mass index Alcohol/drug use disorders (ICD-10) Mental health disorders (ICD-10)

Notes: † Outcomes other than opioid prescriptions are measured at baseline, 6, and 12 months. BPI = brief pain inventory; ICD = International Classification of Diseases; MME = morphine milligram equivalents; PROMIS = Patient-Reported Outcomes Measurement Information System.

their opioid SDM discussion and management in an EHR note template.

3.2.3. Motivational interviewing + cognitive behavioral therapy for chronic pain

MI + CBT-CP participants received one MI session plus up to eight weekly CBT-CP group sessions. CBT participants started the intervention as a cohort, and no new members were added through the course of the eight sessions. Cohorts were typically formed from participants who had enrolled in the past 1 to 3 months. For each CBT-CP session attended, participants were remunerated $10. The INSPIRE MI + CBT-CP intervention was designed to be delivered by licensed clinicians, including master's- or PhD-level psychologists, licensed clinical social workers, or licensed professional counselors. Clinicians attended a 45-min prerecorded session covering the goals of the INSPIRE study, recruitment, safety issues, MI + CBT-CP, and documentation requirements. Clinicians reviewed the therapist manual and the CBT-CP packet given to participants.

The 30- to 60-min individual MI session was designed to be delivered early in the intervention, ideally before the first CBT-CP session, but sometimes after the first session or even after several CBT-CP sessions occurred [30]. The purpose of MI was to 1) enhance motivation for the CBT-CP intervention and voluntary opioid reduction or cessation, 2) build rapport between the therapist and the participant that would be useful in the subsequent CBT-CP, and 3) give the therapist a diagnostic sense of the participant.

CBT-CP posits that thoughts, emotions, and behaviors are linked, that they each act bidirectionally with the others, and that they can influence the interpretation of pain, pain coping skills, and overall functioning [25]. For example, a patient may have the negative thought "nothing can be done to help my pain," a type of thought known as "catastrophizing" that can lead to negative emotions like depression and anger. Depression, anxiety, and anger can worsen pain perception and make pain more difficult to treat. Further, depression can affect behaviors. A depressed person may be less likely to engage in activities that might decrease the pain, such as moderate exercise or pleasurable activities that might improve mood. This, in turn, reinforces the pain cycle.

We chose group CBT-CP therapy, which has been shown to be as effective as individual CBT-CP therapy [33]. The CBT-CP intervention consisted of eight sessions; the manual was adapted from John Otis's 12-session CBT-CP, a standard text in the field [25]. Based on historical practices at each site, the session length was 60 min at Duke and 90 min at UNC and VUMC. We felt that the optimal number of participants per session was 6 to 8 [33] and, therefore, planned to invite 10 to 12 for a group to allow for cancellations and participants who did not present for an intervention visit. The content of the eight sessions included the following components: (1) Introduction to Group, CBT-CP, and Diaphragmatic Breathing; (2) Relaxation Techniques and Behavioral Activation; (3) Self-Care and Wellbeing: Sleep Hygiene and Exercise; (4) Automatic Thoughts, Cognitive Errors and Pain; (5) Cognitive Restructuring and Cognitive Distancing (Distraction); (6) Stress Management and Time-Based Pacing; (7) Working with Painful Emotions (e.g., anger, frustration); and (8) Review and Trouble-shooting. MI-CBT + CP clinicians documented intervention delivery in an EHR note template. To monitor adherence, study coordinators completed a case report form indicating when MI and CBT sessions were completed. No make-up CBT-CP sessions were held.

3.3. Data collection

3.3.1. Clinical data extraction

We extracted existing EHR data to measure the primary outcome of opioid dosage. Clinical data were extracted from each site's PCORnet Common Data Model data warehouse. EHR data were collected for all enrolled participants through 18 months, including those lost to follow-up, except for participants who explicitly withdrew from the study.

3.4. Self-report survey

Participants completed questionnaires at baseline, 6 months, and 12 months, for which they were remunerated $30, $25, and $25, respectively.

3.5. Outcomes

3.5.1. Primary outcome

Change in average daily opioid dose, measured in MME, from baseline to 12 months is the primary study outcome, with secondary time points at 6 and 18 months. Prescription opioid data were derived from the EHR. For all analyses, average daily opioid dose is defined in 90-day increments at baseline (average over 90 days before randomization) and at 3, 6, 9, 12, 15, and 18 months post-randomization. We did not assess non-prescribed opioid use.

3.5.2. Secondary outcomes

Pain interference and physical function were measured using standardized measures from PROMIS. Pain interference, which refers to the extent to which pain limits physical, mental, and social activities, was measured with PROMIS Short Form v1.0 – Pain Interference 8a (PROMIS-PI) [34]. Physical function, which refers to the capability to perform physical activities, was measured with PROMIS Short Form v1.0 – Physical Function 8a (PROMIS-PF) [35]. Both scales are t-scores based on PROMIS normative data with a mean score of 50 and a standard deviation of 10. For each measure, the outcome is defined as the change in t-score from baseline to 6 and 12 months.

3.5.3. Other outcomes

Other outcomes (Table 3) included change from baseline in self-reported measures of 1) pain intensity, measured with PROMIS Scale v1.0 – Pain Intensity 3a; 2) anxiety, measured with PROMIS Short Form v1.0 – Anxiety 4a [36]; and 3) depression, measured with PROMIS Short Form v1.0 - Depression 4a [36]. The Brief Pain Inventory (BPI) Pain Severity and Pain Interference measures were also assessed at baseline, 6, and 12 months [37]. Self-reported intent to taper opioid use and relative opioid use were assessed at 6 and 12 months.

3.5.4. Covariates

Covariates from the baseline questionnaire include age, sex assigned at birth, race, ethnicity, health literacy level using the Health Literacy Skills Instrument [38], and patient-centered communication using the Patient-Centered Communication in Cancer Care instrument [39]. EHR-based covariate data included health insurance type; number and type of CNCP conditions based on *International Classification of Diseases*, 10th edition (ICD-10) codes; overall comorbidity using the Charlson Comorbidity Index per ICD-10 codes [40]; body mass index; alcohol/drug use disorders; and mental health disorders using ICD-10 codes.

3.6. Statistical analysis

As of the writing of this manuscript, data analyses are still ongoing. We will test the single primary hypothesis that the change in MME differs between arms at 12 months using an 0.05 significance level. We will also test arm differences for the two secondary outcomes, change in PROMIS-PI and PROMIS-PF at 12 months, with adjustment for multiple comparisons using the Hochberg modification to the Bonferroni adjustment [41]. All other statistical comparisons will be considered descriptive in nature.

Analyses will be based on an intention-to-treat population [42] using data from all participants, analyzed according to the arm to which they were randomized irrespective of type or amount of intervention received. Because the true intervention effect might be attenuated for participants receiving only a small amount of the intervention, we will also conduct analyses using a per-protocol population who received a substantial portion of the randomized intervention, defined as at least four SDM sessions and at least four MI + CBT-CP sessions.

A mixed linear model for repeated measurements will be used to estimate intervention arm differences for the change in opioid dose from baseline to 3, 6, 9, 12, 15, and 18 months. Although the primary time point is at 12 months and secondary time points are at 6 and 18 months, all available opioid prescription data through 18 months will be included. The model will have fixed effects for intervention arm, time interval (as a categorical variable), intervention-by-time interaction, baseline opioid dose, and the stratification factor of study center.

We will compare intervention arms for change from baseline in all secondary and other outcomes collected as a continuous score using a similar mixed linear model for repeated measures. Incidence of self-reported intent to taper opioid medication and reported opioid use at 12 months will be compared between arms using logistic regression with adjustment for baseline dose, baseline intent, and study site.

Secondary analyses will also assess potential differential intervention effects for two preplanned subgroups defined by participants with co-morbid mental health conditions and by sex assigned at birth. A subgroup-by-intervention interaction at the primary 12-month point will be tested within the mixed model for opioid dose reduction. To account for the inherent decrease in power associated with interaction tests, these tests will be conducted at a significance level of 0.1.

The study will evaluate differences by age, baseline pain score, comorbidities—including physical comorbidities and mental health disorders, and past or current alcohol or other substance abuse and related disorders—those taking other medications, patient health literacy level, BMI, baseline opioid dose, and intervention delivery mode (in-person vs. telehealth) in exploratory analyses.

Fidelity was assessed through reviews of EHR notes, case report forms, and qualitative input from study clinicians in 2019 and will be assessed again at the end of the intervention. Specifically, we assessed the extent to which GCC, SDM, MI, and CBT intervention components were implemented as planned in the study protocol. For example, the purpose of the SDM assessment was to identify whether clinicians used the SDM educational materials (if so, which materials they used), and discussed patient preferences, values, and goals during the visit.

3.7. Sample size and power

The planned sample size is 608 participants, 304 per intervention arm, to achieve 80% power for identifying a difference between intervention arms in opioid dose reduction of 10 MME/day, assuming a baseline model-adjusted standard deviation of 40 MME/day and including an increase in size of 20% to account for expected attrition and correlation within the MI + CBT-CP groups. We estimated a mean baseline opioid use of 55 MME/day based on anecdotal information from the study clinicians and data available from Liebschutz [43] and Sullivan et al. [44]. Study clinicians indicated that differences in dose reduction of 10 MME/day or greater were clinically meaningful. The standard deviation was also estimated from Liebschutz and Sullivan et al.

Based on 608 randomized participants, the power for PROMIS-PI is 96%, while the power for PROMIS-PF is 57%, assuming a 25% attrition rate for PROMIS Scale responses, a standard deviation of 10, and a minimally important difference of 3.5 units for PROMIS-PI and 2 units for PROMIS-PF, which are within the range of estimates in the literature [45,46].

4. Discussion

The INSPIRE trial helps provide more evidence on interventions to promote dose reduction by examining the impact of non-pharmacotherapeutic interventions on opioid dose and pain and physical functioning outcomes among CNCP patients receiving LTOT. The ultimate goal is to inform evidence-based practices that support those who struggle with pain.

Three study features are noteworthy. First, this study compares the effectiveness of two behavioral interventions that promote patient-centered care by enhancing motivation and addressing both the physical and psychological aspects of pain through patient education, patient-clinician communication, and promotion of informed decision making. Both interventions provide patients with information, support, and a diversified set of coping skills.

Second, opioid reduction, decreased pain interference, and improved physical function are patient-centered outcomes. We believe physical function and pain interference are co-equal with opioid dose reduction or tapering. Further reflecting a patient-centered approach, a patient's decision to taper or lower dose is voluntary and not required for study participation.

Third, the study is a pragmatic clinical trial. This design maximizes external validity and generalizability in contrast with an explanatory RCT, which would attempt to maximize internal validity and reduce confounding but would have limited generalizability. Inclusion criteria were broad, and exclusion criteria were minimal. Clinicians had some flexibility in how to apply SDM and MI + CBT-CP. The study was conducted in both specialty pain and general medical clinics. Because of a general shortage of therapists trained to deliver MI + CBT-CP, we chose a group format rather than individual therapy. With the current shortage of therapists trained to deliver CBT-CP, using a group approach allows one therapist to treat several patients simultaneously, increasing access and doing so more cost-effectively. The Stakeholder Advisory Committee also told us that the social component of group CBT-CP was an added benefit.

These factors strengthened INSPIRE's external validity and make it easier to disseminate the study; however, INSPIRE was conducted in academically affiliated outpatient clinics, which may limit its generalizability. Participants did not have to pay for their MI + CBT-CP sessions, or only paid a modest amount early on before all costs were removed. In usual clinical settings, out-of-pocket costs for these services may serve as a barrier to participation.

In summary, once complete, this pragmatic, multisite trial will provide data on the real-world effectiveness of SDM versus MI + CBT-CP in potentially reducing opioid dose, decreasing pain interference, and

improving pain functioning. Study results will help to develop and implement evidence-based strategies to promote patient-centered CNCP treatment while mitigating the risk of opioid-induced adverse outcomes.

Trial sponsor

RTI International.

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Declaration of Competing Interest

M.S. has disclosed that he is an unpaid Board member of Physicians for Responsible Opioid Prescribing and is a paid consultant in opioid litigation. M.E., S.T., L. Wagner, J.T., L. Wu, R.D., P.C., T.I., K.A., C.D., and L.M. have no conflicts of interest to report.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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References

[1] Institute of Medicine of the National Academies, Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, 2011.
[2] M. Von Korff, A.I. Scher, C. Helmick, et al., United States national pain strategy for population research: concepts, definitions, and pilot data, J. Pain 17 (10) (2016) 1068–1080, https://doi.org/10.1016/j.jpain.2016.06.009.
[3] E.E. Krebs, A. Gravely, S. Nugent, et al., Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial, JAMA. 319 (9) (2018) 872–882, https://doi.org/10.1001/jama.2018.0899.
[4] R. Chou, J.A. Turner, E.B. Devine, et al., The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop, Ann. Intern. Med. 162 (4) (2015) 276–286, https://doi.org/10.7326/M14-2559.
[5] R. Chou, D. Hartung, J. Turner, et al., Opioid Treatments for Chronic Pain, Rockville (MD), 2020.
[6] D. Dowell, K.R. Ragan, C.M. Jones, G.T. Baldwin, R. Chou, CDC clinical practice guideline for prescribing opioids for pain — United States, 2022, MMWR Recomm. Rep. 71 (3) (2022) 1–95, https://doi.org/10.15585/mmwr.rr7103a1.
[7] D. Dowell, T. Haegerich, R. Chou, No shortcuts to safer opioid prescribing, N. Engl. J. Med. 380 (24) (2019) 2285–2287, https://doi.org/10.1056/NEJMp1904190.
[8] U.S. Food and Drug Administration, FDA Identifies Harm Reported from Sudden Discontinuation of Opioid Pain Medicines and Requires Label Changes to Guide Prescribers on Gradual, Individualized Tapering. https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes, 2019. Published 2019.
[9] N. Avery, A.G. McNeilage, F. Stanaway, et al., Efficacy of interventions to reduce long term opioid treatment for chronic non-cancer pain: systematic review and meta-analysis, BMJ. 377 (2022), e066375, https://doi.org/10.1136/bmj-2021-066375.
[10] C. Charles, A. Gafni, T. Whelan, Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango), Soc. Sci. Med. 44 (5) (1997) 681–692, https://doi.org/10.1016/s0277-9536(96)00221-3.
[11] G. Elwyn, D. Frosch, R. Thomson, et al., Shared decision making: a model for clinical practice, J. Gen. Intern. Med. 27 (10) (2012) 1361–1367, https://doi.org/10.1007/s11606-012-2077-6.
[12] G. Makoul, M.L. Clayman, An integrative model of shared decision making in medical encounters, Patient Educ. Couns. 60 (3) (2006) 301–312, https://doi.org/10.1016/j.pec.2005.06.010.
[13] Agency for Healthcare Research and Quality, The SHARE Approach—Essential Steps of Shared Decision Making: Expanded Reference Guide with Sample Conversation Starters, Agency for Healthcare Research and Quality, Rockville, MD, 2020.
[14] L.A. Shay, J.E. Lafata, Where is the evidence? A systematic review of shared decision making and patient outcomes, Med. Decis. Mak. 35 (1) (2015) 114–131, https://doi.org/10.1177/0272989X14551638.
[15] G. Milky, J. Thomas 3rd., Shared decision making, satisfaction with care and medication adherence among patients with diabetes, Patient Educ. Couns. 103 (3) (2020) 661–669, https://doi.org/10.1016/j.pec.2019.10.008.
[16] Y. Tousignant-Laflamme, S. Christopher, D. Clewley, L. Ledbetter, C.J. Cook, C. E. Cook, Does shared decision making results in better health related outcomes for individuals with painful musculoskeletal disorders? A systematic review, J. Man. Manip. Ther. 25 (3) (2017) 144–150, https://doi.org/10.1080/10669817.2017.1323607.
[17] A.R.J. Sanders, N.J. de Wit, N.P.A. Zuithoff, S. van Dulmen, The effect of shared decision-making on recovery from non-chronic aspecific low back pain in primary care; a post-hoc analysis from the patient, physician and observer perspectives, BMC Prim. Care 23 (1) (2022) 22, https://doi.org/10.1186/s12875-022-01624-y.

[18] V.M. Montori, M. Kunneman, J.P. Brito, Shared decision making and improving health care: the answer is not in, JAMA. 318 (7) (2017) 617–618, https://doi.org/10.1001/jama.2017.10168.
[19] V.C. Somohano, C.L. Smith, S. Saha, et al., Patient-provider shared decision-making, trust, and opioid misuse among US veterans prescribed long-term opioid therapy for chronic pain, J. Gen. Intern. Med. 38 (12) (2023) 2755–2760, https://doi.org/10.1007/s11606-023-08212-5.
[20] W.R. Miller, S. Rollnick, Motivational Interviewing: Helping People Change, 3rd ed, Guilford Press, 2012.
[21] M.J. Armstrong, T.A. Mottershead, P.E. Ronksley, R.J. Sigal, T.S. Campbell, B. R. Hemmelgarn, Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials, Obes. Rev. 12 (9) (2011) 709–723, https://doi.org/10.1111/j.1467-789X.2011.00892.x.
[22] G. Ekong, J. Kavookjian, Motivational interviewing and outcomes in adults with type 2 diabetes: a systematic review, Patient Educ. Couns. 99 (6) (2016) 944–952, https://doi.org/10.1016/j.pec.2015.11.022.
[23] J. Nijs, A.J. Wijma, W. Willaert, et al., Integrating motivational interviewing in pain neuroscience education for people with chronic pain: a practical guide for clinicians, Phys. Ther. 100 (5) (2020) 846–859, https://doi.org/10.1093/ptj/pzaa021.
[24] Department of Veterans Affairs and Department of Defense, VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain, May 2010.
[25] J.D. Otis, Managing Chronic Pain: A Cognitive-Behavioral Therapy Approach. Therapist Guide, Oxford University Press, New York, NY, 2007.
[26] S. Morley, C. Eccleston, A. Williams, Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache, Pain. 80 (1–2) (1999) 1–13, https://doi.org/10.1016/s0304-3959(98)00255-3.
[27] J. Yang, W.L.A. Lo, F. Zheng, X. Cheng, Q. Yu, C. Wang, Evaluation of cognitive behavioral therapy on improving pain, fear avoidance, and self-efficacy in patients with chronic low back pain: a systematic review and meta-analysis, Pain Res. Manag. 2022 (2022) 4276175, https://doi.org/10.1155/2022/4276175.
[28] H. Richmond, A.M. Hall, B. Copsey, et al., The effectiveness of cognitive behavioural treatment for non-specific low back pain: a systematic review and meta-analysis, PLoS One 10 (8) (2015), e0134192, https://doi.org/10.1371/journal.pone.0134192.
[29] D. Dowell, T.M. Haegerich, R. Chou, CDC guideline for prescribing opioids for chronic pain – United States, JAMA. 315 (15) (2016) 1624–1645, https://doi.org/10.1001/jama.2016.1464.
[30] Agency for Healthcare Research and Quality, SHARE Approach Curriculum Tools. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/index.html, 2021. Published February 2021. Accessed April 10, 2023.
[31] I. Hargraves, A. LeBlanc, N.D. Shah, V.M. Montori, Shared decision making: the need for patient-clinician conversation, not just information, Health Aff. 35 (4) (2016) 627–629, https://doi.org/10.1377/hlthaff.2015.1354.
[32] National Institute for Health and Care Excellence (NICE) Medicines and Prescribing Centre (UK), Patient decision aids used in consultations involving medicines, in: Medicines Optimisation: The Safe and Effective Use of Medicines to Enable the Best Possible Outcomes, 2015. Manchester.
[33] B.E. Thorn, M.C. Kuhajda, Group cognitive therapy for chronic pain, J. Clin. Psychol. 62 (11) (2006) 1355–1366, https://doi.org/10.1002/jclp.20315.
[34] D. Amtmann, K.F. Cook, M.P. Jensen, et al., Development of a PROMIS item bank to measure pain interference, Pain. 150 (1) (2010) 173–182, https://doi.org/10.1016/j.pain.2010.04.025.
[35] M. Rose, J.B. Bjorner, B. Gandek, B. Bruce, J.F. Fries, J.E. Ware Jr., The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency, J. Clin. Epidemiol. 67 (5) (2014) 516–526, https://doi.org/10.1016/j.jclinepi.2013.10.024.
[36] P.A. Pilkonis, L. Yu, N.E. Dodds, K.L. Johnston, C.C. Maihoefer, S.M. Lawrence, Validation of the depression item bank from the Patient-Reported Outcomes Measurement Information System (PROMIS) in a three-month observational study, J. Psychiatr. Res. 56 (2014) 112–119, https://doi.org/10.1016/j.jpsychires.2014.05.010.
[37] C. Cleeland, K. Ryan, Pain assessment: global use of the brief pain inventory, Ann. Acad. Med. Singap. 23 (2) (1994) 129–138.
[38] C.M. Bann, L.A. McCormack, N.D. Berkman, L.B. Squiers, The Health Literacy Skills Instrument (HLSI): a 10-item short form, J. Health Commun. 17 (Suppl. 3) (2012) 191–202.
[39] B.B. Reeve, D.M. Thissen, C.M. Bann, et al., Psychometric evaluation and design of patient-centered communication measures for cancer care settings, Patient Educ. Couns. 100 (7) (2017) 1322–1328, https://doi.org/10.1016/j.pec.2017.02.011.
[40] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (5) (1987) 373–383, https://doi.org/10.1016/0021-9681(87)90171-8.
[41] Y. Hochberg, A sharper bonferroni procedure for multiple tests of significance, Biometrika. 75 (4) (1988) 800–802, https://doi.org/10.2307/2336325.
[42] D. Fergusson, S.D. Aaron, G. Guyatt, P. Hebert, Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis, BMJ. 325 (7365) (2002) 652–654, https://doi.org/10.1136/bmj.325.7365.652.
[43] J.M. Liebschutz, Z. Xuan, C.W. Shanahan, et al., Improving adherence to long-term opioid therapy guidelines to reduce opioid misuse in primary care: a cluster-randomized clinical trial, JAMA Intern. Med. 177 (9) (2017) 1265–1272, https://doi.org/10.1001/jamainternmed.2017.2468.
[44] M.D. Sullivan, J.A. Turner, C. DiLodovico, A. D'Appollonio, K. Stephens, Y.F. Chan, Prescription opioid taper support for outpatients with chronic pain: a randomized controlled trial, J. Pain 18 (3) (2017) 308–318, https://doi.org/10.1016/j.jpain.2016.11.003.
[45] C.X. Chen, K. Kroenke, T.E. Stump, et al., Estimating minimally important differences for the PROMIS pain interference scales: results from 3 randomized clinical trials, Pain. 159 (4) (2018) 775–782, https://doi.org/10.1097/j.pain.0000000000001121.
[46] A.C. Lee, J.B. Driban, L.L. Price, W.F. Harvey, A.M. Rodday, C. Wang, Responsiveness and minimally important differences for 4 patient-reported outcomes measurement information system short forms: physical function, pain interference, depression, and anxiety in knee osteoarthritis, J. Pain 18 (9) (2017) 1096–1110, https://doi.org/10.1016/j.jpain.2017.05.001.