Research Participation in Substance Use Disorder Trials: Design and Methods of a Multi-Site Nested Qualitative Study

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Abstract

Background: Given the health and social harms of problematic substance use, randomized controlled trials (RCTs) are critical in developing and testing pharmacotherapies for substance use disorders. However, substance use RCTs can be challenging to conduct, considering the social and structural barriers to participating in research among people with substance use disorders (PSUD), including stigma, poverty, and criminalization—factors that can shape trial recruitment, enrollment, protocol adherence and study retention. Despite these barriers, adequate representation and participation of PSUD in RCT research is essential to assessing and developing treatments, and thus a deeper understanding of RCT participation dynamics among PSUD is needed to support clinical trial research.

Methods: We conducted a nested qualitative study within a Canadian, multisite, phase IV, open-label, pragmatic RCT that tested two approved opioid agonist treatments, methadone and buprenorphine/naloxone, among patients with prescription opioid use disorder. A subset of individuals (n = 60) participating in this RCT were interviewed across four different regions in Canada at the beginning and end of their trial involvement, as well as study clinicians (n = 16) and staff (n = 16) operating the trial.

Conclusion: As a nested study within a real-world addiction medicine trial, this research offers an innovative approach to investigating the experiences, strategies, and challenges associated with RCTs among PSUD. While we acknowledge challenges related to the operations of multisite research and engaging marginalized populations in experimental research, this study has the potential to generate critical insights around the RCT experiences of PSUDs and trial staff to inform the conduct of future RCTs.

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Keywords
qualitative nested study, opioid use disorder, RCT participation, addiction medicine

Background

Globally, substance use disorders are associated with significant health and social harms, including the unprecedented rise of overdose-related fatalities in recent years (Ciccarone, 2021; Degenhardt et al., 2013; Public Health Agency of Canada, 2020). Medication-assisted treatments can be used to address problematic substance use. However, in North America, there are limited approved medications for opioid use disorder (MOUD; Connelly, 2015). Thus, one key strategy is to test and develop novel pharmacotherapies for people with substance use disorders (PSUD) through randomized controlled trial (RCT) research. Indeed, addiction medicine research is rapidly expanding (Hering et al., 2014; Lembke & Humphreys, 2018).

However, there remain a range of social, operational and ethical issues related to the conduct of RCTs among vulnerable populations linked to ethnicity, age, socioeconomic status, health, and gender, all of which have been implicated in consent processes related to clinical trial literacy (e.g., randomization, placebo, blinding; Barata et al., 2006; Bonevski et al., 2014; Braunstein et al., 2008; Doab et al., 2009; Glover et al., 2015; Svensson et al., 2012), as well as ethical concerns about undue inducement to participate (Denny & Grady, 2007; Grady, 2009; Macklin, 1981). Even in pragmatic trials with lower experimental risk (Simon et al., 2019), disadvantaged populations may experience other types of vulnerability in which individual characteristics interact with key trial components, such feeling internal pressures to enroll due to potential study benefits or deference to medical authority that may conceal unwillingness to participate (Welch et al., 2015). In studies of HIV and HCV trials, which sometimes include people who use illicit drugs facing unique configurations of disadvantage, researchers have identified trial attributes, trial literacy, and motivations and barriers that shape research participation (Dhalla et al., 2010; Maher et al., 2010; Mills et al., 2004; Park et al., 2012; Treloar et al., 2010; White et al., 2013; Yakovenko et al., 2019; Young et al., 2015). For instance, when considering joining a trial, participants without a clear understanding of trial concepts may have concerns about the safety of the trial or feel skepticism toward researchers and their trustworthiness (Abadie et al., 2018; Bardwell et al., 2021; Bell & Salmon, 2011; Jaffe, Nosova, et al., 2021; Mills et al., 2004; Neale et al., 2018; Tompkins et al., 2019), especially given that those who use illicit drugs remain subject to criminalization in most jurisdictions. Researchers have identified a range of participant motivations for enrollment, including altruism, accessing a new treatment, or financial renumeration (Bell & Salmon, 2011; Fry & Dwyer, 2001; Jaffe, Korthuis, et al., 2021b; Neale et al., 2018; Park et al., 2012; Treloar et al., 2010). Conversely, they have also noted that participants may encounter significant barriers during the trial period, such as social pressures (e.g. involvement in drug scenes) or environmental constraints (e.g. transportation or scheduling challenges; Buchbinder et al., 2004; Jaffe, Korthuis, et al., 2021a; Mills et al., 2004; Park et al., 2012; Thomson et al., 2008) that often vary by study location. How these factors shape research participation must be a consideration in assessing study design, trial outcomes, and the generalizability of findings to key populations.

To date, there are few studies that focus on research participation among PSUD, and those that do commonly focus on individual and trial-level attributes or measure willingness to participate in hypothetical, rather than actual trials (Neale et al., 2018). However, as prior research illustrates, there are social and structural elements of the broader research context for PSUD that may play a significant role in their study experiences (Jaffe, Korthuis, et al., 2021a), and, in multisite trials there may be considerable variation in consequential features of local contexts (e.g., local or regional policies or treatment guidelines). To further understand the experiences of RCT participants who use drugs, we designed a nested qualitative longitudinal interview study within Optimizing Patient Centered-Care: A Pragmatic Randomized Control Trial Comparing Models of Care in the Management of Prescription Opioid Misuse (OPTIMA), a pan-Canadian multi-site pragmatic trial evaluating models of care for prescription opioid use disorder, whose full protocol has been published previously (Socias et al., 2018). By identifying the individual, social, and structural factors affecting trial recruitment, enrollment, protocol adherence and study retention in addiction RCT research, we seek to promote the effective conduct of RCTs in this field and to maximize the likelihood of successful trial completion and effective application of results.

Methods

Overview of Study Aim and Hypotheses

We designed a nested qualitative study within an ongoing substance use disorder RCT in order to understand trial-specific, individual, social, and structural influences on motivations, barriers, and willingness to participate; protocol adherence; and study retention or trial completion, as well as participants’ and staff attitudes and perceptions of RCT research. Our study hypotheses build on existing research related to clinical trial participation among vulnerable populations that points to the potentially considerable impacts of social, economic and structural disadvantage (Chiu & Katz, 2011; Grady, 2009; Stone, 2003). We additionally considered more general research on the social-structural production of harm among people who use illicit drugs (Collins et al., 2019).
We focus on different critical stages of the experimental research process as these may each have distinct interfaces with drug-using populations. For example, individuals’ motivations to participate may be linked to their own experiences of substance use and treatment (or lack thereof) or a desire to reduce socioeconomic vulnerability that commonly accompanies high-intensity substance use (Richardson et al., 2015; Timmermans & McKay, 2009). Barriers to participation may be a function of reluctance to engage produced by strong social integration in drug use scenes (Saberi Zafarhhandi et al., 2021) or negative interactions with surveillance from wide-ranging institutions (Brayne, 2014). Willingness to participate may be predominantly shaped by institutional interactions supportive of enrollment, such as positive interactions with healthcare professionals or social services (Friedmann et al., 2003).

Separate from enrollment decisions, participants’ attitudes and beliefs about their actual experiences in the study may be connected to positive interpersonal interactions or trust in study staff (Abadie et al., 2018; Gallups et al., 2016; Treloar et al., 2010), or, conversely, by challenges related to perceived exploitation or intrusive data collection (Bell & Salmon, 2011; Damon et al., 2017). There may also be a range of processes and dynamics that shape participation outcomes, ranging from trial characteristics (e.g., honoraria, data collection intensity; Davidson & Page, 2012; Newman et al., 2006) and study intervention perceptions (Bardwell et al., 2021) to how participants value their participation and their broader social-structural circumstances (Fry & Dwyer, 2001; Jaffe, Korthuis, et al., 2021a). Many of these linkages will vary across research sites even though RCT protocols seek to standardize research procedures for all participants. Further, the perspectives of research staff and clinicians in the conduct of RCTs may provide critical insight into the successes and challenges of conducting this research specifically among PSUD, with direct relevance to future studies. While assuredly an inexhaustive list of the dynamics surrounding RCT enrollment, experiences and participation outcomes, we conducted a preliminary survey of existing literature and integrated knowledge from prior nested studies (Bardwell et al., 2021; Jaffe, Korthuis, et al., 2021a; Jaffe, Nosova, et al., 2021) to develop the following initial study hypotheses:

**H1.1** Motivations to participate in the trial will be shaped by patterns of drug use, health-related and socio-economic vulnerability, previous experiences of and access to addiction treatment, and access to health services.

**H1.2** Barriers to participate in the trial will be linked to drug scene involvement, healthcare and surveillance avoidance, recent incarceration, past criminal justice system involvement and a lack of social support.

**H1.3** Willingness to participate in addiction RCTs will be linked to past experiences of research, relationships with healthcare professionals, patterns of drug use, existing addiction treatment access and past criminal justice system involvement.

**H2.1** Attitudes and beliefs about trial participation will be complex and heterogeneous, including positive (e.g., positive relationships with staff, community benefit) and negative (e.g., perceived exploitation, over-surveillance/social control) dimensions.

**H3.1** Protocol adherence and trial completion will be shaped by specific trial characteristics (e.g., supports, incentives, demands), valuation of participation (e.g., altruism, desire for treatment), living conditions (housing, income), and drug scene involvement.

**H4.1** Study staff and clinicians will identify successes and challenges in how they navigate perceptions of their role, recruitment and retention of marginalized populations, and understandings of trial design by participants.

**Study Design**

The OPTIMA Research Participation Ancillary Study (ORAS) study is a nested, qualitative ancillary study that took place alongside the OPTIMA trial (Jutras-Aswad et al., 2022; Socias et al., 2018).

**OPTIMA trial.** OPTIMA is a multicentre, phase IV, open-label, pragmatic randomized controlled trial that compared models of care of two approved MOUD in Canada: (1) flexible take-home dosing buprenorphine/naloxone and (2) supervised methadone in patients with prescription opioid use disorder. Outcomes assessed included non-medical prescription-type opioid use, treatment retention and satisfaction, safety, quality of life, medication adherence and patient engagement, among others. The OPTIMA trial recruited participants at seven sites (Vancouver, Edmonton, Calgary, Montreal [two sites]; Sudbury, Toronto) within the four regions (British Columbia, Prairies, Quebec-Atlantic, Ontario) of the Canadian Research Initiative in Substance Misuse (CRISM) network. The trial aimed to randomize 276 participants (69 participants per node), each of which was to be enrolled in the study for six months. OPTIMA study enrollment took place from October 2017 to July 2020. The OPTIMA trial has been approved by institutional research ethics boards across all sites.

**Current study.** The ORAS study is a nested qualitative study that is exploring patient experiences in the OPTIMA study over time, interviewing participants and study staff and clinicians located in each of the CRISM regions. After participants completed OPTIMA screening, informed consent, baseline, and randomization procedures, a sub-sample of participants were asked if they were interested in a qualitative ancillary study. Participants who were interested and completed informed consent procedures for the ORAS study were interviewed once upon entry to the OPTIMA study and a second time, either at withdrawal from or completion of OPTIMA study procedures. These semi-structured qualitative interviews aimed to generate knowledge and understanding of
Participants for ORAS were comprised of a subsample of the existing enrolled OPTIMA participants as well as OPTIMA staff and physicians. To be eligible for participation in OPTIMA, candidates were required to be between the ages of 18 and 64 (inclusive); diagnosed with a prescription-type opioid use disorder; not pregnant; demonstrate willingness to be randomized to 24 weeks of either methadone or buprenorphine/naloxone and to comply with study procedures; provide written informed consent; and be able to communicate in English or French. Those potential participants who met OPTIMA eligibility criteria were also eligible for ORAS if they: (a) enrolled in the OPTIMA trial; and (b) provided written informed consent to be in the ORAS study. To balance operational constraints with adequate representation across study sites, at study initiation it was projected that at least 60 OPTIMA participants would participate in the ORAS ancillary study: 15 from each of the OPTIMA/CRISM regions, seven to eight participants from each of the methadone arm and buprenorphine/naloxone arm at each site, and including participants who complete all study protocols and those who withdraw from the OPTIMA study prior to completion. Additional interviews were conducted among OPTIMA participants who have withdrawn from the study or have notable study experiences. Recruitment aimed for equal numbers of men and women participants and from each study arm. OPTIMA study staff and physicians were eligible for the ORAS study if they: (a) were OPTIMA staff; and (b) provided written informed consent. The study aimed to recruit at least four staff from each node (16–20 total) and four clinicians from each node (16 total).

Data Collection Procedures

Recruitment. ORAS participants were recruited directly from the OPTIMA study sample. Once participants were enrolled in OPTIMA and randomized, OPTIMA site research coordinators read a recruitment script providing full details of the ORAS study. If participants were interested, they consented to release their contact information to the ORAS interviewer. Individuals who were not interested or did not consent to be contacted were not approached for ORAS study participation. The ORAS interviewer met with interested candidates to explain the study proceedings, what participation would entail, and answer any remaining questions, and if participants remained interested, the interviewer obtained written informed consent as per the protocol and Good Clinical Practice guidelines. Given budgetary and logistical constraints, not all OPTIMA participants could be interviewed, and thus OPTIMA research coordinators recruited a subset of participants, asking every other eligible participant. If OPTIMA recruitment slowed, research coordinators referred all incoming OPTIMA participants. Additionally, research coordinators were able to refer participants who had notable study experiences and participants who withdrew from the study or failed to initiate treatment.

If participants were lost to follow-up for the ORAS study or did not wish to complete exit interviews, new ORAS study candidates were prospectively recruited to complete an exit interview as they ended their study enrollment, replacing those that were lost to follow up. Prospectively recruited participants were selected from the same study arm as the individual lost to follow-up to maintain equal representation from both arms at each site of the study. If possible, prospectively recruited participants also reflected those lost to follow-up in terms of their demographic characteristics. For these additional new participants, interviewers administered full recruitment and informed consent procedures to orient the participant to the ORAS study.

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To recruit OPTIMA staff and clinicians, details of the ORAS study and interviewer contact details were passed on to OPTIMA staff and clinicians to avoid the perception of pressure to participate from ORAS staff. Interested candidates contacted the ORAS interviewer to schedule a time to obtain informed consent and conduct the interview.

Informed consent. If after explaining the study in detail, the candidate was still interested in participating, the interviewer obtained written informed consent prior to the conduct of any study-related procedures. Informed consent procedures covered both the entry and exit interviews for OPTIMA participants, however informed consent and study procedures were also reviewed briefly before the exit interview. Participants could withdraw their consent to participate in the ORAS study at any time with no penalty or loss of benefits. ORAS participants were reminded that they could revoke permission for the use of their data at any time. It was important that if a participant discontinued participation in the main OPTIMA trial, they were still able to take part in the ORAS qualitative interviews; experiences of those who withdrew from the parent OPTIMA study were of particular relevance to understanding dynamics of study retention. Additionally, no information about staff participation was shared with other staff members or with study site Principal Investigators.

Interviews. For ORAS participants, the semi-structured entry interview occurred at the beginning of the OPTIMA trial within one month of randomization. Entry interview topics included: participants’ background; housing; income generation; substance use patterns; social support; previous experiences in healthcare; substance use treatment, and criminal justice systems; previous research experience; perceptions of research and addiction treatment; motivations to join the RCT; and their experiences beginning the study, including recruitment, eligibility, informed consent, randomization, and baseline procedures. The final exit interview took place within a month of study completion. Exit interview topics included: changes in participants’ lives, such as housing, income generation, substance use patterns; study medication experiences; challenges and facilitators of protocol adherence; and perceptions of study processes.

OPTIMA staff and clinicians were interviewed toward the end or following the completion of the trial. Staff and clinician interview topics included: how staff navigate, where relevant, dual roles as medical care provider and researcher; strategies employed to improve trial recruitment with a hard-to-reach population; processes of relationship-building with participants and communities; and general perceptions of the design and implementation of the trial. All interviews were recorded and transcribed, with French language interviews translated into English prior to data analysis. Only the ORAS coordinator and the study principal investigator had ongoing access to interview data.

Participant honoraria. In addition to regular compensation received during the OPTIMA trial, participants in ORAS received $30 CAD for their time and expertise for each semi-structured qualitative interview. OPTIMA staff participating in ORAS were compensated $50 CAD and OPTIMA physicians participating in ORAS were compensated $80 CAD, consistent with market hourly rates and estimated interview duration.

Data Analysis

Qualitative interview transcripts are being analyzed in nVivo qualitative data analysis software through the use of flexible coding, a method that emphasizes abductive theory construction and is ideal for large datasets that will be used for multiple analyses (Deterding & Waters, 2018; Timmermans & Tavory, 2012). Flexible coding supports recursive and iterative analyses that incorporate reviews of previous literature, the incorporation of existing theories, and a multi-step coding process. This process involves applying index codes roughly aligned with the interview guide to large portions of text while concurrently developing respondent-specific and cross-case conceptual memos that identify connections across themes and between participant groups. Subsequently, more fine-grained analytic codes are applied to text within indices of interest for analysis, and data analytic software tools are used to verify reliability of codes across cases and test hypotheses. Processes of recontextualization then compare coding structures back to original qualitative data, modifying and adjusting the conceptual basis for the coding structure and referencing any conceptual memos to ensure all important aspects of content are covered in relation to study aims (Burnard, 1991). The subsequent articulation of study findings describes systematic dynamics present in the themes, conceptual categories and subcategories.

Analyses of the ORAS study data will include a series of systematic analytic procedures and verification processes designed to support consistently robust approaches to qualitative rigor. Researchers will engage in reflexive memoing throughout the research process to consider the researchers’ understandings of their positionality as well as anticipate and minimize any resulting bias (Elo et al., 2014). To ascertain the stability of our coding schematic, we will undertake assessments of reliability (Campbell et al., 2013). For a given analysis we will select a representative sample of interview transcripts that comprised approximately 10% of the data, demarcate units of text to be coded, and train an independent coder on our thematic framework, analytic approach, and the specific context in which the study took place. The independent coder will analyze the sample text using the coding schematic and we will assess interrater reliability to confirm intersubjective coding stability. Additional measures, such as member checking (Koelsch, 2013), the checking of inconsistent cases (Baškarada, 2014), triangulation with quantitative data (Morse, 1991) and interpretation verification with people with lived and living experience (Neufeld et al., 2019).
and clinical researchers will be undertaken on an analysis-specific basis wherever feasible and appropriate.

In addition to qualitative findings, mixed methods analyses will be conducted to examine the relationship between participant experiences and study outcomes. By integrating qualitative interview data with trial records, analyses will reveal ways in which accounts of external influences (e.g., social support, income generation, housing, criminalization, etc.) map onto measures of study retention, medication experiences, and protocol completion. Further, by utilizing quantitative measures on topics that are also asked in qualitative interviews, analyses may be able to explore convergent and divergent findings that generate additional insights into participant RCT experiences. An additional focus will be context-specific dynamics at each of the participating research sites with a view to capturing participant experience dynamics that may vary across research locales. This is a critical and innovative component of our multi-site qualitative research design that will specifically seek out data that assesses how contextual differences across study sites may affect participant experiences and study participation outcomes.

Discussion

Randomized controlled trials are essential to test and develop new treatments for substance use disorders. However, there remain social, ethical, and logistical challenges to conducting RCTs among PSUD, who may be more vulnerable, due to their socioeconomic status, criminal justice involvement, health status and the stigmatization of substance use (Bell & Salmon, 2011; Fisher et al., 2008; Fisher & Jaber, 2019; Treloar et al., 2010; Yakovenko et al., 2019). Previous studies have identified potential issues with trial research among vulnerable groups, such as limited clinical trial literacy resulting in misunderstanding or mistrust (Abadie et al., 2018; Bardwell et al., 2021; Bell & Salmon, 2011; Jaffe, Nosova, et al., 2021; Tompkins et al., 2019). Prior research has also highlighted motivations, barriers, and facilitators of participation among PSUD, primarily in hypothetical trials (Dhalla et al., 2010; Maher et al., 2010; Mills et al., 2004; Park et al., 2012; Treloar et al., 2010; White et al., 2013; Yakovenko et al., 2019; Young et al., 2015), but further research is needed to understand the experiences of PSUD in active, real-world trial research (Neale et al., 2018).

With the growth of addiction medicine research (Hering et al., 2014; Lembke & Humphreys, 2018), results from this nested qualitative study have the potential to provide critical recommendations to inform future RCTs testing pharmacotherapies for substance use disorders. For instance, feedback from participants may offer insight into how broader structural influences shape experiences in the study or highlight underutilized strategies for improving recruitment, protocol adherence and study retention. Staff and clinicians who share experiences working with participants and interacting with key study features could identify best practices that inform the design and implementation of future RCTs, particularly as these individuals are often subject or privy to unique contextual conditions that might prompt study design or program delivery variations optimized for different environments. Qualitative interviews allow for flexibility in interview topics and for deeper discussion around themes deemed salient by participants—opportunities that may not be feasible through standardized RCT participant feedback—thereby identifying previously unobserved influences on participation that should become standard measures in addiction trials that support the application and generalizability of results.

Still, we acknowledge some challenges in implementing this multisite qualitative study given the complexity of design and the need to coordinate with an ongoing clinical trial. First, in planning the study, there have been logistical obstacles involved in managing a multisite study across multiple provinces, time zones, institutions, and staff teams. For instance, each institutional research ethics board had different requirements and procedures, leading to varying study approval and operation timelines across sites. The OPTIMA national coordinator was knowledgeable in all institutional requirements and harmonized ethics procedures and proved a critical asset to the successful and timely ethical approval of the OPTIMA and ORAS studies. Additionally, the multi-site nature of the trial made it challenging to develop specific hypotheses and a common interview guide given the differences in context across study sites, making some lines of questioning less relevant at some sites while critical at others. Second, the study sample of people with prescription opioid use disorders may involve participants who are socioeconomically marginalized, criminalized, or have experienced substance use-related discrimination, and may encounter notable difficulties in following the OPTIMA study requirements. For instance, participants without stable housing may have found it difficult to attend follow-ups, or participants with previous negative healthcare experiences may feel distrust toward health researchers or research institutions (Abadie et al., 2018; Bell & Salmon, 2011; Fisher et al., 2008; Tompkins et al., 2019). Importantly, any participant recruitment or retention challenges in the parent trial would, because of the nested nature of the ORAS study, be passed along to the auxiliary qualitative study. Further, study retention may be shaped by the burden of study requirements and so additional qualitative interviews on top of existing trial requirements may pose an unacceptable extra time burden for participants. However, we aimed to reduce study burden by conducting interviews on days where participants did not have a scheduled study follow-up or when participants were at the site for other shorter appointments (e.g., prescription refill). Despite a number of challenges, the potential application of understandings drawn from nested qualitative research in the context of a large multi-site trial in light of the expansion of experimental substance use disorder research is clear.
Conclusion

This multisite qualitative nested study within a substance use RCT offers an original design for understanding the best practices and challenges associated with conducting clinical trial research with people with substance use disorders, a population for which there is a pressing need for RCT-tested pharmacotherapies. In this study, we interviewed a subset of participants and staff involved in a multisite, pragmatic, phase IV study across Canada that is testing supervised methadone versus buprenorphine/naloxone flexible take-home dosing models of care for people with prescription opioid use disorder. Through the collection and analysis of these qualitative interviews, we aim to 1) examine trial-specific, individual, social and structural influences on motivations, barriers and willingness to participate in medical research; 2) explore attitudes about and experiences of participation in medical research; and 3) identify individual, social and structural influences in RCT protocol adherence and trial completion. Throughout the design and conduct of this research, we encountered some challenges, including logistical complexities of operating a multisite nested study and working with a study population facing substantial barriers to participation. Nevertheless, through strong coordination efforts with the parent study, we are confident the ORAS study will be one of the first successful multisite qualitative studies of RCT participation among people with substance use disorders. In conducting this research, we seek to solidify the importance and utility of nesting qualitative research within multi-site experimental studies, that holds the potential to identify context-specific contingencies that are often overlooked in more stringent formalized research protocols. In so doing, this research holds the potential to maximize the effective conduct and application of experimental studies in the burgeoning area of research.

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Declaration of Conflicting Interests

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Ethical Approval

The OPTIMA and the ORAS studies have received ethics approval from Providence Health Care/University of British Columbia’s Research Ethics Board.

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