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Design, recruitment outcomes, and sample characteristics of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial

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ABSTRACT

This manuscript describes the study protocol, recruitment outcomes, and baseline participant characteristics for the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial. SPACE is a pragmatic randomized comparative effectiveness trial conducted in multiple VA primary care clinics within one VA health care system. The objective was to compare benefits and harms of opioid therapy versus non-opioid medication therapy over 12 months among patients with moderate-to-severe chronic back pain or hip/knee osteoarthritis pain despite analgesic therapy; patients already receiving regular opioid therapy were excluded. Key design features include comparing two clinically-relevant medication interventions, pragmatic eligibility criteria, and flexible treat-to-target interventions. Screening, recruitment and study enrollment were conducted over 31 months. A total of 4491 patients were contacted for eligibility screening; 53.1% were ineligible, 41.0% refused, and 5.9% enrolled. The most common reasons for ineligibility were not meeting pain location and severity criteria. The most common study-specific reasons for refusal were preference for no opioid use and preference for no pain medications. Of 265 enrolled patients, 25 withdrew before randomization. Of 240 randomized patients, 87.9% were male, 84.1% were white, and age range was 21–80 years. Past-year mental health diagnoses were 28.3% depression, 17% anxiety, 9.4% PTSD, 7.9% alcohol use disorder, and 2.6% drug use disorder. In conclusion, although recruitment for this trial was challenging, characteristics of enrolled participants suggest we were successful in recruiting patients similar to those prescribed opioid therapy in usual care.

1. Introduction

Chronic musculoskeletal pain conditions are among the most prevalent and disabling of chronic diseases [1]. As a result of a decades-long expansion in opioid analgesic prescribing, treatment of chronic pain with long-term opioid therapy has become common practice. [2,3] Evidence has not kept up with practice. Although short-term trials suggest that opioids can produce small short-term reductions in pain intensity [4,5], evidence for long-term effectiveness is largely absent. A systematic review conducted in 2014 and updated in 2016 found no controlled opioid trials that examined effects on pain, function or quality of life at one year or longer [6]. Evidence regarding harms of long-term opioid therapy is mostly derived from retrospective observational studies and few studies have published data on patient-reported adverse symptoms.

A 2014 National Institutes of Health Pathways to Prevention panel on the role of opioids in the treatment of chronic pain identified "a clear need for well-designed longitudinal studies of effectiveness and safety of long-term opioid use in the management of chronic pain." [7] The panel report noted barriers to conducting standard randomized controlled trials, such as difficulty recruiting and retaining participants, and suggested alternate and pragmatic study designs to address evidence gaps and inform clinical decision-making.

This manuscript describes the study protocol and recruitment outcomes for the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial, a pragmatic randomized comparative effectiveness trial conducted in a VA health care system. The objective of the trial was to compare benefits and harms of opioid versus non-opioid medication therapy over 12 months. The study was designed to be maximally relevant to pain management in primary care practice and

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inform an important decision point in the care of patients with moderate-to-severe chronic pain—whether or not to initiate long-term opioid therapy. We chose non-opioid medication therapy as the comparison intervention for opioid therapy because we believed it to be the most clinically-relevant alternative pain management strategy.

2. Methods

2.1. Design overview

SPACE is a pragmatic randomized comparative effectiveness trial with masked outcome assessment comparing opioid therapy versus non-opioid medication therapy over 12 months for patients with chronic back pain or hip or knee osteoarthritis pain. Both interventions (opioid therapy and non-opioid therapy) were delivered using a telecare collaborative management model and a treat-to-target approach aiming for 30% improvement in pain and progress toward individualized goals.

Patients treated for back, hip, or knee pain at primary care clinics in the Minneapolis Veterans Affairs (VA) Health Care System were identified through automated searches of the electronic medical record (EMR) and screened by telephone for eligibility. Patients with chronic back pain or hip or knee osteoarthritis pain of at least moderate severity despite analgesic use were eligible. Eligible patients who provided informed consent and completed a baseline assessment visit were randomized to either the opioid therapy arm or the non-opioid therapy arm. Randomization was at the individual level, restricted by primary pain location (back or hip/knee), and implemented using a computer program to conceal allocation.

Each arm included multiple medications that were available by prescription within the VA health care system during the study period. In both arms, pain medication management was provided for 12 months, with medication therapy tailored to individual patient preferences and adjusted within the assigned treatment arm to achieve therapeutic targets. Outcomes were evaluated by masked assessors at 3, 6, 9, and 12 months after enrollment. To offset costs of participation, participants were paid $100 in cash after completion of baseline, 6, and 12 month assessments and $20 by check after completion of the 3 and 9 month assessments. No incentives were provided for attendance at clinical intervention visits. The study was approved by the Minneapolis VA Institutional Review Board.

2.2. Pragmatic trial design

The intent for the SPACE trial was to be as pragmatic as possible, evaluating benefits and harms of opioid therapy in close to usual care conditions, and to maximize applicability to primary care practice settings. We considered pragmatic design principles outlined in the pragmatic-explanatory continuum indicator summary (PRECIS) in SPACE trial development [8]. Table 1 and Fig. 1 show pragmatism of trial domains according to the updated PRECIS-2 tool [9].

2.3. Eligibility

The target population was primary care patients with moderate-to-severe chronic back pain or hip or knee osteoarthritis pain despite analgesic therapy. Inclusion criteria were further defined as follows:

- Moderate-severe pain intensity and interference with function: The PEG scale, a 3-item multidimensional pain measure, was used to define pain severity [14]. Eligibility criteria were a) a score of ≥ 5 on the average pain intensity item and b) a mean score of ≥ 5 on the two functional items (interference with enjoyment of life; interference with general activity).
- Chronic back pain or hip or knee osteoarthritis pain as the primary pain condition: These conditions were selected because they are among the most common indications for long-term opioid therapy [15–18]. Chronic pain was defined as pain present nearly every day or every day for ≥ 6 months. The primary pain diagnosis was identified by patient self-report during the screening interview and confirmed by a targeted review of each patient's medical records. At least minimal documented evidence of the diagnosis (such as inclusion in a primary care problem list or visit note) was required. Patients with both chronic back pain and hip/knee osteoarthritis pain were stratified based on the most bothersome condition at the time of eligibility screening.
- Despite analgesic therapy: To ensure participants were appropriate for opioid therapy, eligibility criteria required ongoing pain despite use of at least one analgesic medication.

Patients were excluded if they were currently receiving long-term opioid therapy, had conditions that could interfere with outcome assessment, or had contraindications to all drugs in either arm. Specific exclusion criteria were as follows:

- Current long-term opioid therapy: EMR data were used to identify patients with any long-acting opioid (i.e., methadone, transdermal fentanyl, or any sustained-release opioid) dispensed in the prior three months or any prescription for ≥ 60 tablets/capsules of short-acting DEA schedule II or III opioid dispensed in the prior three months.
- Conditions that could interfere with outcome assessment: Patients were excluded if they met any of the following criteria: a) schizophrenia, bipolar disorder, or other psychotic disorder; b) moderately severe cognitive impairment, defined as ≥ 2 errors on a brief cognitive screener; [19] c) anticipated back, knee, or hip surgery within 12 months; d) anticipated life expectancy of < 12 months; or e) unable to complete outcome assessments for 12 months for any reason.
- Contraindications to all drugs in either arm: In general, contraindications for individual medications include known allergy, previous serious adverse effect, or failure of a previous adequate trial. Because of the diversity of drug classes in the non-opioid therapy arm, contraindications to all drugs in that arm were much less common than contraindications to all drugs in the opioid therapy arm. Class-level contraindications to opioid therapy were consistent with VA/DoD clinical practice guidelines [20] and included the following:
  - Psychiatric instability: This was defined as current uncontrolled severe depression, severe PTSD, or suicidal ideation and patients were excluded only if they had severe symptoms that were not actively treated. Patients with severe untreated symptoms on the initial screening interview were provided with information about accessing mental health care and offered the opportunity of re-screening later.
  - Active substance use disorder (SUD) or history of opioid use disorder: We did not exclude patients with SUD (other than opioid use disorder) in remission or those with recent illicit drug use but no apparent SUD. In addition to information obtained during the eligibility screening process, urine drug test (UDT) results obtained at the baseline assessment were considered in evaluation of this criterion. Patients who reported drug use or had a UDT positive for an illicit drug were asked if they were willing to discontinue drug use during the study. If they agreed, follow-up questions from the NIDA-modified ASSIST questionnaire [21] were asked and, for those with a positive UDT, follow-up testing was done prior to randomization. Participants who had a lower risk substance involvement score (0–3) on the ASSIST questionnaire and a negative follow-up UDT were randomized to a treatment group and continued in the study; those with a substance involvement score ≥ 4 and a negative follow-up UDT were considered by the PI on an individual basis.