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Design and methods of the Care Management for the Effective Use of Opioids (CAMEO) trial

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ABSTRACT

Low back pain is the most common pain condition seen in primary care, with the most common treatment being analgesic medications, including opioids. A dramatic increase in opioid prescriptions for low back pain over the past few decades has led to increased non-medical use and opioid overdose deaths. Cognitive behavioral therapy (CBT) for chronic pain is an evidence-based non-pharmacological treatment for pain with demonstrated efficacy when delivered using collaborative care models. No previous studies have tested CBT compared to analgesic optimization that includes opioid management in primary care. This paper describes the study design and methods of the CAre Management for the Effective use of Opioids (CAMEO) trial, a 2-arm, randomized comparative effectiveness trial in seven primary care clinics. CAMEO enrolled 261 primary care veterans with chronic (6 months or longer) low back pain of at least moderate severity who were receiving long-term opioid therapy and randomized them to either nurse care management focused on analgesic treatment and optimization (MED) or cognitive behavioral therapy (CBT). All subjects undergo comprehensive outcome assessments at baseline, 3, 6, 9, and 12 months by interviewers blinded to treatment assignment. The primary outcome is pain severity and interference, measured by the Brief Pain Inventory (BPI) total score. Secondary outcomes include health-related quality of life, fatigue, sleep, functional improvement, pain disability, pain beliefs, alcohol and opioid problems, depression, anxiety, and stress.

1. Introduction

Low back pain is the most common pain condition seen in ambulatory care and ranks second only to cough as a reason that patients seek care [1,2]. Low back pain accounts for an enormous burden in patient suffering, quality of life, disability, and health care costs, especially when it persists chronically [3]. The use of opioid analgesics to treat low back pain has been increasing in the United States [3,4], with more than half of long-term opioid users reporting back pain [3,5]. Despite recent decreases in the number of opioid prescriptions in the United States, prescription rates remain as high as 46.7 prescriptions per 100 residents in 2019 [6], with survey data from 2012 to 2014 suggesting a prevalence of long-term opioid use in the United States as high as 5.4%. While recent literature reviews have demonstrated efficacy of opioids in treating chronic pain in the short term (1 to <6 months), there was limited evidence to evaluate long-term benefits [7]. A recent survey of 9253 patients prescribed opioids found that 56.1% of patients reported the effectiveness of their pain treatment to be fair or poor [8]. While

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both pharmacological and non-pharmacological treatments for pain are available as adjuncts or alternatives to opioid therapy, there is a lack of studies comparing different treatments head-to-head in patients on long-term opioid therapy.

Among non-pharmacological treatments, the strongest clinical trial evidence supports cognitive or behavioral approaches [9,10]. Cognitive-behavioral therapy (CBT) is a skills-based approach to chronic pain, which posits that patients' maladaptive appraisals of pain directly contribute to the persistence of pain and pain-related disability. CBT teaches patients to identify maladaptive thoughts and behaviors and to replace them with alternatives that are more helpful to improve their coping and experience of chronic pain [11].

Despite strong evidence supporting CBT and other non-pharmacological treatments, analgesics are the most common and pragmatic approach to treating pain in clinical practice. Analgesics, including opioids, are the second most prescribed class of drugs, after cardiovascular drugs, and account for 11% of all medications prescribed during office visits [12]. Moreover, the prescription of opioid analgesics rose sharply in the 1990s and 2000s, with the number of prescriptions outnumbering the population in many parts of the United States at the prescribing peak of 2010 [13,14]. The increase in opioid prescribing over the past few decades has been followed by a commensurate increase in nonprescription non-medical opioid use and overdose deaths [15,16]. By some estimates, the opioid-related overdose death rate has risen 20-fold since 1999, with 49,860 opioid-involved overdose deaths reported in 2019 [17]. That decreases in opioid prescribing has coincided with an increase in overdose deaths illustrates the importance of a thoughtful, evidence-based approach to making treatment adjustments for patients on long-term opioid therapy.

Prior trials have demonstrated that both pharmacological and non-pharmacological interventions for pain can be delivered to primary care patients using collaborative telecare strategies [18–20]. The effective pharmacological approaches in these trials used step-based algorithms to optimize simple analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) followed by co-analgesics medications such as antidepressants and gabapentinoids [19,20]. While these prior trials have included patients taking opioids, none have exclusively targeted patients receiving long-term opioids. Additionally, these trials have compared either pharmacological treatment, non-pharmacological treatment, or both compared to a usual care arm, rather than comparing a pharmacological and non-pharmacological treatment head-to-head. This paper describes the study design and methods of the CAre Management for the Effective use of Opioids (CAMEO) trial. The primary aim is to compare CBT versus analgesic treatment and optimization on pain severity and interference over 12 months in primary care patients with chronic low back pain on long-term opioids.

2. Methods

2.1. Overall design

CAMEO is a 2-arm, randomized clinical trial conducted to compare the effectiveness of nurse care management focused on analgesic treatment and optimization (MED) compared to a psychologist-delivered cognitive behavioral therapy-based pain self-management intervention (CBT). The study population comprises veterans with chronic low back pain (CLBP) with persistent moderate to severe pain despite long-term opioid therapy. Veterans receiving primary care treatment for CLBP at the Richard L. Roudebush Veterans Administration (VA) Medical Center (VAMC) general medicine clinics and two community-based outpatient clinics (CBOC) were identified through automated searches of International Classification of Diseases – 9th Revision codes (ICD-9721.x; 722.x, or 724.x) related to low back pain in the electronic health record (EHR). Of note, the CAMEO protocol was developed prior to the transition from ICD-9 to ICD-10. Eligibility was determined by phone screening. Patients with CLBP of at least moderate severity despite current use of long-term opioid therapy were eligible, and those who completed a baseline interview and provided informed consent were randomized to receive either the MED or CBT intervention. Participants were block randomized using a computer program to conceal allocation and stratified by study site (VAMC vs. CBOC).

Fig. 1 highlights the timeline and key elements of the study design. The intervention period for each arm is delivered over 6 months, followed by an additional 6 months of follow-up for outcome assessments. Outcomes are assessed at baseline, 3, 6, 9, and 12 months post-randomization by interviewers blinded to treatment arm. The primary outcome is the Brief Pain Inventory (BPI) total score, a composite of pain severity and interference scores. Secondary outcomes include health-related quality of life, fatigue, sleep, functional improvement, pain disability, pain beliefs, alcohol and opioid problems, depression, anxiety, and stress. The Indiana University Institutional Review Board and VA Medical Center Research Committee approved the study. The trial is monitored by an independent data and safety monitoring board. All enrolled patients provide written informed consent.

2.2. Eligibility

Potential participants are veterans with CLBP, defined as pain of at least moderate severity (score $\geq$ 5 on 0 to 10 point scale) lasting at least 6 months, who have been on long-term opioid therapy (3 or more prescriptions of $\geq$28 days for opioids in previous 12 months). Access to a working telephone is also a pre-requisite for enrollment, as most of the outcome assessments are conducted via phone. Exclusion criteria are determined during a baseline eligibility survey and are designed to eliminate potential participants for whom the interventions may be unsafe or inappropriate. In particular, we excluded patients with medical conditions that would either be a contraindication to receiving intervention medications or whose severity made it unlikely they would be able to fully engage in a CBT program. Medical conditions excluded are: 1) significant cardiovascular disease: New York Heart Association functional class 3 or 4 congestive heart failure; systolic blood pressure $\geq$ 180 or diastolic blood pressure $\geq$ 105 mmHg; myocardial infarction, stroke, or transient ischemic attack within the previous 6 months; chest pain or dizziness with exercise; (2) chronic obstructive pulmonary disease or asthma needing home oxygen; (3) cancer (other than skin cancer) receiving treatment or treatment planned in the next 6 months.

Additional exclusion criteria are: 1) active psychosis; 2) schizophrenia; 3) active suicidal ideation; 4) history of back surgery or pending back surgery; 5) moderately severe cognitive impairment defined by a 6-item validated screener [21]; 6) involvement in an ongoing pain trial; 7) pregnancy or trying to become pregnant; and 8) active treatment for substance use disorder in a designated substance use treatment program, including patients on methadone maintenance. Patients prescribed buprenorphine are not excluded, per se, but are rarely encountered in this population of patients prescribed full agonist opioids. To maximize generalizability, veterans with a history of substance use disorder are not excluded. To further maximize generalizability and expand our potential sample size, we decided not to exclude veterans with current (or applying for) disability (service-connected or social security) for CLBP.

2.3. Recruitment and enrollment

Primary care providers (PCPs) are informed of CAMEO study details and provided signed approval for the study team to contact potentially eligible participants. Potential participants are principally identified by query of the VA electronic health record (EHR) to create a master list of patients who meet the following criteria: 1) primary care visit in past 2 years; 2) moderate pain severity according to numeric rating scale recorded in the EHR; and 3) long-term opioid use. The list of potential participants is updated monthly during the enrollment period, and a

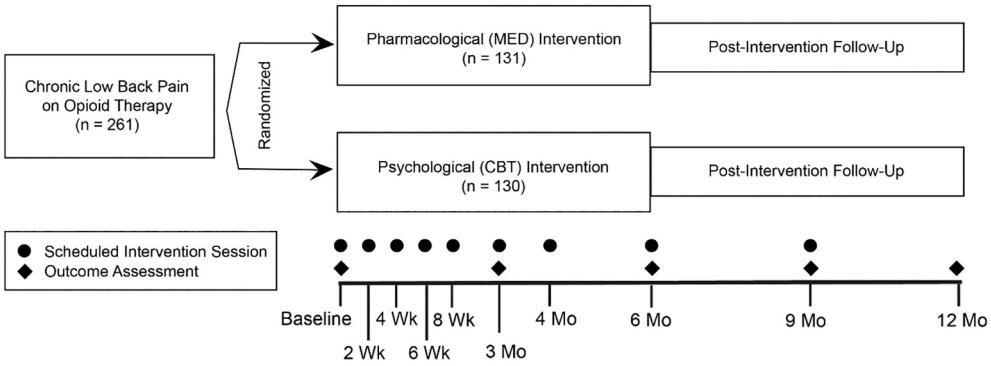

Fig. 1. Schematic overview of CAMEO trial.

recruitment letter signed by their PCP is mailed to qualifying veterans describing the study. The research team determines eligibility by applying the inclusion/exclusion criteria during an eligibility interview. Potential participants are contacted by phone within a week of receiving letters to assess eligibility and determine their interest in participating. For eligible and interested veterans, an appointment is scheduled to obtain signed informed consent, signed HIPAA authorization, and complete a baseline interview.

2.4. Randomization

After providing written-informed consent and completing their baseline interview, participants are block randomized in block sizes of 2, 4, 6, and 8 to one of two arms: 1) nurse care management focused on analgesic treatment and optimization (MED); or 2) psychologist-delivered cognitive behavioral therapy-based pain self-management intervention (CBT). Randomization lists are computer-generated and treatment assignments are supplied in sealed opaque envelopes. Randomization is stratified only by study site.

2.5. Interventions

The CAMEO interventions are delivered over 6 months. The length of the follow-up and schedule of outcome assessments at 3, 6, 9, and 12 months were chosen to detect three types of treatment effects: 1) "early" (3-months) intervention effects; 2) immediate post-intervention effects at 6-months; and 3) sustained effects at 9- and 12-months post-randomization.

2.5.1. Nurse care management in MED treatment arm

The multi-component aspects of nurse care management have proven effective in multiple trials, including monitoring symptoms, assessing adherence, addressing adverse effects, communicating with the primary care provider, and staffing cases with supervising physicians [18–20]. The MED treatment arm is designed to optimize pharmacological treatment for CLBP in the primary care setting. Nurse care managers (NCMs) deliver algorithm-based co-analgesic treatment coupled with guideline-concordant opioid management (MED) ("as detailed in 2.5.3, below"). The NCMs meet weekly with physician and pharmacist-investigators to review cases and provide advice on treatment plans. Also, a physician-investigator is available at all times to discuss any management issues that arise between the weekly case meetings.

The timeline of NCM contacts with patients in the MED arm is outlined in Fig. 1. Participants are scheduled to receive at least 8 contacts with the NCMs over the trial period. Participants have an initial visit at baseline to assess their current and past treatments for CLBP, pain severity, and pain-related limitations. Typically, there will be some change in analgesic dose or medication at the baseline NCM visit since all enrolled patients have pain of moderate severity despite being on long-term opioids. During follow-up calls, patients' pain severity, response to treatment, adherence to analgesics, adverse effects, and desire to change current treatment are assessed. Follow-up NCM telephone contacts are scheduled to occur at 2, 4, 6 and 8 weeks after baseline, and at months 3, 4, 6, and 9. On average, these calls are expected to last 10 to 20 min. The goal is to have at least 7 contacts between the NCM and the study participant after the initial assessment, with flexible timing of contacts built in as this has been shown to improve effectiveness [22].

2.5.2. Pharmacological management protocol

During the baseline assessment, the NCMs determine current and past treatments for CLBP and establish whether participants have had an adequate trial (i.e., were co-analgesics dosed to the maximum of their therapeutic range). If not, the NCM (in consultation with study physicians) will usually recommend an adjustment to an existing co-analgesic or initiate a new co-analgesic. Occasionally, adjustments to opioid therapy are made.

After prescriptions are written or entered electronically by the study physicians, all study medications are dispensed through the medical center pharmacy. The NCM regularly interacts with the research pharmacist, who oversees study medication dispensing. Participants' PCPs are integrated as a partner and informed of medication changes in two ways. First, when opioid changes are recommended, the NCM or study PI pages PCPs to speak with them directly about the change. To avoid patient care disruptions these exchanges are conducted prior to or after the PCP's clinic time. Second, for co-analgesic changes, a study physician enters a note in the EHR reflecting the change and then sends a "view alert" to PCPs to keep them informed.

Two weeks after adjustment/initiation of analgesics, the NCM contacts participants by telephone to assess treatment response, adherence, and side effects. If bothersome side effects prompt non-adherence, discontinuation, or patient reluctance to continue the analgesic(s), the analgesic is changed. Subsequently, the NCM assesses treatment response at four weeks (after baseline) and at months 2, 3, 4, 6, and 9. The study physicians supervise the weekly care management meetings to discuss patients as well as consultation between meetings as needed. Treatment response is evaluated in three domains: (1) pain severity; (2) pain-related disability; and (3) global improvement. To simulate clinical practice and enhance patient-centeredness of CAMEO, treatment preferences (i.e., desire to change treatment) are also assessed and considered prior to any treatment changes.

The NCM follows a modified evidence-based medication algorithm that lists simple analgesics and co-analgesics to guide treatment decisions. The algorithm (Table 1) is based upon a synthesis of relevant research [23–25]. This algorithm primarily focuses on optimizing non-opioid analgesics (NSAIDs and acetaminophen) and other co-analgesics. If pain does not improve after working through the algorithm, adjustments in opioid therapy are considered.

Table 1
Step-wise co-analgesic algorithm.

Step 1 Medications:
Simple analgesics

1. Acetaminophen 650 mg every 6 h (max 2000 mg per day if cirrhosis or ≥ 3 alcoholic drinks/day)
2. NSAIDs: try at least two (except in patients with renal impairment or peptic ulcer disease)
   a. 1st line: naproxen 500 mg every 12 h or 500 mg in the morning plus 250 mg twice daily (max 1000 mg per day)
   b. 2nd line: (i) salsalate 1000 mg every 8 h or 1500 mg every 12 h (max 3000 mg per day); (ii) etodolac 300 mg every 8 h or 500 mg every 12 h (max 1000 mg per day); (iii) ibuprofen 600 mg every 6 h (max 2400 mg per day); (iv) piroxicam 10 mg daily

Step 2 Medications:
Tramadol

1. Start 25 mg twice or three times daily and titrate to 100 mg four times daily (max 300 mg per day if age > 75; max 100 mg twice daily if creatinine clearance <30, or 50 mg twice daily if creatinine clearance <10; max 50 mg twice daily if cirrhosis)
2. Use concurrent acetaminophen, 500–1000 mg dosed with tramadol three to four times daily

Step 3 Medications:

1. Gabapentin, titrate up to 900-1200 mg three times daily
2. Cyclobenzaprine 5–10 mg at bedtime, titrate up to three times daily
3. Venlafaxine, titrate up to 225 mg daily
4. Duloxetine (60 mg daily) and/or Pregabalin (300–450 mg daily, divided into two doses)

Step 4 Medications:
TCAs

1. Amitriptyline (avoid if age ≥ 65 years), start at 10–25 mg, titrate to 100 mg daily*
2. Nortriptyline, start at 10–25 mg, titrate to 100 mg daily*

* Max 50 mg daily if taking a selective serotonin reuptake inhibitor (SSRI) or selective serotonin and norepinephrine reuptake inhibitor (SNRI).

2.5.3. Guideline-concordant opioid management in MED treatment arm

In clinical practice "doing well" on long-term opioid therapy means: (1) achieving meaningful pain relief; (2) improving one's ability to function; (3) experiencing minimal or no side effects on steady doses; and (4) adhering to the guidelines of opioid therapy outlined in an opioid treatment agreement [26]. This trial followed the principles of the VA/DoD clinical practice guideline for opioid therapy for chronic pain [26]. Of note, treatment delivery for the trial was completed prior to the 2017 guideline revisions. Principles of opioid treatment used in this trial include: (1) When appropriate, participants are given a reasonable short-acting "opioid trial," i.e., continuing an opioid or switching to a second short-acting opioid to find the best balance between relief and adverse effects; (2) Long-acting opioids are initiated at low doses in patients who do not fully respond to short-acting agents; (3) Long-acting morphine is used as the first-line, long-acting opioid; (4) Methadone is considered if morphine is ineffective or poorly tolerated; (5) Long-acting opioids are titrated in a conservative and measured way if only partially effective; (6) Short-acting opioids are considered for breakthrough pain; (7) opioid rotation is considered for patients only partially responding to a particular opioid; (8) pain intensity, functioning, and aberrant behaviors are regularly monitored during NCM calls.

2.5.4. Opioid adherence monitoring

Participants are asked to sign an opioid treatment agreement at study enrollment. Any opioid-related problems observed during the study are discussed with the patient's PCP to develop a consensus on resolution. Risk of opioid misuse and possible diversion is assessed using clinical and medication history. Urine drug tests are collected at least twice during the study: at baseline, at 6 months, and randomly if concern for diversion arises. Unexpected findings prompt a discussion with the patient and primary care physician to guide treatment decisions and would not exclude a patient from participation in the study.

2.5.5. Psychologist-led cognitive behavioral therapy (CBT) arm

Veterans randomized to the CBT arm continue to be prescribed medications, including opioids and other analgesics, by their treating physician without monitoring or input from the study team. Additionally, these participants receive a series of 8 pain self-management/coping skills training sessions delivered in one-on-one sessions by PhD-level clinical psychologists. The CBT intervention, especially the pain self-management skills manual, evolved from material used in our prior trials [18,19] and proven effective by Damush et al.'s primary care trial of low back pain [27] as well as arthritis trials by Lorig and Von Korff [28,29]. As is customary for treating pain, this CBT program involves a highly-manualized and moderately didactic process. To complement the behavioral focus of self-management, the pain self-management skills training draws upon a manualized cognitive behavioral program applied in the ESCAPE trial, modeled after previous CBT interventions [30], and empirically validated in prior studies of pain. Self-management training is focused on increasing self-efficacy to manage low back pain and skills training is focused on the basic CBT concept that pain is a complex experience affected by thoughts, feelings and behaviors.

Since optimal application of non-pharmacological interventions for pain involves tailoring to patient needs [31], participants are introduced to a "menu" of self-management and coping skills (Table 2) over a series of 8 sessions, with a "booster" session being given at the final session. Delivery of the CBT intervention employs a flexible approach adapted to individual preferences and perceived need for learning specific pain coping skills. Tailoring includes the selection of relevant content and skills to the individual participant. Participants choose skills to learn and behaviors to modify that they perceive most relevant to them.

Participants learn to modify and attempt to sustain healthy behaviors through goal setting and problem-solving techniques. Barriers to engaging in self-management behaviors are discussed. Each session involves a discussion of patients' thoughts and feelings about their pain, past treatments for pain, and identification of barriers to reducing pain severity and interference with activities. These discussions are framed using content from Emery's "4 A's model" to help participants modify

Table 2
Pain self-management content provided to the CBT intervention group.

Session	Topic	Content
1	Introduction and Pain Education	• Biopsychosocial Model of Pain • Acute vs. Chronic Pain • Chronic Pain Cycles • Hurt vs. Harm • Gate Control Theory of Pain • Fight or Flight vs. Relaxation Response
2	Relaxation Skills	• Diaphragmatic Breathing • Progressive Muscle Relaxation • Breath-Focusing Exercises • Autogenic Training • Visualization Exercises
3	Activity Pacing	• Cycle of Pain • Time-Based Pacing • Pleasurable Activities • Activity Pacing Logging
4 & 5	Cognitive Behavioral Skills	• Stress-Appraisal-Coping Model of Pain • Interactive Model of Pain • Cognitive Distortions • Cognitive Restructuring
6	Self-Care Skills	• Sleep Hygiene • Sexual Health • Goal-Setting
7	Interpersonal Skills	• Effective Communication Skills • Anger and Pain • Communicating with Healthcare Professionals
8	Relapse Prevention	• Planning for Pain Flare-ups • Identifying a Relapse • Coping Strategies for Intense Pain Episodes

dysfunctional cognitions related to pain [32]. Participants are asked to be **aware** of dysfunctional cognitions; **answer** dysfunctional cognitions (restructure); **act** on the more accurate and/or helpful beliefs; and **accept** imperfection.

2.5.6. CBT treatment arm sessions

The sessions are planned to last a maximum of 45-min to optimize participants' attentiveness and performance required by the cognitive demands of CBT training. Each session adheres to a common structure organized into three parts: 1) check-in; 2) intervention, and 3) wrap-up. Prior to each session participants are asked to rate the strength and perceived impact for up to four pain beliefs that participants and the psychologist identified together. This exercise sets the stage for problem identification and provides a bridge from the last session. The check-in includes welcoming, a brief pain update on progress and concerns, and collaborative agenda setting of at least one priority item that provides structure for the session. The intervention represents the bulk of the session and includes a discussion of old and new barriers identified while applying self-management behavioral and cognitive skills. For example, this process generally includes addressing a participant's selected dysfunctional cognitions about pain and its impact by disputing their accuracy and developing a more adaptive cognition (i.e. cognitive restructuring). The wrap-up involves participant refection on what was and was not helpful, a summary, collaborative goal setting for the next session, and discussion of progress and practice assignments. The purpose of these assignments is to apply lessons learned and help assess understanding of the material. Participants receive individualized feedback from the psychologists about their progress.

The CBT sessions are delivered by psychologists using standardized, written manuals. The sessions occur during the scheduled clinical contacts (by telephone or face-to-face depending on patient preferences) at baseline, weeks 2, 4, 6 and 8, and months 3, 4 and 6, and skills are reinforced at month 9. The content of these sessions is designed to modify behavioral and cognitive strategies found to be related to pain and disability. Briefly, participants are trained in a variety of evidence-based skills found to help reduce pain and improve function. For example, participants are trained in three different attention diversion methods: relaxation, imagery, and distraction. Relaxation training follows a protocol and relaxation tape described by Surwit [33,34]. Patients are instructed to practice using pleasant imagery and changing from one image to another. Distraction techniques include focusing on physical or auditory stimuli [33]. Another skill introduced to participants is activity-rest cycling and pleasant activity scheduling [35–37] which enables participants to pace and increase their activity level. Participants are tasked to identify enjoyable activities such as reading, doing hobbies, or visiting friends and set and record weekly activity goals. Each participant is instructed to develop a written maintenance plan that includes a list of coping skills, home practice, and a plan for dealing with setbacks and pain flare-ups.

2.5.7. Fidelity monitoring in the CBT arm

Several steps are taken to ensure that the CBT treatment protocol is delivered uniformly by all psychologists involved in the study. First, all psychologists receive training through workshops led by Dr. Outcalt. Second, all psychologists are provided detailed treatment scripts, and the treatment strategies are taught through didactic instruction, taped illustrations of techniques from model cases, and role-play of common scenarios. Third, the psychologists are instructed to document treatment delivery details (content, time, mode of delivery). Finally, to provide supervision, sessions are discussed weekly with a supervisory psychologist (Dr. Outcalt).

2.6. Data collection protocol

2.6.1. Measures schedule and mode of administration

The schedule of a comprehensive set of outcomes and key variables to evaluate the effectiveness of the CAMEO interventions are listed in Table 3. Research assistants blinded to treatment allocation conduct all baseline and follow-up assessments. Language or education barriers are not anticipated in this sample of U.S. veterans. After obtaining informed consent, a research assistant administers an in-depth baseline assessment to gather socio-demographic data (including information on disability compensation), reviews the participant's history with an emphasis on previous treatments for their pain (including prior opioid treatment history, prior co-analgesic history, and prior pain psychotherapy (including CBT)), and comorbidities including substance use. Several validated measures of overall health, pain, mental health, and substance use are also administered. Optimism regarding the likelihood of benefitting from each of the two potential treatment arms is assessed at baseline. At each follow-up assessment, a brief history of interim pain treatments received is conducted along with other measures. All participants are assessed with a brief battery of objective functional measurements of strength, range of motion, and flexibility. The data collection protocol was informed by Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommendations [38], biopsychosocial conceptual model, and our previous studies.

These assessments are conducted by research assistants blinded to the treatment assignment and are completed by telephone, except for the baseline and 6-month interviews, which are performed in person to establish rapport with participants and to assess functional measures. If participants cannot be reached by phone, alternative strategies are used to capture all outcome assessments: (1) sending a mailed questionnaire to the participant with a postage paid, self-addressed envelope; and 2) face-to-face interviews in conjunction with the patient's clinic visit. If participants are unable to arrange transportation for face-to-face interviews, taxicab rides to and from the VA facility ware arranged. Data on analgesics prescribed for both groups during the trial will be obtained by electronic health record review.

2.6.2. Primary outcome measure

The Brief Pain Inventory (BPI) was developed to assess the severity of pain and the impact of pain on daily functioning, and has been validated in primary care studies [18,39]. The short form of the BPI used in this study is an 11-item measure that provides scores for pain severity and pain-related functional impairment. The *BPI pain severity* score is an average of four ratings of 0 ("no pain") to 10 ("pain as bad as you can imagine") for current, least, worst, and average pain in the past week. The *BPI pain interference* score averages seven ratings from 0 ("does not interfere") to 10 ("interferes completely") of interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The *BPI total* score is the average of the severity and interference scores.

2.6.3. Secondary outcome measures

Pain Outcomes: In addition to the BPI, pain severity and interference are also assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) pain scale [40,41]. The PROMIS measures are a publicly-available bank of measures that can assess multiple domains of physical and mental health [40,42], which includes an 8-item pain interference scale and a 1-item pain severity scale. To further characterize the quality of pain, the McGill Pain Questionnaire is utilized [43].The McGill Pain Questionnaire is a 15-item scale that provides four responses (None-Mild-Moderate-Severe) for respondents to rate the degree that they feel pain described in 15 different ways. During all assessments after baseline, participants are asked a single "global pain change" item to rate on a 7-point scale from "much better" to "much worse" on how they would describe their pain compared to starting the study.

We also measure several other pain outcomes recommended by the IMMPACT guidelines [38] and consonant with the biopsychosocial model, including pain-related disability and pain beliefs. Pain-related disability is measured by the Roland-Morris Disability Questionnaire

Table 3
CAMEO outcome assessment measures and schedule of administration.

	Domain	Measure	Number of Items	Schedule				
				BL	3 mo	6 mo	9 mo	12 mo
Overall Health	Covariates	Demographics	8	X				
		Disability Compensation	1					
		Comorbid conditions	14					
		Pain History	9					
		Substance Use History	6					
		Optimism	3					
	Physical Function	Functional Improvement Scale	NA	X		X		
	Health-Related Quality of Life	36-Item Short Form Survey (SF-36)	36	X		X		X
	Fatigue	PROMIS fatigue	4	X		X		X
	Sleep	PROMIS sleep	4	X		X		X
Pain	Pain Management	Self-Management Behaviors	7	X		X		X
		Interim pain treatments	3		X	X	X	X
	Pain severity/interference	Brief Pain Inventory	11	X	X	X	X	X
		PROMIS pain	12	X		X		X
		McGill Pain Questionnaire	15	X		X		X
		Global Pain Change	1		X	X	X	X
	Pain disability	Roland-Morris Disability Questionnaire	24	X	X	X	X	X
		Disability Days	1	X				
	Pain beliefs	Pain Catastrophizing Scale	13	X		X		X
		Centrality of Pain	10	X		X		X
Mental Health	Mood	PHQ-9 Depression*	9	X	X	X	X	X
		PROMIS Depression	9	X				
		Global Mood	1	X				
	Anxiety	GAD-7 Anxiety	7	X	X	X	X	X
	PTSD	VA PTSD Screener**	4	X		X		X
	Stress	PHQ Stressor Scale	9	X		X		X
	Alliance	Working Alliance Inventory-SF	12		X	X		
Substance Use	Alcohol Use	AUDIT-C	10	X		X		X
	Opioid Misuse	Current Opioid Misuse Measure	16	X		X		X
	Opioid Side Effects	Numerical Opioid Side Effect	10	X	X	X	X	X
	Drug Screen	Urine Drug Screen	NA	X		X		

Abbreviations: BL = baseline, NA = Not applicable, PROMIS = Patient-Reported Outcomes Measurement Information System, GAD-7 = Generalized Anxiety Disorder 7-item questionnaire, PHQ = Patient Health Questionnaire, VA = Veterans Administration, PTSD = Post-Traumatic Stress Disorder, AUDIT-C = Alcohol Use Disorders Identification Test-Concise.

* SCID (9 items) is triggered by a PHQ-9 score of 5 or greater on baseline interview only.

** PTSD-Checklist C (17 items) is triggered by answer of "yes" to any of PTSD screener questions for every time point.

(RMDQ), a 24-item pain-specific measure of physical disability originally validated in patients with back pain [44]. The RMDQ has been used widely in low back pain trials because of its high degree of reliability, validity, and responsiveness to change. Additionally, we assess "disability days" by asking participants to report how many days in the prior 4 weeks they had to cut down on their activities due to pain, with scores ranging from 0 to 28 [45]. The Pain Catastrophizing Scale (PCS) is a 13-item scale that assesses catastrophizing—a pain belief that has been found to be strong predictor of poor treatment response [46]. Pain beliefs are also assessed using the 10-item Centrality of Pain scale [47]. Pain self-management behaviors (SMB) utilized by participants are assessed with questions about exercise, cognitive and relaxation strategies using a previously validated assessment [27,48].

Mental Health Outcomes: We assess for common mental health conditions known to be highly comorbid with and to affect pain. Depression is assessed using the Patient Health Questionnaire 9-item depression scale (PHQ-9) [49]. Participants with PHQ-9 scores $\geq$5 at baseline are asked 9 questions from the Structured Clinical Interview for DSM-5 (SCID) to formally assess for the presence of major depressive disorder [50]. Depression at baseline is also measured using the PROMIS 8-item Depression measure [51], as well as a single "global mood" item that asked participants to rate their general mood over the past 7 days on a 5-point Likert Scale from "Not unhappy or down at all" to "Very severely unhappy or down". The Generalized Anxiety Disorder 7-item scale (GAD-7) is used to assess anxiety [52]. Symptoms of Post-Traumatic Stress Disorder (PTSD) are screened using the Primary Care PTSD Screen (PC-PTSD), which has been validated for use in primary care. The sum of the four yes/no items yields a score ranging from 0 to 4, with scores $\geq$3 considered positive for active PTSD. Participants who respond "yes" on any of the PTSD screener questions are administered the 17-item PTSD Checklist-C [53]. The intensity of perceived stressors is assessed using a 9-item Stressor Scale derived from the Stressor subsection of the Patient Health Questionnaire [54,55]. The Working Alliance Inventory short-form (WAI-SF) [56,57] is given at 3 and 6 months to assess the strength of the perceived alliance between the participant and either the NCM (MED group) or psychologist (CBT group).

Substance Use Outcomes: We also assess for substance misuse and side effects. The Alcohol Use Disorders Identification Test-Concise (AUDIT-C) is used as a screening test and diagnostic tool for alcohol misuse [58]. To assess for opioid misuse, we use the Current Opioid Misuse Measure (COMM), a 17-item instrument designed to monitor misuse and aberrant behaviors in patients prescribed opioids [59]. Opioid-related side effects are assessed using the Numerical Opioid Side Effect (NOSE), a 10-item tool designed to assess the most common opioid-related side effects (e.g., nausea, constipation, sleepiness) [60]. Urine drug screens are collected at the baseline and 6 month visits to detect substances that should not be present in the urine and to detect the absence of prescribed opioids. Mean daily opioid dose in milligram equivalents of morphine is assessed by chart review.

Other secondary outcomes: We assess general health status including physical and mental functioning with the Medical Outcomes Study SF-36 measure [61]. The Patient Global Impression of Change (PGIC) is used as a single item measure to assess overall clinical response [62]. The Functional Improvement Measure developed by Gottlieb et al. [63] provides a performance-based measure to quantify functional capacity and helps identify the level of change associated with treatment among participants. Fatigue and sleep are assessed using the PROMIS 4-item short form assessments for each [64,65].

2.7. Statistical considerations

The CAMEO trial involves a 2-arm, parallel group, randomized trial design with two active treatment arms. Since the participants of this trial are not blinded to treatment assignment, it is possible that the observed outcomes may be partially attributed to expectation bias. We decided to randomize at the participant rather than the provider level for two reasons: (1) randomization at the provider level would require a substantially larger sample size; and (2) participants from the same provider in the two treatments arms will adjust for "provider effect." We expect contamination to be low because there is relatively minimal involvement required of PCPs in CAMEO. Also, any contamination that occurs will make estimates of between-group differences conservative.

2.7.1. Sample size justification

Our sample size is calculated based on estimated intervention effects on the primary outcome; the Brief Pain Inventory (BPI) total score. In the SCAMP trial [18,66], the standard deviation (SD) was 2.4 for the BPI total score. In multiple clinical trials, a 1-point difference has been shown to be a minimally important difference (MID) in comparing BPI total changes between groups [67]. Assuming a common standard deviation of 2.4 across the two treatment arms, a between-group treatment difference of 1 point in the BPI total would correspond to a 0.4 SD effect size. A between group difference smaller than 0.3 SD would not be expected to be meaningful [68], which would equate to a 0.7 point difference with a pooled SD of 2.4. With a two-sided test at alpha = 0.05, we would have 80% power to detect a 1-point difference in BPI score with 91 participants in each arm, while it would require 185 participants per arm to detect a 0.7 point change. Setting a recruitment goal at the midpoint between these two estimates (136 participants per arm) seemed a reasonable approach to give us sufficient power to find a difference in this range of MID estimates.

2.7.2. Statistical analyses

Due to the size of this study, we expect that randomization will produce comparable and balanced treatment groups. To test this assumption, we will tabulate baseline characteristics of the two trial arms for potential imbalance in variables such as socio-demographic variables, medical and psychiatric comorbidity, duration of back pain, and current and prior pain treatments. Continuous variables were assessed with graphical displays and summary statistics (means, standard deviation, range, etc.). Frequency distributions and percentages are calculated for categorical data.

We will summarize the primary outcome at each time point (3, 6, 9 and 12 months) for both study arms. The difference between time points will be compared between the two treatment arms. To compare the

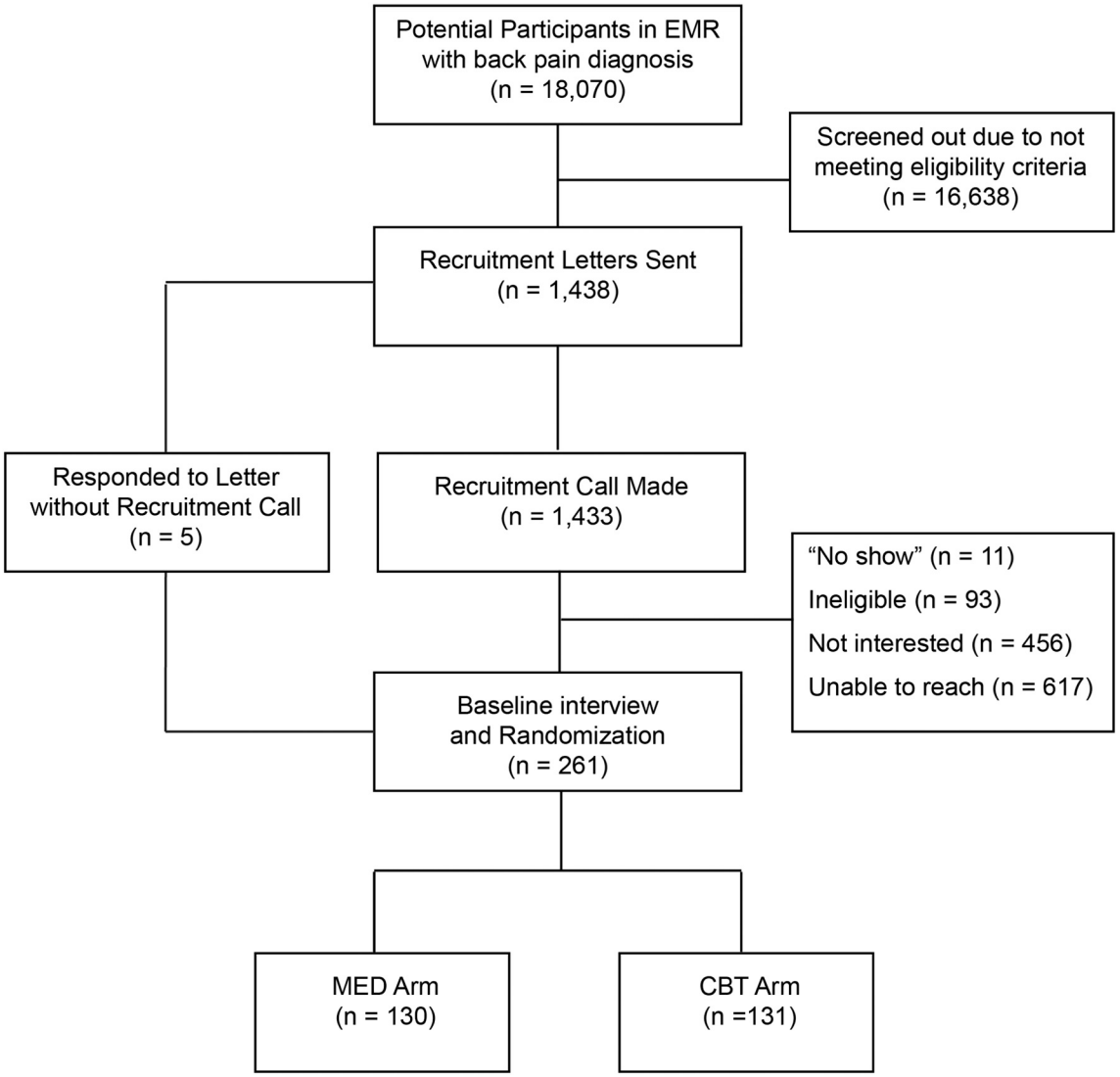

Fig. 2. Screening & recruitment flow diagram.

primary outcome at each time point relative to baseline within each arm, paired *t*-tests will be used for continuous variables and Chi-square tests for categorical variables. Between-arm comparisons will be based on similar statistical tests. The primary endpoint will be assessed at 6 months. Secondarily, "early" response will be assessed at 3 months and "sustained" response at 9- and 12-months. An intent-to-treat analysis approach will be utilized.

3. Results

3.1. Recruitment outcomes

Fig. 2 shows the results of the recruitment process. A total of 18,070 potential participants were identified using the EHR search as having CLBP, of whom 1438 (7.9%) met additional screening criteria of moderate pain severity of at least 6 months on long-term opioid therapy and were sent a study invitation letter. Two hundred sixty-one (18.2%) of those interviewed were found to be eligible and agreed to participate, and were randomized to the MED ($n = 130$) and CBT ($n = 131$) arms of the trial.

4. Discussion

This trial is the first to compare a nurse care manager-delivered pharmacological optimization intervention compared to a psychologist-led cognitive/behavioral intervention in patients with chronic low back pain. The effectiveness of collaborative care for treating depression has been well-established in more than 40 trials [69,70]. Collaborative care programs have also been demonstrated to be effective for treating chronic pain, where a combination of care management, analgesic adjustment, patient and/or provider education, and cognitive behavioral strategies have been employed, often in combination and predominantly compared to usual care [18–20,71,72]. No studies have directly compared an analgesic management approach to cognitive behavioral therapy head-to-head. CAMEO is designed as a randomized comparative effectiveness trial to directly compare these two intervention types, both delivered over 8 sessions over a 6-month period. Key design features include targeting the clinically-relevant population of patients on long-term opioid therapy, using an analgesic optimization arm that includes opioids, and utilizing a collaborative care approach for both arms to aid in scalability and implementation. Outcomes are assessed at time points that allowed an assessment of both immediate and extended effects of the interventions.

As previously documented, recruitment of participants on long-term opioid therapy for enrollment in a clinical trial of pain management can be challenging [73]. Of the 1438 veterans who met initial study criteria by electronic record review and were sent letters, a total of 261 participants were enrolled. This represents 18% of the total participant pool. However, since 617 participants could not be reached, the recruitment percentage of veterans actually contacted was 32% (261 of 821).These percentages fall within the range of what we have observed in prior collaborative care trials of veterans with chronic pain [18–20] . While our enrollment total was modestly lower than our initial target, the BPI total pooled SD for enrolled participants was also lower at 1.73, representing a smaller variance in the sample than anticipated. With a two-sided test at alpha = 0.05, we achieved 100% power to detect a 1.0 point difference in BPI total, and 90% power to detect a 0.7 point difference.

We considered alternative design strategies for this trial including a 3-arm design including a usual care control. However, the strong evidence demonstrating the efficacy of NCM-led medication optimization and psychologist-led CBT interventions for pain justified the exclusion of a usual care arm [18,19]. Further, including a third arm would have required a corresponding increase in overall recruitment, which would have been impractical given the difficulty in recruiting sufficient subjects to achieve the necessary power with this 2-arm design. Further, we believe a head-to-head comparative effectiveness study design best answers the question of how to most effectively treat chronic low back pain, especially for patients who are refractory to other treatments and those on long-term opioid therapy. The National Academy of Medicine (formerly the Institute of Medicine) recently prioritized topics in need of comparative effectiveness research and listed the comparison of available treatments for low back pain within the upper quartile on its top 100 list [74].

In this study, we are interested in studying patients on long-term opioid therapy, which limits generalizability but addresses a complex and clinically important patient group. Studying interventions that had been effective in other populations are important to evaluate in this population, especially given the prevalence of opioid prescribing in the United States, where, even with a significant decrease in recent years, 17.4% of the U.S. population received an opioid prescription in 2017 [75]. That this is a sample of US veterans also may limit generalizability, but again, we believe that this is a highly relevant population to target given the preponderance of chronic pain and opioid prescription in this population.

Providers are faced with numerous challenges in treating patients with CLBP. The interventions being tested in the CAMEO trial have the potential to provide primary care settings with new treatment models that will help to guide providers while at the same time providing much needed relief for patients suffering from CLBP.

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Disclaimer

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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