PARTICIPATION AMIDST PRECARITY: MEDICAL RESEARCH EXPERIENCES AMONG PEOPLE WHO USE DRUGS

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Abstract

To demonstrate the efficacy of an intervention, randomized controlled trials (RCTs) are considered the "gold standard" of study design. Yet RCTs are challenging to conduct, given the difficulty in recruiting and retaining representative study populations and ensuring external generalizability. These challenges may be amplified in substance use research with people who use drugs (PWUD), who often experience drug-related stigma, socioeconomic marginalization, and criminalization, that can deter them from trial engagement. Given these potential barriers, research has started exploring RCT participant perspectives, with a focus on individual and trial features, such as barriers or incentives to attending follow-ups. However, few studies have investigated features of the broader social and structural context in which clinical knowledge around substance use is produced. Considering this area for further research, I conducted a nested qualitative study with PWUD in a multi-site, pragmatic RCT for opioid use disorder. Using data from 115 interviews across five Canadian cities, I develop three analyses investigating micro-, meso-, and macro-level influences on PWUD trial experiences and processes of knowledge production in experimental substance use research. First, I characterize participants by their experience with treatment and drug cultures to demonstrate how participants' accumulated experiences shape medication beliefs (e.g., safety, efficacy), as well as stigma and the sourcing of health information. Second, I link sociological concepts around alienation to drug use and research participation in order to investigate participants' underlying reasons for trial enrollment, including instrumental (e.g., employment opportunities), altruistic (e.g., community benefit), and social (e.g., rebuilding social ties) motivations. Finally, I draw on theoretical linkages between place and health to compare participant experiences across Canada and demonstrate how spaces (e.g., proximity to drugscapes) and interactions within them (e.g., healthcare provider stigma) shape

study experiences. I also consider how macro-level forces (e.g., medication coverage) structure treatment contexts, thus impacting the study (e.g., incentivizing enrollment). By applying a sociological lens to RCT processes, this dissertation reveals how contextual features, from drug-related stigma to drug policy, underlie supposedly objective processes of knowledge production. Building on these results, I provide key recommendations for adapting RCT processes to improve the research experiences of marginalized PWUD.

Lay Summary

Randomized controlled trials (RCTs) are a critical step in developing new medical treatments, but the rigor and precision they require can pose challenges for researchers and participants. In RCTs testing treatments for substance use, participation may be difficult for people who use drugs (PWUD), as they can experience barriers related to drug-related discrimination, socioeconomic marginalization, and criminalization. To understand their experiences in RCTs, this dissertation draws from interviews conducted with PWUD across Canada who were actively enrolled in a trial for opioid use disorder. In exploring broader social and environmental considerations around substance use, results showed how individual (e.g., medication perceptions), social (e.g., family relationships), institutional (e.g., experiences with healthcare providers), and structural (e.g., provincial medication coverage) factors could shape participants' study experiences. These findings emphasize the relevance of context, even in RCT research, and highlight opportunities to improve the conduct of future substance use trials and experiences of PWUD.

Preface

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Table of Contents

List of Tables

List of Abbreviations

CRISM	Canadian Research Initiative in Substance Misuse
MOUD	Medications for Opioid Use Disorder
OPTIMA	Optimizing Patient Centered-Care: A Pragmatic Randomized Control Trial Comparing Models of Care in the Management of Prescription Opioid Misuse
ORAS	OPTIMA Research participation Ancillary Study
PWUD	People Who Use Drugs
RCT	Randomized Controlled Trial

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1 Introduction

How can sociological inquiry improve the conduct of, and knowledge gained from randomized controlled trials? Since the mid-20th-century, randomized controlled trials (RCTs) have been used in research to demonstrate the efficacy of an intervention, eventually emerging as the so-called "gold standard" study design in the early 1980s (Bothwell et al., 2016). The RCT design aims to reduce bias in evaluating new interventions through experimental manipulation (i.e., random allocation of participants) to account for differences across study arms, rather than through natural observation. Substantial epistemological and methodological debates continue over the relevance and unchallenged dominance of RCTs in the construction of clinical evidence (Bothwell et al., 2016; Cartwright, 2007; Grossman & Mackenzie, 2005; Pearce et al., 2015; Reddon et al., 2020), but RCTs remain central to processes of medical knowledge production.

Alongside this debate, there exist immense challenges to conducting clinical trials, related to the recruitment and retention of a representative study population, ethical concerns, and external generalizability across treatment contexts. In efforts to improve the design and implementation of RCTs, scholars have begun to investigate key study elements from the perspective of participants. This line of inquiry has identified a number of considerations that influence RCT participation and potentially undermine the effective and ethical conduct of human subject research. For example, mistrust of research has been cited as a notable barrier to RCT recruitment and enrollment (Carrera et al., 2018; Hall et al., 2006; Jaffe et al., 2021a; Jenkins et al., 2013; Volkmann et al., 2009), particularly among racial and ethnic minority groups who have historically faced exploitation and abuse from medical researchers (Braunstein et al., 2008; Durant et al., 2011; Yancey et al., 2006). Upon enrollment, participant preferences for randomization to a specific study arm may shape treatment and study expectations, as well as adherence to the trial protocol (e.g., attending follow-

ups) or retention in the study (Donovan et al., 2014; McPherson & Britton, 1999; Ross et al., 1999). Retaining trial participants in these complex and often demanding studies for weeks, months, or years may also present challenges, closely associated with time constraints (e.g., due to employment or childcare responsibilities), logistical concerns (e.g., transportation), side effects from study treatments, and/or discomfort with study procedures (e.g., weekly blood draws or the possibility for placebo medications; Glover et al., 2015; Mills et al., 2004; Ross et al., 1999). Through these parallel studies, researchers have successfully moved beyond trial data to investigate processes of RCT design and implementation, with the aim of improving clinical trial experiences.

1.1 Considerations for RCTs with PWUD

Though scholarship on RCT participation has yielded considerable insights, this work has primarily been focused on trials for HIV, Hepatitis C, cancer, and other chronic illnesses. Less research has focused on RCTs in the field of substance use research—a field rapidly expanding amidst the need for novel pharmacological treatments to address the unprecedented rise of overdose-related fatalities (Ahmad et al., 2020; British Columbia Coroners Service, 2018; Degenhardt et al., 2013; Tai et al., 2021). While substance use research expands, significant social and ethical issues remain that specifically relate to the conduct of RCTs with people who use drugs (PWUD), a population that is often socioeconomically marginalized, criminalized, and stigmatized in healthcare settings (McCradden et al., 2019; Paquette et al., 2018; Room, 2005). For instance, previous research has highlighted how marginalized PWUD may feel skeptical toward research studies, mistrust researchers, or have concerns about the safety of the trial (Abadie et al., 2018; Bell & Salmon, 2011; Mills et al., 2004; Neale et al., 2018; Park et al., 2012; Tompkins et al., 2019). PWUD may also encounter significant barriers during the trial period, such as social

pressures (e.g., involvement in drug scenes) or environmental constraints (e.g., traveling or scheduling challenges; Buchbinder et al., 2004; Mills et al., 2004; Park et al., 2012; Thomson et al., 2008). Amidst these challenges, it is critical to recruit and retain diverse populations of PWUD in RCTs in order to make recommendations that are valid, generalizable, and informative for key affected subpopulations.

Despite these recruitment priorities, a significant proportion of PWUD are systematically excluded from clinical trials due to narrow eligibility criteria (e.g., health comorbidities or ability to follow strict protocol), often resulting in study samples that may not be generalizable to the broader population of PWUD (Dennis et al., 2015; Moberg & Humphreys, 2017; Susukida et al., 2017). In light of such observations, there has been an increase in *pragmatic trials* as a means to produce more generalizable evidence in substance use and across health research (Montgomery, 2017). In contrast to highly controlled *early phase trials* (e.g., safety and efficacy trials) that aim to generate explanatory data and establish the safety and efficacy of interventions, pragmatic trials aim to inform clinical practice or policy guidelines by reflecting real-world treatment conditions (Ford & Norrie, 2016). Some science and technology studies scholars have argued pragmatic trials constitute "mode 2" knowledge production, in which knowledge is contextualized and co-constructed between science and society, compared to "mode 1" knowledge production where research occurs in single institutions (e.g., a university) within disciplinary boundaries (Rushforth, 2015; Will & Moreira, 2010). However, others have argued that while pragmatic trials aim to generate contextualized, real world evidence, "what the real world is made of is a question needing more granular and transparent treatment" (Montgomery, 2017, p. 40). Even in a pragmatic trial, the demand for standardization persists and thus elements of the trial (e.g., data collection procedures, study medication dosing, monitoring and evaluation practices) are made uniform

across sites and study populations (Montgomery, 2017), even while the social world remains far from standardized (Timmermans & Epstein, 2010). In addition, methodological limits in RCTs exist regarding what can be manipulated or randomly allocated in real world settings (e.g., prescription coverage), and what can be measured by quantitative trial metrics without supplemental qualitative data. These are fundamental issues in multi-site, pragmatic trials. In substance use research, the depth and quality of data gleaned from pragmatic trials may be particularly important, as marginalized PWUD face persistent barriers to treatment and healthcare access, including stigma and discrimination in healthcare settings; entrenchment in drug scenes; and/or inconsistent engagement in income-generating activities (Bell & Salmon, 2011; Fisher & Jaber, 2019; Fisher et al., 2008; Treloar et al., 2010; Yakovenko et al., 2019). Prior research has also highlighted motivations, barriers, and facilitators of participation among PWUD, 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). However, further research is needed to understand the experiences of PWUD in active trial research (Neale et al., 2018). By employing qualitative nested research within pragmatic trials, researchers can elucidate how RCTs are "deeply entangled in local social conditions, economics, and politics" (Bothwell et al., 2016, p. 2178).

1.2 Sociological linkages to the study of RCTs

To date, few studies have focused on research participation among PWUD. Those that do generally focus on attributes of individuals (e.g., demographic indicators) and trials (e.g., burden of study procedures) or measure willingness to participate in hypothetical studies rather than actual trials (Jaffe et al., 2021a; Neale et al., 2018; Park et al., 2012). Also, conceptual and empirical gaps exist regarding the broader social (e.g., networks) and structural (e.g., treatment access)

considerations in enrollment decision-making and study retention among PWUD that are critically important for understanding processes of biomedical knowledge production and the development of novel treatments. However, research from three subareas of the sociology of health and illness may have key contributions to fill these gaps.

1.2.1 Social constructionism

First, conceptual framings related to the social construction of illness have central relevance to these discussions, as this approach emphasizes how meaning is not inherent in phenomena, but is instead derived from social interactions within particular contexts (Conrad & Barker, 2010). In the world of clinical trials with PWUD, meaning is socially constructed with regard to substances (e.g., criminalization or medicalization of some drugs and not others), diagnoses of substance use disorders (e.g., defining recreational versus problematic use; Boyd et al., 2020; Columbia, 2005), and substance use treatment, as further discussed below. Likewise, the data collected and analyzed within a clinical trial are also socially constructed, as this process necessitates that participants recognize and recall salient symptoms or report outcomes within a set of pre-defined responses and specified metrics (McKinlay, 1996). These data are then subjected to researcher interpretation (Latour & Woolgar, 1979; Will & Moreira, 2010), and translated into clinical evidence by a narrowly defined set of medical experts (Arksey, 1994; Pearce et al., 2015). In contrast, people with lived experience are rarely consulted for their lay expertise (Arksey, 1994; Pearce et al., 2015) and are often altogether excluded from clinical trial participation due to restrictive trial eligibility criteria (Dennis et al., 2015). Thus, by applying a social constructionist lens to the clinical trial, we can begin to understand how cultural and social systems shape trial perceptions and experiences as well as produce broader impacts on knowledge production.

1.2.2 Stigma

Related to the social construction of illness and centrally relevant to this study are sociological approaches to stigma, or the processes through which individuals are socially discredited due to particular attributes or behaviors (Goffman, 1963). Substance use can be a marker by which PWUD are labeled, stereotyped, and experience status loss and discrimination (Link & Phelan, 2001; Lloyd, 2013; Pescosolido & Martin, 2015; Simmonds & Coomber, 2009). Extensive research has highlighted how PWUD experience discrimination in employment (Baldwin et al., 2010), housing (van Olphen et al., 2009), healthcare settings (Earnshaw et al., 2013; Paquette et al., 2018), and policing and criminal justice systems (Kerr et al., 2005; McNeil et al., 2015; Small et al., 2012). Stigma can be internalized if individuals accept the social meaning behind stigma and adjust their behavior according to prescribed norms (Link & Phelan, 2001). Among PWUD, internalized drug stigma can result in negative impacts on mental health (Cama et al., 2016; Kulesza, 2013; von Hippel et al., 2018) and deter them from accessing healthcare or substance use treatment (Tsai et al., 2019; von Hippel et al., 2018). Furthermore, for PWUD who are people of color, drug-related stigma and discrimination may be compounded by interpersonal and institutional racism, particularly in healthcare and criminal justice settings (Hansen & Roberts, 2012; Kulesza et al., 2016; McKnight et al., 2017).

With respect to trial participation, given the similarities between and potential conflation of healthcare settings and pragmatic trial settings (Bell & Salmon, 2011; Hall et al., 2006), negative previous experiences in healthcare and internalized stigma could directly shape study recruitment and retention (e.g., unwillingness to visit hospital research sites), as well as the collection of study data (e.g., hesitancy in reporting drug use or "negative" outcomes; Smye et al., 2011; Tang et al., 2015). Indirectly, stigma can inform motivations for accessing treatment or enrolling in a trial (e.g.,

to reduce substance use thus reducing stigma), as well as shape participants' social support for study participation as participants navigate decisions to disclose substance use and seek loved ones' support during a trial. While stigma is largely discussed in the context of diagnoses or direct healthcare provision, sociological understandings of stigma may have direct relevance for the conduct of RCT research testing treatments for stigmatized illnesses.

1.2.3 Health and place

Third and finally, drawing from sociological understandings of "place"-based meaning and power (Gieryn, 2000), health sociologists have explored how compositional (e.g., social networks), contextual (e.g., neighborhood characteristics), and relational (i.e., situated processes and interactions) features of place shape individual and community wellbeing (Carpiano, 2007; Cummins et al., 2007; Macintyre et al., 2002; Veenstra & Burnett, 2014). These sociological understandings of place and health may have applicability to an analysis of place-based effects across multiple sites of an RCT for opioid use disorder. As Epstein (1997) argued in his analysis of early HIV/AIDS trials, clinical trials do not occur in a vacuum but rather "reflect and propel controversy" (Epstein, 1997, p. 716), particularly for stigmatized illnesses. For a contentious, stigmatized, and criminalized illness like opioid use disorder, a pragmatic clinical trial cannot be separated from its localized social and political context. In understanding and analyzing substance use RCTs, researchers may consider the local climate and public perceptions around drug use (Morin et al., 2017; Small et al., 2007), the liminal and fluctuating status of drug use as criminalized or medicalized across jurisdictions (Hansen & Roberts, 2012; Kolla & Strike, 2021), and variations in treatment resources and drug policies (Eibl et al., 2017; Morin et al., 2017; Priest et al., 2019; Socías & Ahamad, 2016).

Using these three sociological frameworks as a guide, I develop three related analyses that

aim to generate a more comprehensive understanding of the complex perceptions and experiences of PWUD in clinical trial research. My first analysis focuses on how participants' previous experiences shape their perceptions of the study medications (e.g., safety, efficacy, side effects) and medication stigma. The second part of my study links sociological concepts around alienation to participants' underlying motivations for enrollment, as related to instrumental (e.g., study stipend), altruistic (e.g., community benefit), and social (e.g., role expectations) motivations. The third analysis draws on linkages between health and place to explore how physical spaces as well as local features across multiple trial sites, can structure study and treatment experiences.

1.3 Medications for opioid use disorder

The current study is focused on participants in a pragmatic trial comparing medications to treat opioid use disorder ("MOUD") in real-world settings. While treatment for substance use disorders ranges from pharmacological approaches to psychosocial interventions, the use of MOUD in clinical care has increased, with tens of thousands of patients in Canada accessing this treatment (Eibl et al., 2017). The expansion of MOUD availability and uptake reflects growing acceptance of the medicalization of substance use and increasingly common framing of problematic substance use as a medical issue, as opposed to a sort of moral deficiency or criminal issue (Campbell, 2012). It should be noted, however, that the medicalization and criminalization of substance use can and often do occur simultaneously (Hansen & Roberts, 2012; Kolla & Strike, 2021). A medicalized framing of substance use may facilitate an increase in the allocation of funding, resources, and policy support for the research, prevention, and treatment of substance use disorders (Campbell, 2012). However, such perspectives often overlook broader social and structural considerations involved in problematic substance use, such as intergenerational trauma, underlying mental health issues, untreated physical pain, and socioeconomic marginalization

(Hansen & Roberts, 2012; Kolla & Strike, 2021). Although detailing the contentious debates around the medicalization of substance use (e.g., "addiction as a brain disease"; Conrad & Schneider, 1992) falls beyond the scope of this dissertation, the general context is relevant as it informs individuals' decisions around treatment and study participation. For instance, a person who subscribes to the medical model of addiction may place more emphasis on the efficacy of the trial medication, whereas someone else may discount the potential value of medical research on pharmacotherapeutic interventions or the effectiveness of the study medication. As a result, those who enroll in a substance use trial may favor the use of medication to a greater degree than non-participants, a limitation that has implications for the generalizability of addictions RCTs to the larger population of PWUD.

1.3.1 Methadone and buprenorphine/naloxone

This dissertation focuses on participants in the Optimizing Patient Centered-Care: A Pragmatic Randomized Control Trial Comparing Models of Care in the Management of Prescription Opioid Misuse (OPTIMA) study. The OPTIMA study is a pragmatic trial that compared methadone and buprenorphine/naloxone for the treatment of prescription opioid use disorder in clinical settings. Since methadone and suboxone have been previously proven safe and efficacious through early phase clinical trials, they are primarily studied in the research context in pragmatic or phase IV trials to test their effectiveness in the real world, potentially among different populations, under different conditions, compared to existing treatments, or to inform clinical practice guidelines in some way (Ford & Norrie, 2016).

First available in the 1960s, methadone is a long-acting, synthetic opioid agonist that acts as replacement therapy for other opioids and can reduce symptoms of withdrawal (e.g., fever, chills, body aches, gastrointestinal side effects), without producing the same magnitude of

cognitive and other types of impairment commonly associated with opioid use. For patients on methadone maintenance therapy, the treatment is typically dispensed in a mixed liquid form at pharmacies or specialized methadone clinics (Pecoraro et al., 2012). In the early 2000s, buprenorphine, a partial opioid agonist, was approved for use in opioid detoxification as well as maintenance therapy. As a partial agonist it has a higher safety profile because physical dependence and withdrawal symptoms are considered less severe than methadone (Pecoraro et al., 2012). Suboxone, approved for use in the US in 2002 and in Canada in 2008, is a medication that combines buprenorphine with naloxone, an opioid antagonist that blocks the effect of opioids and can be used to reverse the effects of overdose (i.e., "Narcan"; Pecoraro et al., 2012). While researchers continuously debate the merits of methadone versus buprenorphine/naloxone in terms of safety (Kimber et al., 2015), cost effectiveness (Maas et al., 2013), efficacy (Ahmadi, 2003; Fischer et al., 1999; Mattick et al., 2003), patient preference (Pinto et al., 2010; Yarborough et al., 2016), quality of life (Ponizovsky & Grinshpoon, 2007), and retention in treatment (Burns et al., 2015; Gryczynski et al., 2013; Hser et al., 2014), both medications have been proven effective for the treatment of opioid use disorder. Additionally, suboxone and methadone both have the potential to reduce health- and drug-related harms, for instance by providing a safer alternative to potentially toxic, adulterated drugs, lessening the financial burden of acquiring unregulated opioids, decreasing the risk of arrest and further criminalization for drug use, and reducing the use of injection drugs and associated health harms (e.g., Hepatitis C, HIV, infections, etc.; Ahmadi, 2003; Eibl et al., 2017; Wild et al., 2017). However, these two medications vary in several key respects that have the potential to influence participant perceptions and trial experiences.

First, the process of starting treatment is unique for each medication. In clinical practice, MOUD prescriptions must be prescribed by a physician, but to prescribe methadone, physicians

are required to have an exemption through Health Canada, limiting the number of family doctors that are willing, knowledgeable, and/or able to prescribe it (Bruneau et al., 2018). Some provinces have adapted with innovations, such as Ontario's Telemedicine Network that remotely links providers to patients seeking MOUD, while other provinces still have a limited number of prescribing physicians (Eibl et al., 2017). Conversely for suboxone, while physicians may lack clinical knowledge around suboxone guidelines, physicians typically do not require an exemption to prescribe it. Methadone and suboxone also vary in terms of treatment initiation. Once patients have access to methadone they can generally begin treatment immediately, while those initiating suboxone are required to cease opioid use and go into withdrawal, a process that may be incredibly uncomfortable and serve as a formidable deterrent to treatment (Bruneau et al., 2018). Further, at the start of the OPTIMA study, Canadian clinical guidelines still required methadone as a first-line treatment, and only after patients "failed" methadone were doctors able to prescribe buprenorphine/naloxone (Bruneau et al., 2018).

Second, dosing recommendations and regulations between methadone and suboxone are different. Methadone is a highly controlled medication, given the risks associated with overdose and to public safety if diverted (Bruneau et al., 2018). Thus, methadone must be dispensed under the supervision of a qualified medical professional, which typically requires patients to attend a pharmacy or clinic daily. Patients may find it challenging to plan their life around adherence to this daily visit, and patients without access to transportation or those in rural and remote areas may need to travel long distances to reach their clinics (Eibl et al., 2017). Some patients may be able to access "take-home" methadone doses (also known as "carries"), but only after demonstrating adherence for significant period of time, an average of eight months across Canada (Eibl et al., 2017; McElrath, 2018; Pecoraro et al., 2012). In contrast, after a short monitoring period, suboxone

can be prescribed as a take-home dose, as there are lower safety risks or risks of diversion. Both treatment modalities have been characterized as being highly regimented and a means of control, but previous research around methadone regulations allude to authoritarian medical surveillance (Harris & McElrath, 2012; Rhodes et al., 2019) while buprenorphine/naloxone regulations has been characterized as more reflective of trends in self-surveillance of health, or "internalized vigilance and self-scrutiny" (Campbell, 2012, p. 22). OPTIMA participants may be resistant to these forms of control or find that preexisting perceptions of these medications and their associated regulations influence their preference for one trial medication over the other.

Finally, drug use is greatly stigmatized (Easton, 2016; Kulesza, 2013; Room, 2005; Tsai et al., 2019), by extension so too are medications for opioid use disorder (Allen et al., 2019; Hansen & Roberts, 2012; McCradden et al., 2019; Neale, 2013). However, in most contexts, methadone use is stigmatized to a far greater degree (Earnshaw et al., 2013; Harris & McElrath, 2012; McCradden et al., 2019), in part because of the way it has historically been linked to socioeconomic marginalization, crime, and racialized narratives and imagery (Hansen & Roberts, 2012; Kulesza et al., 2016; Netherland & Hansen, 2016). For instance, in their work on the racial politics of opioid treatments, Hansen and Roberts (2012) observed that in the process of developing buprenorphine, the US National Institutes of Drug Abuse (NIDA) worked to pass legislation allowing buprenorphine to be prescribed by private physicians and facilitated training for and marketing to these physicians. In effect, this protected more white, middle-class patients from the War on Drugs as they were more likely to be prescribed buprenorphine, which distinguished them from "presumably less trustworthy, nonwhite, low-income heroin injectors who would need more tightly regulated treatments such as methadone" (Hansen & Roberts, 2012, p. 95; Netherland & Hansen, 2016). In the public eye, methadone became effectively linked to racialized groups and

heroin while buprenorphine or buprenorphine/naloxone became associated with white, suburban and rural Americans and (typically) legal prescription opioids (Netherland & Hansen, 2016). In contrast to RCTs with less sensationalized and stigmatized trial medications, the social meaning accompanying MOUD may shape the experiences of PWUD participating in the trial. As these concepts are of key relevance to medical sociologists, they will be discussed at greater length in the following empirical chapters.

1.3.2 A note on terminology

While studying and writing on a stigmatized and politicized issue like substance use, it is important to elucidate the rationale behind the language employed. Substance use has been described as occurring on a spectrum of "beneficial" and "recreational" to "chronic dependence," with the recognition that placement upon this spectrum is subjective (Health Officers Council of British Columbia, 2005). Over the past several decades, a range of different terms has been employed to describe more "problematic" chronic substance use, but there is an increased emphasis on avoiding stigmatizing language (e.g., "misuse," "abuse") and using person-first language (Kelly et al., 2016; Saitz et al., 2021). In adherence to these norms, I employ the use of several terms throughout this dissertation. As this study is situated within a clinical trial, at times I use the language of "substance use disorder" or "opioid use disorder" to mirror the language of the OPTIMA trial, which uses definitions and eligibility criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V; American Psychiatric Association, 2013). However, I recognize that this term reflects a normative, medicalized approach to substance use (Boyd et al., 2020), and that applications of this term have been historically shaped by race, class, culture, context, and access to resources (Hansen & Roberts, 2012). I refer to the study population as "people who use drugs" (PWUD), which is the currently accepted term in substance use research

and advocacy, but there are some critiques of this term as well. First, "PWUD" may be misleading in that it can imply all people who use psychoactive substances (e.g., cannabis, alcohol, etc.), which would comprise a significant portion of the population. Depending on the study population and research aims, it may be more useful at times to specify "marginalized PWUD" or people who use illicit drugs to recognize the impact of the criminalization of drug use. Second, some drug user groups prefer the term "drug user" over "PWUD," in part to signal a collective identity as they advocate for drug policy change (Bartoszko, 2021; Madden et al., 2021). However, the participants in this study may not identify with a collective "drug user" group. It should also be noted that in my dissertation some participant quotes employ terminology that is considered derogatory or stigmatizing (e.g., "addict," "junkie"). I retain these terms when used by participants to reflect participants' voices and because they may offer some insight into the function of labels, stigma, and the management of identity. In essence, language around drug use is heavily laden with meaning and has real consequences, but it is constantly evolving. Eventually, the language used in this dissertation may appear dated, but my intentions are to demonstrate respect for the participants in the study and the broader community of people who use drugs.

1.4 Methods

Data for this dissertation comes from a qualitative study nested within an RCT. In this mixed-methods approach, qualitative data collection occurs simultaneously within the larger quantitative study—a study design increasingly used within RCTs (Creswell & Plano Clark, 2017; Maher & Neale, 2019; Small, 2011).Though quantitative approaches to understanding RCT processes have provided useful preliminary data and rationale for further study, the decision to participate in research with PWUD may be more complex than can be encapsulated within a single analytical approach. The majority of RCT participation studies are survey-based and have tended

to focus on either hypothetical "willingness to enroll in an RCT," or simply list individual-level barriers and facilitators (e.g., study stipends), while ignoring broader social and structural influences, such as limited economic opportunity (Maher & Neale, 2019). However, qualitative studies nested within these trials have been used to gather valuable insight from PWUD experiences during and after a trial in order to understand the impacts of the treatment and trial (Cooper et al., 2014; de Salis et al., 2008; Mannell & Davis, 2019; Neale et al., 2018).

1.4.1 Parent study

Using this mixed-methods design, the study data for this dissertation come from a qualitative ancillary study nested within the OPTIMA trial, which is a multisite, open-label (i.e., not blinded), pragmatic, Phase IV RCT testing methadone versus buprenorphine/naloxone ("suboxone") among people with (prescription) opioid use disorder. Conducted between 2017 and 2020, OPTIMA was the first multi-site study of the recently established Canadian Research Initiative in Substance Misuse (CRISM) network, which coordinates the conduct of national, multi-site, clinical trials of key relevance to Canadian populations of PWUD and seeks to emulate the clinical trials network of the U.S. National Institutes of Health National Institute on Drug Abuse (NIDA). The CRISM network has four major regions ("nodes") across Canada (British Columbia, the Prairies, Quebec-Atlantic, and Ontario) and the OPTIMA trial was implemented at seven sites in each of these regions, although two study sites closed during the study. Each of the four nodes aimed to recruit 69 participants, for a total of 276 participants across all sites. Participants were deemed eligible for OPTIMA if they were between the ages of 18 and 64, spoke French or English, could provide consent, met clinical criteria for (prescription) opioid use disorder, were willing to be randomized, had no serious medical condition that would preclude them from participating, and had not taken methadone or suboxone in the previous four weeks.

Participants were enrolled in the study for up to 28 weeks, which included time between screening and randomization (up to 28 days), a 14-day window to initiate treatment once randomized, and a 24-week intervention period. During the 24-week intervention, participants attended follow-ups every two weeks to complete study questionnaires and undergo intermittent medical testing (e.g., urine screening). The trial was projected to last two years but ultimately concluded after three years. In addition to the current nested qualitative study, there were four additional ancillary studies focused on pharmacogenomics, sexual functioning, pain evaluation, and treatment cost-effectiveness. Further details on the OPTIMA trial design have been published previously (Socias et al., 2018).

1.4.2 Study overview

The qualitative data for this study come from the OPTIMA Research participation Ancillary Study (ORAS). This ancillary study aimed to explore participant experiences in OPTIMA over time via semi-structured interviews with participants across five Canadian cities: Vancouver, Calgary, Montreal, Toronto, and prior to the study site closing, Sudbury, Ontario. After participants completed OPTIMA enrollment procedures, a sub-sample of participants were asked about their interest in a separate qualitative study investigating their trial experiences. Participants were eligible for ORAS if they: (a) enrolled in the OPTIMA trial; (b) agreed to be contacted by the ORAS interviewer; and (c) provided written informed consent to be in the ORAS study. I interviewed all participants in Vancouver and some participants in Calgary. Over the course of the study, I also trained and supervised multiple interviewers in Calgary (two), Montreal (one), Toronto (two), and Sudbury (two). Interviewers were not affiliated with the OPTIMA project and participants were reassured that interview data would not be shared with the OPTIMA study team nor impact their trial participation. ORAS participants were compensated $30 CAD

per interview for their time and expertise. Ethics approval was obtained from the research ethics board at each study node: University of British Columbia, University of Alberta, University of Toronto (for Toronto and Sudbury), and University of Montreal.

Participants were interviewed once upon trial enrollment and a second time, either at study exit or upon withdrawing from the study. After completing an entry interview, some participants were lost to follow-up (n=26 across five sites), generally because they were lost to follow-up in the parent study. These participants may have been lost to follow-up for several reasons. For instance, many socioeconomically marginalized PWUD do not have permanent housing or cell phones, or their phones are regularly stolen, making consistent communication difficult. In other instances, participants were incarcerated due to the criminalization of drug use or hospitalized due to drug-related harms or other health comorbidities. Unfortunately, at least one participant died during the study, but his death was not attributed to study participation. When participants were considered lost to follow-up, new ORAS study candidates were prospectively recruited to complete an exit interview upon their study completion, with the aim of recruiting participants from the same study arm to maintain equal representation. Most ORAS interviews took place in the same location as OPTIMA trial activities, except for two interviews that took place at an alternate location at the request of participants. Additionally, some exit interviews were conducted over the phone due to COVID-19 restrictions.

Semi-structured entry interview topics were derived from a pre-specified topic guide that included: participants' background; housing; income generation; substance use patterns; social support; previous experiences in healthcare; substance use treatment; criminal justice involvement; previous research experience; perceptions of research and addiction treatment; motivations to join an RCT; and experiences beginning the study including recruitment, eligibility, informed consent,

randomization, and baseline procedures. Exit interviews took place within a month of study completion and topics included: changes in participants' lives such as housing, income generation and substance use patterns; study medication experiences; challenges and facilitators of protocol adherence; and perceptions of study processes. All interviews were recorded and transcribed by professional transcriptionists. Interviews conducted in Quebec were first transcribed in French and then translated into English by a certified translator. In addition, I kept memos to document my interviews and my experiences as the coordinator of the multi-site study, as well as the other interviewers' experiences as they were relayed to me in several group meetings as well as individual phone conversations.

1.4.3 Study sample

In total, there were 115 interviews conducted with 75 participants, including 24 participants in Vancouver (21 entry interviews, 16 exit interviews), 20 participants in Calgary (18 entry interviews, 12 exit interviews), 12 in Toronto (10 entry interviews, six exit interviews), three in Sudbury (three entry interviews, one exit interview) and 16 in Montreal (16 entry interviews, 12 exit interviews). Of these participants, 46 (61%) were cisgender men, 28 (37%) were cisgender women, and one (1%) was a trans woman. Across all sites, 50 (66%) participants identified as White, 21 (28%) as Indigenous (i.e., First Nations, Métis, or Inuit), one (1%) as East Asian, one as Middle Eastern, one as mixed race, and one declined to respond. I also interviewed 26 study staff and clinicians as a part of this study. The staff and clinician data are not included in this dissertation but may have indirectly informed its conceptualization.

1.4.4 Analysis

Prior to analysis, I systematically cleaned transcripts and checked them for accuracy against the audio recordings. All interviews were anonymized to protect participant confidentiality,

and in addition to the assignment of an independent alphanumeric code to each participant, pseudonyms are used in the text in place of participant names or codes to support readability. To analyze these interviews, I used flexible coding, a systematic approach designed for use with large qualitative datasets in sociology and particularly useful when analyzing across groups (Deterding & Waters, 2018). As opposed to the widely cited grounded theory inductive approach, flexible coding encourages abductive theory construction, a process that supports recursive and iterative analyses and allows for previous literature review and the incorporation of existing theories to generate new insight (Deterding & Waters, 2018; Tavory & Timmermans, 2014; Timmermans & Tavory, 2012). The process of flexible coding within qualitative analysis software also facilitates the reanalysis of large datasets for subsequent investigation.

Flexible coding involves a multi-step coding process using nVivo software. First, as opposed to line-by-line coding characterized by grounded theory, "index codes" were applied to large portions of text that roughly aligned with the sequence of interview guide. The result was an entirely indexed transcript, verified using data analysis software (e.g., "matrix coding query"). Concurrently, respondent memos and cross-case conceptual memos were developed to identify connections across themes and between different participant groups. Next, analytic codes were applied more specifically to text within the indices of interest for analysis (Deterding & Waters, 2018). Further detail on the specific analytic codes is provided within each empirical chapter. Finally, tools within the data analysis software were used to verify the reliability of codes across cases or otherwise test hypotheses (Deterding & Waters, 2018), including case classification and query tools (i.e. "crosstabs," "coding comparison") when comparing different groups.

1.5 Overview of the dissertation

While analyses in all three empirical chapters of this dissertation are based on the same set of qualitative interviews, each of these chapters is written in the style of a self-contained academic journal article with the intention to publish each substantive chapter as a standalone article. To avoid repetition of the introductory chapter, I have omitted some information from the methods section (e.g., demographic details) in each chapter, focusing only on what is pertinent to the analysis. In my first empirical chapter, I analyze how participants' previous MOUD treatment and drug cultural experiences shape: a) their constructed meaning of study medications, b) conceptions of medication mechanisms, c) lay expertise, ~~and d) adherence to trial medications~~. In my second empirical chapter, I explore motivations for trial participation as informed by feelings related to alienation (e.g., stigma, social isolation, and the search for meaning or purpose). I argue feelings of alienation underlie enrollment motivations, which are expressed by participants as instrumental objectives (e.g., stipend), altruistic intentions (i.e., to benefit other PWUD), or social concerns (e.g., to reconnect with family). My third empirical chapter draws on contextual and relational understandings of place for trial participants. Specifically, it investigates a) how physical spaces and interactions within them shape participant experiences and b) how provincial differences across trial sites (e.g., health coverage policies, treatment context) structure participants' trial enrollment, medication access, and medication adherence. Taken together, this dissertation aims to advance sociological understandings of knowledge production in substance use research and build conceptual and empirical linkages between sociology, public health, drug policy research, and science and technology studies. Further, this research has practical implications for the future design and implementation of RCTs with marginalized PWUD, and by extension, the testing and development of treatments and interventions for substance use disorders.

2 "I thought it was for guys that did needles": Medication perceptions, stigma, and lay expertise among medical research participants

The overdose crisis has devastated families and communities across North America, and in Canada more than 17,000 people have died of drug poisoning within the past four years, in part due to illicitly manufactured, unregulated opioids (Public Health Agency of Canada, 2020). One response to this crisis has been to increase the availability and range of medications for opioid use disorder (MOUD; Connery, 2015; McElrath, 2018). Concurrently, randomized controlled trials (RCTs) are expanding to test the efficacy of emerging treatments and effectiveness of existing treatments for opioid and other substance use disorders (Del Boca & Darkes, 2007). While RCTs are regarded as the "gold standard" of clinical evidence, RCTs are time-consuming, expensive, and logistically challenging, especially with study populations such as people who use drugs (PWUD), who often experience social and structural disadvantage, including socioeconomic marginalization (Collins et al., 2017), criminalization (Abadie et al., 2018), and discrimination (Bell & Salmon, 2011), and who may be unable or unwilling to participate in research (Bell & Salmon, 2011; Fisher et al., 2008; Neale et al., 2018).

To develop effective pharmacotherapies for problematic substance use, clinical trials must enroll representative study populations that reflect the broader population of PWUD (Susukida et al., 2017). Though some research has sought to understand PWUD's willingness to participate or how RCTs can be better designed to improve retention (Caldwell et al., 2010; Jenkins et al., 2013; Walter & Davis, 2016), few studies have analyzed the relationship between social (e.g., drug scene involvement) and structural factors (e.g., healthcare access) that shape participation and PWUD's perspectives on research, to ensure beneficial and ethical study experiences. To address this gap, I draw on 115 interviews with 75 PWUD participants enrolled in a pragmatic RCT for prescription opioid use disorder. By highlighting the role of participant backgrounds, experiences, and lay

expertise, I investigate differences in medication perceptions, stigma, and sources of information across participant groupings. From this analysis, findings will provide insight on the potential benefits and drawbacks to participant expertise and experience within research settings as well as recommendations for improving the future design of RCTs with people who use drugs.

2.1 Background

2.1.1 MOUD and its cultural significance

Methadone and buprenorphine/naloxone, the latter more often referred to by its brand name, "suboxone,"[1] are the most widely used pharmacological treatments for opioid use disorder in North America (Eibl et al., 2017; Pecoraro et al., 2012; Priest et al., 2019). As a long-acting synthetic opioid agonist, methadone eases opioid cravings and reduces withdrawal symptoms (e.g., body aches, vomiting, diarrhea, chills, fever, etc.) as patients transition off of other opioids. While methadone initiation is less complex than suboxone initiation, it remains highly regulated, and in most cases, doses must be dispensed daily and consumption witnessed by health professionals (e.g., pharmacists). This daily routine can present significant logistical challenges, such as managing time and transportation according to the pharmacy operating hours and patients' employment schedules (Bruneau et al., 2018; Richardson et al., 2012). Suboxone contains buprenorphine, a partial agonist that mimics the effects of opioids and suppresses withdrawal symptoms, combined with naloxone, an opioid antagonist that blocks the effects of opioids and can reverse overdose (Pecoraro et al., 2012). With fewer requirements around its dispensation, suboxone can be prescribed as a "take-home" dose, but patients may encounter difficulty starting suboxone treatment as they cannot use opioids prior to initiating and must present in moderate

[1] From this point, I refer to the medication as "suboxone" to avoid confusion with standalone buprenorphine and to reflect participants' own terminology.

withdrawal, or risk experiencing "precipitated withdrawal" (i.e., sudden and intense withdrawal). Both medications have been proven safe and efficacious for the treatment of opioid use disorder in previous clinical trials but continue to be tested in RCTs for effectiveness and acceptability in real-world settings and to inform clinical guidelines (Ford & Norrie, 2016).

Despite their demonstrated efficacy, significant barriers to accessing MOUD remain, including drug- and treatment-related stigma. Although conceptualizations of stigma vary, generally substance use is seen as a "mark" or condition that is devalued, and stigma results as PWUD are distinguished and labeled, stereotyped, separated, and subjected to status loss and discrimination (Link & Phelan, 2001; Pescosolido & Martin, 2015). The stigma associated with substance use, and opioid use in particular, has been well-documented (Easton, 2016; Kulesza, 2013; Room, 2005; Tsai et al., 2019). Much of the history of drug-related stigma is tied to racism, xenophobia, and classism, and previous scholars have illustrated how drug laws and policies were enacted to penalize racial and ethnic minorities, immigrants, and socioeconomically marginalized people under the guise of drug prohibition (Carstairs, 1999; Kulesza et al., 2016; Marshall, 2015; Netherland & Hansen, 2016). Research has also explored internalized stigma among PWUD, in which they accept stereotypes or believe drug-related stigma is deserved (Pescosolido & Martin, 2015; Tsai et al., 2019). Internalized stigma, or self-stigma, has been demonstrated to negatively impact PWUD's psychological wellbeing and self-esteem (Cama et al., 2016; Kulesza, 2013; von Hippel et al., 2018) and is associated with reduced engagement in substance use treatment (Tsai et al., 2019; von Hippel et al., 2018).

As the stigma surrounding opioid use has persisted and evolved over time, stigma around treatment for opioid use disorder has developed in parallel (Allen et al., 2019; Hansen & Roberts, 2012; McCradden et al., 2019). People accessing suboxone and methadone are both targets of

stigma (Madden, 2019), but the stigma around methadone is especially pernicious (Earnshaw et al., 2013; Harris & McElrath, 2012; McCradden et al., 2019). As a Schedule I/II controlled substance typically requiring witnessed dosing, methadone may be perceived as dangerous or potentially diverted (i.e., sold in unregulated markets; Harris & McElrath, 2012), a perception that can extend to people accessing methadone who are stereotyped as threatening, incompetent, untrustworthy, or lacking willpower to stop using opioids (Woo et al., 2017). Methadone has also been framed as "dependence" (versus treatment), as a "crutch," and as a form of "liquid handcuffs" that renders patients helpless and bound to their methadone clinics (Malvini Redden et al., 2013). Even some healthcare providers do not recognize methadone as a legitimate treatment or avoid prescribing it so as not to draw PWUD to their practice, a stigma that ultimately harms the wellbeing of PWUD and their treatment outcomes (Mackey et al., 2020; Madden, 2019; McCradden et al., 2019). Many drug policy activists, harm reduction advocates, and social scientists have also critiqued the dispensation of methadone and to a lesser extent, suboxone, as a form of social control and surveillance, with roots in stigma processes (Bourgois, 2000; Harris & McElrath, 2012; McElrath, 2018; Neale, 2013). The stigma surrounding opioids and by extension, MOUD, is a unique characteristic of opioid use disorder and adds a complex dimension to the experiences of participants in a substance use RCT.

2.1.2 Medications, meaning-making, and lay expertise

As the case of MOUD demonstrates, medications are far from neutral pharmacological agents in the social world and cannot be separated from their effects on bodies, how these effects are experienced, understood, and explained, and the role of institutions and actors in their production and dispensation (Cohen et al., 2001; Flore et al., 2019). Strang and colleagues (2018) argue that beyond adverse pharmacological effects, medication toxicity can also be "reputationally

mediated" as a medication's reputation can negatively affect its use and outcome, such as when methadone stigma deters uptake among PWUD (Strang et al., 2018; Uebelacker et al., 2016). In this way, medications are rife with cultural, social, and symbolic meaning that form "social facts" about a drug (Cohen et al., 2001; Montagne, 1988), and shape individuals' relationships with their illness identities, their own body, and others (Cohen et al., 2001; Collin, 2016; Flore et al., 2019; Pound et al., 2005; Ridge et al., 2015). Multiple, contradictory meanings may also surround medications, as detailed in Derrida's (1981) writings on *pharmakon,* the Greek word for "drug," that reflects its duality as both "antidote" and "poison." Substance use researchers have applied *pharmakon* to understandings of opioids, in the way that they produce benefit (e.g., pain relief) and harm (e.g., overdose; Buchman et al., 2017; McCradden et al., 2019; Wilbers, 2020). Taken together, these conceptual insights on medication meaning highlight how "a drug *becomes*, rather than *is*" as medication perceptions grow and shift over time amidst a broader social context (Flore et al., 2019, p. 71).

As patients gain experience with medications over time, they may develop a sort of "lay expertise," with experiential illness knowledge (Arksey, 1994; Epstein, 1995; Prior, 2003), or even a "lay pharmacology" comprised of beliefs about the safety, efficacy, and side effects of a medication (Webster et al., 2009). As patients developed their embodied knowledge about the medication, they simultaneously develop their thinking, as they weighed the risks and benefits and considered treatment similarities and differences. While patients largely rely on clinical experts, they may still act as "naïve scientists," formulating hypotheses about a medication's effects on their bodies and experimenting with dosing or administration of the medication (Siegel et al., 1999). Patients may also experiment with medication to produce additional benefit or to resist medical authority and assert their agency (Carder et al., 2003; Conrad, 1985). For instance,

research has documented how patients strategically alter medication schedules by skipping doses on days they intend to drink (contraindicated) alcohol, or by taking "drug holidays" and stopping their medication for periods of time (Pound et al., 2005). In addition to clinical and experiential knowledge, people may rely on informal and local knowledge prior to starting medication, seeking authority from friends, family, or acquaintances about their own treatment experiences (Pound et al., 2005). For instance, previous research found women with HIV relied on observations of how other people fared on anti-retroviral treatment before deciding to initiate treatment (Siegel & Gorey, 1997). Due to the stigmatized and criminalized status of substance use, PWUD may also rely on the "uncredentialed expertise" of other PWUD for their assistance or knowledge (Brothers, 2019). This treatment knowledge, whether developed via clinical authority, personal experience, or second-hand sources, is key to facilitating its uptake and producing embodied effects.

While explorations of medication experiences and lay expertise in medical sociology have expanded over time (Prior, 2003), less research has explored medication perceptions and expertise in the context of RCTs. Previous research has evaluated how randomization preferences influence willingness to participate and recruitment (Ross et al., 1999) as well as retention and trial outcomes (King et al., 2005), but lack acknowledgement of the role of lay expertise, which may be considerable in pragmatic RCTs that test medications already on market. Just as pragmatic trials are critical to evaluating real-world effectiveness (Ford & Norrie, 2016), exploring the perceptions of participants within them is essential for understanding real-world medication acceptability. For RCTs testing substance use treatments, study medications may be particularly embedded with cultural, social, and symbolic meaning (e.g., stigma) which then shape participants' medication beliefs, embodied medication knowledge, social relationships, and overall study experiences. In light of these considerations, this study draws on nested qualitative interviews conducted within a

multisite RCT for opioid use disorder to understand the broader cultural and social considerations surrounding MOUD. By characterizing interview narratives surrounding MOUD, I investigate how PWUD participants' accumulated experiences and insights shape trial medication beliefs, sources of medication information, and perceptions of medication stigma.

2.2 Methods

As described in the introductory chapter, data for this analysis comes from interviews with 75 PWUD enrolled in a multisite RCT for opioid use disorder. To analyze the interviews, I used flexible coding, a method designed for use with large qualitative datasets (Deterding & Waters, 2018). First, using nVivo qualitative analysis software, I indexed the data, anchoring the content to the interview protocol and producing respondent-level and cross-case memos. Following this, I broke down key indices into smaller analytic codes that were applied to focused sections of the transcript, specifically related to medication perceptions and experiences. Additionally, I created case attributes for participants based on existing sociodemographic data, as well as respondents' interview responses (e.g., previous MOUD experience), in order to characterize groups of participants as described in the results. Finally, nVivo matrix coding and crosstab tools were used for further validation, to seek counterexamples, and to understand the saturation of the themes by attribute (Deterding & Waters, 2018).

2.3 Results

2.3.1 Participant characteristics

Unlike many RCTs in other fields, clinical trials with PWUD rarely have homogenous participant pools due to unique comorbidities, substance use patterns, and treatment regimens (Reddon et al., 2020). In the process of analyzing the data and exploring participant case attributes, I also recognized that study participants diverged on two other critical dimensions: in drug-related

"cultural" experiences and in previous MOUD treatment experiences. I define "drug cultural experience" as when an individual possesses the language, knowledge, and experience related to various drugs and their effects, an awareness of various treatment options, and familiarity with drug scenes—places where many people are engaged in using and selling drugs (Hough & Natarajan, 2000). Participants with drug cultural experience tended to have longer histories with substance use (i.e., more than five years), and tended to be socioeconomically marginalized, based on their self-description (e.g., accessing income assistance, social housing, etc.). I define "treatment experience" as previously accessing prescribed MOUD (i.e., methadone and/or suboxone), as self-reported in interview. Some participants recalled accessing non-prescribed MOUD (e.g., trying suboxone from friends), but I did not consider this to be previous treatment experience. In such instances, nonprescription MOUD was used just once or sporadically, typically without adherence to pharmaceutical guidelines or appropriate dosage, and without the mediating influence of clinical care that typified other participants' treatment experiences. However, in the results, I acknowledge when participants described noteworthy experiences with nonprescribed MOUD that marked their perception of the medication. Other participants tried non-pharmaceutical treatments (e.g., "detox," Narcotics Anonymous, etc.), but I was primarily interested in previous clinical treatment with the study medications, as more directly linked to current medication perceptions.

In categorizing participants on these two dimensions, I classify them as "experienced" (i.e., culturally and treatment experienced, n=41), "semi-experienced" (i.e., culturally experienced but treatment naïve, n=16), and "inexperienced" (i.e., culturally and treatment naïve, n=18). There were no participants who were culturally inexperienced but treatment experienced. Across the sites, there were more experienced participants in the study sample at the Vancouver (n=15,

62.5%) and Calgary (n=15, 75%) sites compared to the Toronto/Sudbury (n=4, 26.7%) and Montreal (n=7, 43.8%) sites. Conversely, there was a greater proportion of semi- and inexperienced participants in the study sample from the Toronto/Sudbury (n=11, 73.3%) and Montreal (n=9, 56.3%) sites compared to the Vancouver (n=9, 37.5%) and Calgary (n=5, 25%) sites (see Table 1). This distribution of experience may be linked to the study site characteristics, as noted in the introductory chapter and as further discussed in chapter four. In this chapter, analysis revealed each group to express distinct patterns of medication perceptions that were informed by their previous experience, expertise, and influential sources of information.

2.3.2 Experienced participants

"I knew what to expect": Cultivating a lay expertise. With both drug cultural knowledge about treatments as well as actual MOUD experience, experienced participants were the most informed and vocal in their opinions about the study medications. Experienced participants were especially opinionated about methadone as nearly all had tried methadone in the past, sometimes for years, whereas only about half had tried suboxone. Though they had significant critiques (detailed below), experienced participants' views of methadone were generally more positive than those of other participants, as they "knew what to expect" and believed that at some point methadone had worked for them. They benefitted from embodied knowledge about methadone, or how it felt to take methadone and how to navigate its effects. As Jessica (White woman, Vancouver) stated, "it was actually the third time being on it that I finally understood everything and how to go about it." However, with only previous methadone experience, Jessica was hesitant to try suboxone because it would involve learning how to take a new medication: "I've done [methadone] so much, so long, that I know what my stable dose is. I know how I'm going to react to it and how to incorporate it in my life, right. The suboxone's new and just—I don't know. It's

just new and I don't want to have to learn something new." Though only half of the experienced participants had previously tried suboxone, experienced participants were familiar with suboxone and seemed to have knowledge of its mechanisms. Notably, experienced participants typically discussed suboxone in juxtaposition to methadone. For instance, participants liked suboxone because it lacked the side effects, or the groggy or "high" feelings associated with methadone, or as Andrew (White man, Toronto) recalled, "[when] I just kept increasing the methadone, I felt like a soup noodle half the day," in contrast to suboxone, which worked well for him. Other optimistic views of suboxone centered around its mechanism to block or reverse the effects of opioids, which differs from methadone, which can be used in combination with other opioids. As Amanda (White woman, Calgary) explained, "I like [suboxone] because you really don't have a choice in whether you're going to use or not. Like you can't or you're going to feel horrible. So, I think it's a good idea." In this more positive framing, suboxone was perceived to reduce the temptation to use opioids because it contained naloxone. As typified in these quotes but expressed widely among participants, previous MOUD experience shaped participants' degree of comfort, hesitancy, and expectations.

In addition to practical medication knowledge, experienced participants were explicitly aware of the social and cultural connotations surrounding MOUD, particularly stigma around methadone. However, some participants described a process in previously accessing methadone treatment, where they reassessed their biases surrounding the medication and dispelled internalized myths. Jennifer (White woman, Calgary) described how she was initially influenced by her family's beliefs, who believed methadone was, "trading one drug for another drug. It's a synthetic heroin. The only difference is it is controlled by a physician," but after starting on methadone, she realized it "saved [her] life," and thus shifted her perspective. Zack (White man, Calgary), who

had previously benefitted from methadone, invoked a medicalized framing of substance use and compared methadone to other medications: "people have a bad outlook on it, but the more and more they do studies like this, they look into the addiction and it's, at the end of the day, a form of mental illness. And for most mental illnesses, the best form of treatment is medication." This initial process of revising their previously held beliefs around methadone may have influenced some experienced participants' willingness to be randomized, or potentially protect them against the impact of internalized stigma.

Though experienced participants were open to trying methadone again, some maintained concerns about methadone ensnaring people into long-term dependence. The cultural narrative of methadone as "liquid handcuffs" (Holt, 2007; Malvini Redden et al., 2013; Schlosser, 2018) was frequently invoked in reference to the treatment regimen, signaling the symbolic meaning of medication (Montagne, 1988). Methadone was also commonly described as a "crutch" or just a replacement, echoing previous research on internalized stigma and language (Malvini Redden et al., 2013). For instance, Amanda (White woman, Calgary) shared: "I hate the idea of just replacing a drug with another drug which is why I came off of methadone in the first place." Several participants made similar comparisons, equating with methadone with other unregulated opioids. Andrew (White man, Toronto) believed that his doctor, "just replicated the government juice, 'Jungle Juice' as it's referred to on the street [chuckles]. Instead of me buying heroin on the street, I felt like I was getting the same in a doctor's office." This narrative around methadone as a legally prescribed but harmful opioid was reiterated by several participants, including Patrick (White man, Toronto) who did not see the value of methadone when compared to newer options:

> Methadone is liquid handcuffs. Methadone does not help people. It doesn't. It's a waste of money. It's a waste of time. It's a waste of doctors. Basically, what you're doing is you're making physicians into legal drug dealers, and that shouldn't be happening. You know, especially in a society where we have options, like suboxone

> or subutex, or whatever fucking morphine, or whatever it's called, or naloxone. You know, methadone shouldn't even be an option.

As highlighted by these quotes, experiential and cultural knowledge engendered strong but varied opinions on MOUD. It may be that treatment experience reinforced beliefs about MOUD efficacy, but cultural knowledge fostered medication misperceptions, particularly around the uncertainties of long-term methadone use which could result in greater internalized intervention stigma.

"A toxic insidious thing": Lay pharmacology of MOUD. To contextualize participants' narratives of the medications and their effects, I draw on Webster and colleagues' (2009) conception of "lay pharmacology," in which participants' make sense of the medication through its safety, initiation and efficacy, and effects on the body. As discussed, the familiarity of the methadone was reassuring to some experienced participants, but others expressed wariness about the novelty and safety of suboxone. Thomas (White man, Vancouver) spoke of his suspicion around previously being offered suboxone on several occasions:

> Why would [they] be pushing that so hard when they're doctors, like they should be fairly intelligent and think, "I should sit back and before I start pushing this, wait and see what happens." I mean they've been taking this [methadone] for 90 years or whatever and this [suboxone] is fairly new. I would assume it's new, I don't know, I never heard of it before. Maybe other parts of the world had it for a long time, I don't know. [Interviewer: Methadone's been around so long—] Yeah, so they know what's going on with that. So, they're pretty safe and these days you want to be safe.

In comparing the history of the two study medications, Thomas felt suboxone was still experimental and to be used with caution. Others considered the safety profile of the medication in light of broader health-related risks, such as overdose. For instance, Patrick (White man, Toronto) perceived suboxone as safer, primarily because it cannot be used in conjunction with other opioids:

> I truly think that suboxone is like the best way to cure addicts right now. Like it's the best way to keep them alive, that's for sure. Even if they try to use a high amount

> of drugs, they probably won't kill themselves, just because there is naloxone in their system. And that alone is beneficial. With methadone, it's just the worry of how many people are either going to be addicted to it or die from it, or die because of it, or die from the side effect of being high on it when using drugs. There's no negative things to go along with suboxone. There's so many negative things to say about methadone, and I can't say one negative thing about the suboxone. So that should speak volumes.

In describing the perceived safety of suboxone, Patrick contrasts it with methadone, which can contribute to overdose risk. Some experienced participants made broader critiques of the RCTs testing MOUD, amidst growing support for initiatives that would provide PWUD with a reliable, safe option of pharmaceutical-grade opioids. Jason criticized the mechanisms of the currently available medications:

> They just keep coming out with all these new products that are just as shitty, that don't work. Like fuck. You know, let's take morphine and take the fun out of that too. Let's take this and take the fun out of that. And like oh, buprenorphine? Yeah, this drug's a fucking Narcan. Like whoa. Why even put it in there?

Notably, Jason critiqued suboxone for containing naloxone, a medication commonly used to reverse overdose but one that can produce adverse effects (e.g., withdrawal symptoms, discomfort, hypoxia-induced rage; Kavanaugh, 2020; Kline et al., 2020; Parkin et al., 2020). In considering the safety of the study medications, the relative novelty of suboxone was a concern for some but paled in comparison to the broader threat of the ongoing overdose crisis.

Another primary concern for participants was the initiation and efficacy of the study medication. Drawing on their previous treatment, experienced participants generally presumed methadone would curtail their withdrawal symptoms, but they felt it would take time to access a fully beneficial dose. As Jessica (White woman, Vancouver) remarked, "I'm happy that I'm back on the methadone. I just want to get on a stable dose and start feeling good again. Like not feeling like I have not enough methadone and I have to use at the same time." Another participant, Lisa (Indigenous woman, Vancouver), was also anticipating a higher medication dose: "It's hard. I like

the way they had it before, where they would just give me the whole bunch straight up because, obviously, I got a high tolerance for dope. I think I've only OD'd [overdosed] once when the fentanyl came out. And I think the doctors should know that I'm not going to OD from methadone." As Lisa observed, the potency of fentanyl made it challenging to wait for her methadone dose to be increased to a sufficient amount. Concerns around suboxone efficacy were noted as well, as some participants argued that it did not address opioid cravings. Jason (White man, Vancouver) recalled: "[Suboxone] helps with the symptoms, but it doesn't help with the cravings at all. You still crave the drugs. You just don't feel dope sick but it's really uncomfortable because of that." For this reason, Justin (White man, Vancouver) did not see suboxone as useful, "I just find [suboxone] makes you not get as sick or whatever, but it doesn't do anything for cravings. You get a pill put under your tongue that tastes like metal. It's garbage." However, experienced participants seemed most concerned about suboxone initiation and possible withdrawal symptoms, like Jennifer (White woman, Calgary) who recalled feeling "scared shitless with the suboxone." Several participants had experienced precipitated withdrawal while trying suboxone previously, an experience that seemed most frightening when suboxone was acquired via nonmedical sources and used in isolation. Mary (Indigenous woman, Vancouver) recalled, "I bought it and tried it at home and it was all bad. I was so scared that it was like a bad reaction. It threw me into a withdrawal. Like I was throwing up and just kicking around. Yeah, it was bad. I'm not touching that no more." Greg (White man, Calgary) detailed his hesitation around intentionally experiencing withdrawal prior to suboxone initiation and aptly described the looming threat of precipitated withdrawal:

> I didn't like the fact that you had to get dope sick before you could start taking [suboxone]. Because it's hard to let yourself get dope sick. You know, especially if there's a drug around that makes you feel better. It was hard to let myself get to feel that bad, because if you didn't, then they would have—it's called precipitated

> withdrawal because you're not really in withdrawal yet but because you take that drug, it makes you almost instantly go into withdrawal. And then it's really hard on you. Like it's not a gradual thing, a gradual "I don't feel good. I don't feel good. I'm feeling worse, feeling worse, and I feel horrible." It's right from "I'm okay" to "I feel horrible." There's no in-between because of the suboxone. So I wouldn't want to go on it again if I don't have to.

Donna (White woman, Calgary), who self-medicated for chronic pain, added that the withdrawal prior to suboxone initiation would be compounded by intense pain: "So it's not only dope sick; it's fucking pain too, right? So it's like a double whammy for me. So that kind of scared me away from the suboxone." Like this participant, several people expressed they would prefer methadone, not because they particularly liked methadone, but because they were hesitant to experience withdrawal symptoms. Still, many experienced participants remained open to trying suboxone as they anticipated their experience initiating medication in the trial may be different.

In their lay pharmacology narratives, a final observation among this group was the experienced or anticipated effect of the medication on the body. Methadone was associated with several side effects, including constipation, weight gain ("guys gain so much weight"), grogginess, excessive sweating ("I'd wake up just drenched in sweat at like five in the morning"), decreased libido ("my sex drive is gone with methadone"), or difficulty transitioning off of methadone ("It was a 21-day withdrawal…I survived it and I'll never touch methadone again"). In contrast, many experienced participants viewed suboxone as "healthier," lacking the same side effects on the body as methadone. This "healthy" perception may have been attributed, in part, to its pill formulation, as Louise (White woman, Montreal) explained: "I think that the fact it's a pill, it's less—in my head, right now, it's a new thing. In my brain, a pill is made to heal you." Many participants cited what they believed to be the current medical consensus on suboxone and that most doctors were proponents of suboxone as a healthier MOUD. For example, Zack (White man, Calgary) stated:

> It looks like [suboxone] is healthier. It's not another opiate, right. I guess it takes away that shroud that you're replacing it for another opiate. You're actually kicking all the—well there is a part of an opiate in it, but yeah, it's the better of the two probably. The doctors seem to think so. When you look at the facts alongside each other, the pros and cons of suboxone outweighs methadone by a bunch.

In such instances, experienced participants seemed to bolster their lay expertise around MOUD by referencing medical evidence that prioritized suboxone over methadone. However, when assessing potential long-term health effects, the cultural embeddedness of this lay pharmacology became clear. Experienced participants felt substantial uncertainty about long-term MOUD use, particularly around the effects of methadone on their body. They felt methadone had the potential to rot their teeth, damage their bones ("And I don't know what the danger of the methadone being in your bones is," Sandra, White woman, Vancouver), or that methadone was in some way toxic. Justin (White man, Vancouver) argued that although methadone was better than unregulated opioids, he was wary of long-term use: "Methadone is shit in and of itself because it makes your teeth fall out over time and shit like that. But I've always used it as something to taper off of eventually, but I've never been on it for longer than four or five months." Consistent with this symbolism of methadone as harmful or poisonous, Bill (Indigenous man, Calgary) explained his perception of withdrawing from methadone: "It's not just being clean, it's the severe sickness from methadone. Like it's such a toxic insidious thing in your body that there's something you take to actually have the toxins pushed out of your body. Like because it gets in your bone marrow and stuff." After years of opioid use, experienced participants were searching for long-term treatment solutions and thus concerns about the long-ranging effects of MOUD were a focal point.

"It depends on what you want": Treatment comparisons. Given their treatment and drug cultural experience, these participants were well-positioned to draw distinctions between the perceived effectiveness of methadone versus suboxone. Ultimately, experienced participants were

highly nuanced in their comparisons of the applications of the two study medications and described how each treatment might differently support individuals' goals for their substance use. Many felt suboxone would be most helpful for people who were ready to stop using opioids entirely "if someone's mentally ready for treatment" (Andrew, White man, Toronto). In contrast, they felt methadone could be used as a supplement for those who wanted to reduce their opioid use or try a safer alternative to unregulated opioids. Jason (White man, Vancouver) appreciated methadone "because I get the benefit of getting off of street drugs, but I also get what I need for myself in order to function properly. Like more like as a replacement therapy as opposed to using it to quit." At times, these sentiments echoed the tenets of harm reduction to "meet people where they're at" ("Principles of Harm Reduction," 2020), which likely reflect these participants' cultural experience in drug scenes and the harm reduction services that they were likely to be exposed to as a result. Sam (Indigenous man, Vancouver) compared what he felt were the objectives of the study medications and positioned himself accordingly:

> I think they'll find between methadone and suboxone that the people going on to suboxone are people that are truly wanting and ready to have sobriety and that people on methadone are probably people that are kind of halfway over the fence. You know, still want to use half the time and methadone allows for continued use. Which isn't necessarily a bad thing, but I think it's just a different step to actual sobriety. I think suboxone's a great—I felt great on it, but I just wasn't ready to be sober. I still had the desire to put a needle in my—so I think that when I am ready for it, suboxone'll probably be a great choice for me.

Still, a few participants expressed greater alignment with abstinence-based treatment approaches where "sobriety" is the ultimate goal. Danielle (Indigenous woman, Vancouver) equated suboxone adherence with success: "It depends on what you want, right? It depends. Like the suboxone's more of a long-term success story, you know? And methadone is more a long-term, keep going with your drug addiction [Laughs]." Though these perceptions around "success" reflect broader

societal narratives and norms around drug use, they may also set participants up with weighty expectations for their study participation.

With previous histories of MOUD and significant cultural knowledge around drug use, drug scenes, and treatment, experienced participants cultivated a lay expertise over time and expressed stronger opinions than other groups. They largely relied on their own experiences to inform their medication perspectives in terms of safety, efficacy, and side effects, but this lay pharmacology was still culturally embedded, reflected in participants' narratives of methadone stigma and "toxicity." Still, these negative conceptions did not deter them from enrolling in the OPTIMA study, but perhaps offered them a more realistic understanding of the study medications, which may ultimately have protective effects against misperceptions of the study (Jaffe et al., 2021b).

2.3.3 Semi-experienced participants

"Everybody says...": Second-hand medication perceptions. Semi-experienced participants enrolled in the trial without previous MOUD experience but possessed cultural knowledge and were often entrenched in drug scenes, leaving them privy to others' MOUD narratives. Unlike experienced participants who cultivated a lay medication expertise over time, semi-experienced participants developed medication perceptions through informal knowledge networks. Some of these perceptions were positive, where semi-experienced participants knew someone who had tried MOUD and were "successful," or they had "heard good things," that "people say it's kept them sober" (Cody, White man, Calgary). However, the majority of semi-experienced participants' initial perceptions of the study medications were negative, potentially due to negativity bias, in which people recall negative experiences more readily than positive ones (Rozin & Royzman, 2001). These drug scene acquaintances may have been more likely to recount

instances where they experienced adverse effects or when treatment went poorly, and OPTIMA participants were more likely to recall these stories. For instance, Gary (White man, Vancouver) shared that when he told his network in a local drug scene about the study, they advised him against methadone: "About nine people. Every one of them said the same story. It's a nightmare for them." As recipients of cultural narratives around MOUD without personal treatment experience to temper their expectations, semi-experienced participants were more apprehensive about the study treatments.

Like other participants, semi-experienced participants were most familiar with methadone, but the perceived stigma associated with methadone was substantially greater than for experienced participants. Semi-experienced participants tended to separate themselves from other PWUD they felt to be more appropriate candidates for methadone treatment. These statements included people who used opioids with greater frequency or intensity ("I don't think I'm in that level or bracket of drug users" James, Indigenous man, Vancouver), people who used heroin ("Isn't [methadone] a synthetic heroin? Ugh, no thank you. Might as well shoot me up with a needle of heroin." Kim, Indigenous Trans woman, Vancouver), and people who injected drugs ("But I hadn't done needles before. And I thought [methadone] was mostly for guys that did needles, right?" Robert, White man, Calgary). These statements linking methadone to groups of PWUD demarcated a boundary between semi-experienced participants and a maligned "other." Extending from this "othering" work, semi-experienced participants viewed methadone as something that could be diverted, manipulated, or used incorrectly. Cody (White man, Calgary) noted how methadone can be misused in contrast to its intended purpose: "I had seen some people who were on methadone but maybe they weren't doing it properly, so they kind of seemed like it was altering their sobriety a little bit. Like they kind of seemed like maybe they were getting a little bit of a high from it." In a

similar sense, Tyler (White man, Vancouver) reiterated that he wanted to be randomized to suboxone, "because there's no way—there's no room for a true addict to manipulate it, right? Like, you can get high on methadone. You can manipulate the doctor to get you on a ridiculous high dose before even fucking testing your heart for anything, testing anything." In this quote, Tyler alludes to some internalized drug-related stigma (e.g., "true addict") and frames PWUD as potentially deceitful and manipulative. However, this MOUD narrative also highlights the strategies that stigmatized PWUD employ in order to access adequate treatment in health settings. Without treatment experience to reference, the cultural, social, and symbolic meaning surrounding MOUD may have greater salience for semi-experienced participants, and stigma may extend beyond the treatment and potentially internalized as a trial participant.

While semi-experienced participants were very familiar with methadone, there was range of knowledge around suboxone. Some participants believed the medications to be similar, that "they did the same thing. I thought suboxone's just a pill you take and methadone's just a drink," (Matt, White man, Vancouver). Potentially as a result of misconstrued lay pharmacology, Matt encountered difficulty initiating treatment: "I thought that I was going to be able to continue using opiates while I was on suboxone and I didn't know until I got home when I started researching on my own about how it kicks you into instant withdrawal" and recalls "suffering for two days." In sourcing second-hand information, primarily from people they knew who had tried MOUD, participants came to their own understandings about suboxone. After observing his girlfriend on suboxone and conducting additional internet searches, Chris (White man, Vancouver) developed positive beliefs: "I think the health care professional probably wants to [prescribe suboxone], both the nurses and the doctors. Like I went through the literature too when I was helping my girlfriend and it's pretty much a no-brainer. Methadone is a highly addictive substance. The only worse one's

morphine, which is even worse than heroin." It is noteworthy that again, positive aspects of suboxone are weighed primarily in contrast with and in response to negative evaluations of methadone. However, some participants observed friends that had negative experiences with suboxone, which effectively shaped their perceptions of side effects, medication mechanisms, and efficacy. Jean-Marc (White man, Montreal) recounted that his girlfriend had tried Suboxone, "which meant that I really saw what it did. It really left her with big cravings. She changed to methadone for that, because the methadone would take away her cravings, compared to suboxone, which would leave her with, like, desperate rage." Though open to being randomized, after observing his girlfriend's experience, Jean-Marc expressed a preference for methadone. Finally, there were a few participants who had tried nonprescribed suboxone without medical guidance, and these experiences were largely negative. Sophie (White woman, Montreal) received suboxone from a friend, who had "extras of the suboxone pills. She told me, 'Start with 4 milligrams. After that, you'll see.' Listen, I'd never been that bad before in my whole life!" and went on to describe the withdrawal symptoms as "hell." While Sophie's experience does not constitute a lay expertise developed over time, her quote highlights how even brief, one-time interactions with medication could drastically shift treatment perspectives. Overall, semi-experienced participants relied heavily on the experiences of other PWUD to fill in their own gaps in medication knowledge, and thus their treatment perceptions largely reflected feelings of apprehension, stigma, and criticism.

2.3.4 Inexperienced participants

"I went to look for more information": Sources of authority. Without the lay expertise of previous MOUD experience or access to informal knowledge networks of other PWUD, inexperienced participants were limited to a few other external sources to develop their understanding of the study medications. For many inexperienced participants, study enrollment

was their first opportunity to hear detailed, evidence-based information about the two study medications. Potentially as a result of this lack of previous knowledge, inexperienced participants seemed to have fewer concerns about side effects or long-term toxicity than the other groups. For instance, some inexperienced participants believed methadone to have fewer side effects than suboxone. Keith (man, Toronto, race/ethnicity not given) recalled, "when [the study staff] were describing the side effects of the methadone and the suboxone, methadone sounded a little more pleasant than the other one to me. Just sounds like there were far, far fewer side effects." In contrast to experienced and semi-experienced participants, Keith cites the study staff as his primary source of information about side effects, locating authority and expertise in the researchers conducting the study.

Beyond the information gleaned from study enrollment, participants also developed medication perceptions based on other external sources, including family and friends who were largely not engaged in drug scenes. Brandon (White man, Calgary) relied on his family's guidance: "I probably had the most detailed conversation with my mom about it and she was worried about even being randomized. She's like, 'no, go for suboxone, hundred percent.' Like just based on what she's read in the literature and all the—well, the 'literature.' On the internet mostly." Other inexperienced participants looked further to the few acquaintances they knew who had tried one of the medications, including friends of friends, coworkers, or neighbors. For instance, as Laurent (White man, Montreal) weighed his decision to enroll, he remembered a friend of his girlfriend who struggled with injection drug use, but who was now doing well financially. Laurent noted, "The guy, he succeeded. He's really cool, and he told me, 'Hell no, you nut bar! Suboxone is way better. Methadone bloats you and everything. Suboxone is good, man!' I said, 'well, shit!'" Laurent had been initially leaning toward methadone but after speaking with this acquaintance who was a

suboxone "success story," his treatment preferences shifted. Like semi-experienced participants, without previously trying the study medications, inexperienced participants gathered information from anyone with insight, but unlike the semi-experienced group, this second-hand information was not moderated by cultural knowledge or overtly negative treatment experiences (e.g., MOUD "horror stories").

Despite gathering information from multiple sources, many inexperienced participants were left feeling anxious and confused about how the medications worked. Edgar (White man, Montreal) was cautious about randomization based on his reading: "I hesitated because of the suboxone because when I went to read more—went to look for more information, it said that it was a lot harder to treat chronic pain with that than with methadone. So that gave me a certain kind of stress." Amber (Indigenous woman, Calgary) recalled hearing positive stories about suboxone, as well as a warning that it would, "put you into like an instant withdrawal like a really deadly withdrawal or something, I don't know. That's what confuses me too." Alain (White man, Montreal) voiced similar concern around withdrawal and tapering off suboxone:

> The only worry I could have is, what kind of withdrawal is it? Because you have to make people aware when you give them a medication, the withdrawal that will follow, what happens afterwards? It's hard for a doctor who hasn't taken it, and who doesn't know, and who says, "Yes, you'll have a bit of withdrawal." A bit of withdrawal, what does that mean for you people, a "bit of withdrawal"? A guy who does 100 mg of morphine a day, he doesn't get a "bit" of withdrawal. He collapses at home, and he's in pain, and he rages and cries at home.

Even with well-known, established medications such as those in this pragmatic trial, uncertainty and misperceptions were evident. Though it is unclear why participants did not always consult with the study staff around these concerns, these inexperienced participants lacked the access to informal sources of knowledge reflected among the other groups.

"You really fucked up, now you're on methadone": Medication stigma. Similar to the semi-experienced group, inexperienced participants expressed negative biases related to methadone. This stigma centered around particular groups they associated with methadone, including people who use heroin ("Honestly, I thought it was for heroin addicts") and people who used injection drugs or unregulated opioids ("It's methadone if you're like a fucking street junkie who's addicted to fentanyl"). Methadone was also associated with failure: "if I was to take a step back and speak, methadone in my mind meant that like, you really fucked up, now you're on methadone" (Jacob, White man, Toronto). Susan (White woman, Vancouver) ultimately withdrew from the study because she did not want to take methadone nor be seen around methadone clinics. Susan described these parts of her neighborhood as "sketchy" (i.e., unsafe, suspicious) and feared, "if I'd gone in the study, I might have had to go [to the clinic] and get it every day, and a lot of these people are scary around here. And I just didn't want them to see me going into a place like that, and then see me in the grocery store, see me there. I just—I couldn't do it." Another participant, Nick (White man, Calgary), felt that upon enrolling in the OPTIMA study, his opioid use was not severe, but after initiating methadone, took on a new stigmatized identity: "I'm stuck here on methadone now and they treat me like a drug addict, when I came in as a dependent. It's been awful, awful, awful." This participant had originally been randomized to suboxone but due to adverse effects, he switched to methadone, which was permitted in this pragmatic trial. When asked to compare this to his suboxone experience, Nick did not perceive the same degree of stigma, "because nobody knew; it was just a pill. They don't see me going and taking a shot and signing off every single day at the pharmacy. It's kind of hard to hide something that you do every single day in your neighborhood."

In addition to stigma toward other PWUD accessing methadone, inexperienced participants also held negative perceptions of the medication's mechanisms. Inexperienced participants believed methadone was "really addictive," it was "going to be just another problem afterwards," and that it was "like 10 times worse than the drug I'm on right now. It's harder to get off." Amber (Indigenous woman, Calgary) described it "like replacing a drug with another drug is what I'm told. And it's like a government funded drug, right, so if the government was to stop funding it then I'd be stuck on it and I would probably be, you know—I'd eventually end up suffering anyways in the end." Many participants held the belief that people stayed on methadone long-term and saw this as undesirable. Tina (Indigenous woman, Toronto) recalled, "I know someone who was addicted to Oxys [oxycodone] before and she's on methadone and she's been on methadone for like six years, which is nuts cause I feel like you're just getting addicted to another thing." David (White man, Montreal) echoed this sentiment: "Well, methadone, to be honest with you, my brother is on it and he's always dependent on it. I didn't want to get to that stage." Stigma around long-term MOUD may be especially intuited among inexperienced participants because the duration of their substance use tended to be shorter. These participants may have just recently begun to consider the idea of their opioid use as problematic, along with the idea of treatment. Edgar (White man, Montreal) described the challenge in making this mental shift:

> It's [difficult] to accept that I'm obligated to take a medication, and to have recourse to methadone every day. I'd accepted that I had a problem with no issues. With that, I came here because I knew—I'd accepted it. But when I realized that I was going to be stuck with [methadone] for an indefinite amount of time, that really disturbed me then, because I don't like medications. I'll be honest with you, right now, if I could eliminate everything, I would. I've tried everything all my life to avoid doctors, avoid medications, to avoid all that as much as possible. So for me, it was like a bit of a blow to my ego.

In combination, the emotional challenges of substance use treatment, the logistical burden of a strict medication regimen, as well as an undetermined treatment duration after the study may have

been especially difficult to contemplate for inexperienced participants. Without the lay expertise or drug cultural knowledge of the other groups, inexperienced participations gleaned information from sources they trusted including family or friends, research staff, online sources, and when possible, acquaintances with MOUD experience. In this process of generating information, participants began to make sense of the medication, even before initiating treatment (Cohen et al., 2001). However, through this process inexperienced participants also grappled with the new illness identities (i.e., opioid use disorder) and the new routines that MOUD entailed (Carder et al., 2003).

By characterizing participants beyond surface-level demographics or clinical indicators of addiction, these results highlight how the accumulation of treatment experience and cultural knowledge can shape trial participant perspectives. Experienced participants were outspoken about the study medication; they described their experiences, public perceptions of MOUD, and a lay pharmacology of medication mechanisms, benefits, and side effects. Experienced participants also had a more nuanced perspective of the medications, in terms of treatment goals and around the duality of MOUD as *pharmakon,* as both beneficial and potentially harmful (McCradden et al., 2019). Semi-experienced participants relied on the second-hand treatment perspectives of their friends and acquaintances in drug scenes, where MOUD seemed to have largely negative connotations and greater medication resistance. Inexperienced participants entered the study without much knowledge of the medication other than media representations of methadone, and through their narratives around joining the study, seeking information, and drawing conclusions, the processes of meaning-making around the medication became visible. In all cases, participant narratives belied an important relationship between sources of knowledge and medication perspectives, mediated in specific ways by relative levels of personal experience and exposure to drug culture.

2.4 Discussion

The aim of this nested qualitative study was to explore medication perceptions and lay expertise in the context of a clinical trial. By focusing on the unique impacts of participants' personal experiences and exposures, I observe how lay expertise of MOUD is constructed and how participants access informal expertise through other key sources, all of which shapes their perceptions of the study medication. Depending on their level of drug cultural and treatment experience, participants made diverse assessments of the strengths and weakness of the study medications, their effects and mechanisms of efficacy, and degrees and types of stigma they associated with the treatments.

2.4.1 Medication perceptions

Perceived benefits. By nature of their enrollment in the trial, all participants saw some potential benefit in the study medications but the perceived degree of benefit and countervailing negative perceptions varied across participant groups. Experienced participants had the most developed opinions of the medications, and their preferences were attributable to familiarity ("I knew what to expect"), health (e.g., perceived benefit versus toxicity), and previously experienced efficacy. While some of their MOUD perceptions may be scientifically false as "lay" people, it is more sociologically relevant to focus on beliefs and attributed meanings that directly shape their study experiences and expectations. Generally, experienced participants felt positively, and some remarked on how MOUD had previously saved their life while others commented on the medications' broad potential to reduce overdose and save lives, evoking the study context of the overdose crisis and a potential link between study enrollment and reducing mortality. In addition, experienced participants employed a lay pharmacology to differentiate the mechanisms of the study medications and, by extension, could evaluate how they might be used to meet various

substance use goals, which is consistent with previous research on preferences in clinical care (Bishop et al., 2019). This flexible evaluation contrasted from perceptions of the inexperienced participants who tended to view opioid use as unambiguously negative, but that the two study medications would be similarly helpful in their capacity for addressing problematic use. There were a few semi-experienced and inexperienced participants who recalled motivational "success stories" of people who had fared well on MOUD, highlighting some advantages of social networks for health-promoting behavior. However, for PWUD there may be issues in making such comparisons and setting similar expectations, given the unique circumstances surrounding individual substance use patterns, structural barriers to trial participation and medication adherence and, as this analysis has highlighted, the broader context of social and cultural meaning around MOUD.

Perceived consequences. One of the prominent concerns among experienced and semi-experienced participants was the effects of methadone on the body. With greater certainty about the immediate efficacy, experienced participants felt more apprehension about the unknown, potential long-term toxicity, reflecting previous work on opioids as *pharmakon* (Buchman et al., 2017; Wilbers, 2020), in that MOUD is perceived to be both "remedy" and "poison." Experienced participants may have viewed the short-term, immediate certain benefits of methadone as outweighing any irksome side effects, but they demonstrated the limits of their lay expertise with questions and uncertainty around medication over the long-term. Semi-experienced participants were more concerned about immediate side effects of methadone, which were largely relayed to them by other PWUD. In these narratives, negativity bias may have played a role, where semi-experienced participants were exposed to others' largely critical accounts—a "reputationally mediated toxicity" (Strang et al., 2018, p. 592). An additional consideration is how selection effects

shape the composition of semi-experienced participants' informal knowledge networks, in which they may be more likely to connect with PWUD in drug scenes for whom MOUD was not effective, while people thriving on methadone or suboxone may not be involved in drug scenes or around the neighborhood to encourage others or share positive treatment perspectives. This highlights the "dark side" of information exchange in social networks and the way that ideas, beliefs, and behaviors can become contagion (Rozin & Royzman, 2001; Villalonga-Olives & Kawachi, 2017). In contrast, inexperienced participants seemed to rely primarily on health-related information from staff and were not as concerned with medication side effects or long-term consequences, likely because they had little exposure to the secondhand or informal knowledge about the medications. It may also be that compared to experienced participants seeking longer-term options, inexperienced participants who recently identified their opioid use as problematic may be seeking short-term solutions or conceptualizing the six-month study treatment as time-limited, and so long-term toxicity was not a concern. In some ways, this group of inexperienced participants may be similar to study populations in early phase RCTs with fewer preconceived notions around novel medications, but the stigma around opioid use and MOUD remained.

In comparing treatment preferences in standard clinical care, some scholars have noted that PWUD may prefer suboxone over methadone for its fewer side effects (e.g., less drowsiness) and reduced stigma (Bishop et al., 2019; Hill et al., 2015; Scorsone et al., 2020; Tanner et al., 2011; Yarborough et al., 2016). While this study supports these findings and many participants felt positively toward suboxone, concerns among participants persisted. Although some experienced participants trusted suboxone and were encouraged by the pill formulation as comparable to other standard medical treatments typically in pill form, others worried about its relative novelty compared to methadone, which has been in use since the 1960s. In part, the unfamiliarity with

suboxone likely stems from decades of clinical guidelines recommending methadone as a first-line treatment, so participants who previously accessed treatment were more likely to be offered methadone by past care providers, if offered MOUD at all (Kimber et al., 2015; Mackey et al., 2020; Socias et al., 2018). Recent research has also shown unfamiliarity with suboxone to be associated with hesitation around treatment (Weicker et al., 2019). However, both groups with drug cultural knowledge were most concerned about experiencing precipitated withdrawal when taking suboxone as they were likely familiar with the extreme discomfort of withdrawal. While this issue has been identified in some previous qualitative research (Egan et al., 2011), this analysis found that the threat of precipitated withdrawal was troubling enough that some participants expressed preference for methadone, even if they generally disliked methadone. This finding largely diverges from existing research on patient preferences for suboxone over methadone (Bishop et al., 2019; Hill et al., 2015; Scorsone et al., 2020; Tanner et al., 2011; Yarborough et al., 2016). While reasons for such inconsistency are uncertain, it may be that previous analyses focused on post-initiation treatment satisfaction, in which concerns about withdrawal are less salient in light of treatment progress, whereas this analysis largely draws on interviews conducted prior to treatment initiation and captures participants' real-time expectations and apprehensions. This variation may also be attributed to features of the local environment, as participants in this study may be more experienced, and thus had more treatment knowledge than PWUD in other locations. Additionally, the local drug supply, particularly in western Canada, is largely comprised of illicitly manufactured fentanyl (Bouchard et al., 2020) and, thus, withdrawal preceding suboxone initiation may be more challenging and anxiety-laden than in previous years or other contexts (Brar et al., 2020; Randhawa et al., 2020). These results demonstrate that understandings of medication are

shaped by the local context and constantly in flux—aspects of participation that may be of key relevance to pragmatic RCTs assessing acceptability in real-world settings.

2.4.2 Stigma

Stigma around medications for opioid use disorder has been well documented, with extensive research exploring how MOUD has been equated with poverty, racial biases, and a range of harmful stereotypes (Earnshaw et al., 2013; Gryczynski et al., 2013; Harris & McElrath, 2012; Malvini Redden et al., 2013). This "intervention stigma" (Madden, 2019), or MOUD stigma, has been attributed to a number of adverse health outcomes, including underutilization of treatment and poor patient care (Allen et al., 2019; Mackey et al., 2020; Madden, 2019; Yarborough et al., 2016). However, little research has assessed the perceptions of such highly stigmatized medications in a randomized controlled trial. To address this, the current study analysis reveals how stigma informed participants' perceptions of the medications in distinct ways and to varying degrees, woven into their own lay expertise or informal knowledge they received. Experienced participants recognized MOUD stigma, and some described how they learned to manage or reframe their own perceptions, a form of "stigma resistance," in which participants protect their self-esteem (Thoits, 2011). Other experienced participants perceived stigma around long-term MOUD treatment, reflecting a lay pharmacology (Webster et al., 2009) that was culturally embedded in medication narratives about the toxicity of methadone.

Both semi-experienced and inexperienced participants' narratives revealed how they attributed stigma to MOUD which was expressed among their friends, acquaintances, or in the media. First, both participant groups expressed condition stigma around substance use, particularly against people with more intensive drug use patterns, who they perceived as more deserving of a treatment like methadone. These stigmatizing remarks were especially disparaging within the

inexperienced group, the members of which may be struggling with more recent diagnoses and illness identities around substance use disorders (Carder et al., 2003; McCradden et al., 2019). Engaging in "othering" or expressing stigma toward other PWUD may be a form of "stigma power," enacted to differentiate themselves or protect themselves against widespread social stigma around drug use (Link & Phelan, 2013; McCradden et al., 2019). Second, there seemed to be intervention stigma around mechanisms and components of the treatment itself. For instance, participants referred to the treatment as a "crutch" or "highly addictive." Some feared being seen at the methadone clinic, which may indicate some "treatment carryover" in which participants believed that the disclosure of their treatment would threaten their social position (Pescosolido & Martin, 2015). Finally, there was some evidence of internalized stigma where participants expressed feelings of shame and failure around their prescription opioid use and accessing help—perspectives that are intricately linked to broader social stigma around substance use and MOUD treatment (Pescosolido & Martin, 2015; Tsai et al., 2019). There are few other illnesses or associated treatments that are stigmatized to such an extent and thus very few empirical models of RCTs that incorporate efforts to destigmatize treatments. However, it may be that aspects of research participation, including receiving treatment from nonjudgmental research staff or general feelings around contributing to scientific research, may work to counteract internalized stigma.

2.4.3 Implications for randomized controlled trials

Although significant research has explored concerns around medication preferences, recruitment, and study outcomes (King et al., 2005), these results highlight the potentially beneficial impact of lay expertise on medication perceptions and trial enrollment, as well as treatment-naïve participants. Despite their established views, experienced participants generally expressed openness to both study medications as they had gone through a process of demystifying

and destigmatizing MOUD and possessed the knowledge to weigh medication risks and benefits and consider treatment similarities and differences. These previous experiences may provide some protective effects against internalized stigma as well as other factors that contribute to study withdrawal. For instance, experienced participants may be best prepared for managing the logistical burden of daily witnessed dosing. In terms of data, experienced participants might also provide the most detailed information about dosing and the embodied medication effects, and may even be considered a resource in the design of future pragmatic substance use RCTs to improve the relevance and effectiveness (Dresser, 2018; Greer et al., 2018). However, one potential concern around this expertise is reflected in the fact that very few participants in the experienced or semi-experienced groups mentioned study staff as a primary authority on medication information. The absence of health researchers as a trusted authority in the eyes of experienced participants could allow for the spread of or reliance on misinformation. To avoid the potential for pitting local and experiential knowledge against scientific/medical knowledge, researchers should consider strategies for opening lines of communication around medication perceptions and, with care and respect, address MOUD myths that may be circulating through informal networks. Conversely, inexperienced participants' patterns of confusion, worry, and external pursuits for supplemental medication information highlight the heterogeneity of PWUD and potential assumptions around baseline levels of treatment knowledge across study populations. In order to supplement treatment knowledge and address medication misperceptions, researchers should explore existing conceptions of medications through discussion prior to enrollment and allow additional time for questions and deliberation prior to randomization.

2.4.4 Limitations and conclusion

This analysis has some limitations. First, this sample is composed of a subset of OPTIMA participants whose experiences may vary from those of other PWUD who are not eligible or willing to participate in this RCT or lack access due to structural considerations, such as gaps in medication coverage or distance from providers prescribing MOUD. Second, there was an uneven distribution of treatment and drug cultural experience across study sites (e.g., there were more experienced participants in British Columbia and Alberta). In part, this was due to the larger number of ORAS participants recruited at those sites and site-specific features (e.g., recruitment location) that shaped the overall trial population, as described further in Chapter 4. Third, there are additional factors that fall beyond the scope of this paper (e.g., local drug supply and potency; structural barriers to MOUD) that also inform medication perceptions and stigma. For instance, views may be shaped by the availability of prescription opioids (versus unregulated illicitly manufactured opioids), the acceptability of the treatment regimen, or the broader NIMBY-like stigma that concentrates methadone clinics in some neighborhoods while restricting them in others (McElrath, 2018). Finally, in focusing this analysis primarily around cultural and treatment experience, I was not able to focus on contextualizing all participants' experiences within their unique social positions, but I recognize that gender, race, ethnicity, age, and other characteristics play significant roles in structuring participants' study experiences and perceptions. For instance, previous research has shown that race and ethnicity likely shape MOUD access (Hansen & Roberts, 2012). Future research should grant further consideration to social positions as shaping medication perspectives among potential participants.

Given the need for additional treatments for opioid use disorders, it is crucial that PWUD are included in clinical trial research. But beyond measuring the primary trial outcomes, it is also

essential to understand how study participants themselves are influenced by broader social and structural influences and have the potential to offer key contributions to how medications are socially constructed and perceived. Considering these themes, future research should seek to develop a standardized metric to assess experience, understanding, and preferences around medications to be utilized in pragmatic trials as participants enroll. By drawing on participants' lay expertise and cultural knowledge, researchers can explore both pharmacological mechanisms and embodied effects as well as the meaning embedded in medicines and medication experiences and, particularly for MOUD, the cultural meanings associated with medicine. This study is one of the first to explore medication perceptions outside of clinical care among PWUD as well as lay expertise among PWUD within a real-world substance use trial. These findings contribute to emerging research on the sociological significance of medications, particularly in sites of medical knowledge production, and lay the groundwork for innovations in the design and implementation of RCTs with marginalized populations.

Table 2-1. Distribution of treatment and drug cultural experience across OPTIMA sites, n=75

	British Columbia, n=24	Alberta, n=20	Ontario, n=15	Quebec, n=16
Experienced, n=41	15 (62.5%)	15 (75.0%)	4 (26.7%)	7 (43.8%)
Semi-experienced, n=16	7 (29.2%)	2 (10.0%)	4 (26.7%)	3 (18.8%)
Inexperienced, n=18	2 (8.3%)	3 (15.0%)	7 (46.7%)	6 (37.5%)

Note: Percentages are column percentages.

3 "To become a part of society": Instrumental, altruistic, and social motivations to participate in research among people who use drugs

In randomized controlled trial (RCT) research, investigators have increasingly focused on understanding participant motivations to enroll in health research studies, with particular emphasis on the recruitment of underrepresented, "hard-to-reach" or "hidden" populations such as racial and ethnic minorities and people who are socioeconomically marginalized, unstably housed, or street-involved (Bonevski et al., 2014; Epstein, 2008). In parallel, the growth of addiction medicine and clinical trials for substance use disorders requires the recruitment of people who use illicit drugs (PWUD), another hidden population that experiences structural (e.g., access) and social (e.g., discrimination) barriers to healthcare (McKnight et al., 2017; Paquette et al., 2018; Robbins et al., 2010). While studies in public health and epidemiology have identified recruitment challenges among PWUD in the fields of HIV and Hepatitis C research, much of this research focuses on hypothetical willingness to participate (Buchbinder et al., 2004; Park et al., 2012; Uhlmann et al., 2015; Yakovenko et al., 2019) or distinct design features that shape enrollment, such as study stipends (Festinger et al., 2008), the burden of study procedures (Neale et al., 2018), or the marketing of the study treatment (Tompkins et al., 2019). However, more research is needed around PWUD's motivations within the broader social context, one in which substance use is highly stigmatized and PWUD face varying degrees of social isolation, stigma, alienation, and discrimination. In this chapter, I explore motivations for research participation among PWUD by drawing on 115 qualitative interviews with 75 participants enrolled in a pragmatic randomized controlled trial for opioid use disorder. Through this analysis, I argue that PWUD's motivations and decision-making processes are multifaceted and complex but uniquely informed by their social relationships, socioeconomic position, and feelings of connectedness to community.

3.1 Background

For sociologist Robert Merton, two key components of social structure were relevant to the study of deviant behavior: "culturally defined goals, purposes and interests"; and the regulating mechanisms to achieve those goals, or "institutional norms" (Merton, 1938, p. 672). Merton proposed that "success" implies these two phases are in equilibrium, where an individual satisfactorily accomplishes goals through socially acceptable channels such as, financial advancement through formal employment. Without this balance, Merton argued, "the integration of the society becomes tenuous and anomie ensues" (Merton, 1938, p. 674) or, in other words, social instability results. He proposed five sub-types of resulting adaptations in which the cultural goals and norms are each either accepted, rejected, or substituted with different goals or norms. To Merton, people who use drugs (explicitly, "chronic drunkards and drug addicts") were those who had rejected both cultural goals and institutional norms, making them "true 'aliens'" (1938, p. 677). According to this strain theory and proponents of its subsequent derivations (e.g., general strain theory; Agnew, 1992; Cloward & Ohlin, 1960), such structural tensions directly contribute to alienation and substance use. While etiological understandings of problematic substance use have since evolved, sociological research continues to link the social construction of drug use to stigmatizing processes (Kulesza, 2013; Kulesza et al., 2016; Rhodes et al., 2005; Room, 2005) which can result in social isolation, a feeling of lack of purpose or power, and meaninglessness (Ahern et al., 2007; Cole et al., 2011; Gryczynski et al., 2013; Haritavorn, 2019; March et al., 2005; Sibley et al., 2020)—all key components of alienation (Seeman, 1959).

In reducing feelings of alienation, work can be a central organizing feature of many people's lives as it structures daily schedules, economic and social status, and relationships (Jahoda, 1982; Kalleberg, 1977). However, many PWUD experience barriers to accessing formal

employment due to drug-related stigma from employers, criminal justice involvement, or substance use patterns (Pescosolido & Martin, 2015; Richardson et al., 2013). In most jurisdictions, drug use is simultaneously medicalized and criminalized, and thus PWUD are regularly subjected to mechanisms of surveillance and control within the medical or criminal justice systems, which produce additional barriers to work (e.g., daily witnessed treatment; drug courts; supportive housing surveillance; Boyd et al., 2016; French & Smith, 2013; Harris & McElrath, 2012; Moore, 2011). Further, addiction stigma is amplified when intersecting with race, class, and gender (Kulesza et al, 2016), and with the institutional racism built into medical and criminal justice institutions (Alexander, 2011; Williams & Wyatt, 2015). These processes result in differences in the way and the degree to which PWUD are criminalized, medicalized, or otherwise controlled depending on their race/ethnicity, socioeconomic status, or gender, which can produce further barriers to work (Hansen & Roberts, 2012; Netherland & Hansen, 2016). With limited work opportunities, PWUD are also limited in their ability to achieve culturally-defined goals of economic stability through legitimized means (Agnew, 1992; Merton, 1938). Through these processes of stigmatization and socio-economic marginalization, PWUD may feel further alienated from broader society. To generate enough income to survive, PWUD engage in alternative income-generating activities that may be prohibited, illegal, and/or associated with increased social and structural harms, such as violence or criminalization (DeBeck et al., 2007; Jaffe et al., 2018; Richardson et al., 2015; Small et al., 2013). However, previous work has also found that PWUD would forgo such activities if provided with safe, low-threshold work opportunities (DeBeck et al., 2011). Clinical trial participation may offer such a financial incentive, as scholars have found with socioeconomically marginalized participants in Phase I trials who attempt to make a living as research participants or "professional guinea pigs" (Elliott & Abadie, 2008; Lamkin & Elliott,

2018; Lemmens & Elliott, 1999; Monahan & Fisher, 2015). For PWUD with few beneficial social or institutional connections, paid research participation may provide sense of meaning or offer some temporary existential and economic security (Thoits, 1983).

Still, there are other meaningful undertakings that shape feelings of connectedness but are not economically motivated; altruism is considered one indicator of social solidarity. Just as solidary interactions are characterized by "mutual help, harmony, love, peace, and constructive creativity" (Jeffries et al., 2006, p. 69), altruistic behavior manifests through intentional actions that benefit others, which sociologists have argued should be a universal expectation as a fundamental basis of social life (Durkheim, 1984; Jeffries et al., 2006). In more recent sociological research, altruism has been reframed as socially embedded, "prosocial behavior" (Simpson & Willer, 2015). However, a small body of research continues to focus on altruism as a motivation driven by social norms (Bykov, 2017; Piliavin & Charng, 1990; Simmons, 1991) and has linked altruistic acts to increased self-esteem and happiness, as well as engendering feelings of "mattering" and "existential security" (Simmons, 1991; Thoits, 1983). In the context of health research, extensive attention has been directed to the role of altruism in clinical trial recruitment and study enrollment, resulting in intense debate around definitions of "pure" altruism, whether altruism is necessary, and whether selfless research enrollment is even possible (Chin et al., 2016; Dixon-Woods & Tarrant, 2009; Locock & Smith, 2011; McCann et al., 2010; Williams et al., 2008). Nonetheless, altruism has been widely documented as a primary or secondary motivation to participate in studies across medical subfields, including research around HIV (Buchbinder et al., 2004; Dhalla & Poole, 2014), genetics (Hallowell et al., 2010), oncology and cardiology (Cassileth et al., 1982; Sugarman et al., 1998), and treatments for chronic illnesses (McCann et al., 2010; Scott et al., 2011). There has also been some evidence that altruism is a motivation for trial

enrollment among PWUD (Fry & Dwyer, 2001), particularly in the fields of HIV and Hepatitis C research (Barratt et al., 2007; Park et al., 2012; Treloar et al., 2010; Yakovenko et al., 2019). However, much of this work examines hypothetical willingness to participate or altruistic intentions for future enrollment versus actual enrollment and does not focus specifically on substance use treatments. For PWUD experiencing alienation or substance use stigma, the opportunity to contribute to substance use research may be especially meaningful or motivating.

Finally, social connection can reduce feelings of alienation as relationships offer a sense of meaning and belonging, cultivate a sense of personal control, buffer life stresses, and facilitate social support via emotional, informational, and instrumental assistance (Berkman et al., 2000; Thoits, 2011; Umberson et al., 2010). Role relationships (e.g., parent, sibling, friend) can also shape health behaviors via obligations or behavioral expectations and provide a sense of purpose that may lessen feelings of alienation (Thoits, 2011). In research on problematic substance use, social support has also been associated with the reduction or cessation of drug use (Brookfield et al., 2019; Granfield & Cloud, 2001; Hser et al., 2007; Panebianco et al., 2016; Savage, 2009). However, social support can be difficult to attain for PWUD. People with health conditions that are viewed as "blameworthy," as is often the case with problematic substance use (Frank & Nagel, 2017; Lloyd, 2013), are less likely to receive social support (Thoits, 2011). Further, stigma associated with substance use and stigma processes of separation, status loss, exclusion may also position PWUD for greater risk of social isolation as friends or family distance themselves (Link et al., 1997; Link & Phelan, 2001; Room, 2005). These processes of social isolation may be amplified when stigma is internalized and a fear of discrimination or judgement prevents PWUD from relying on their networks for support in treatment access or study enrollment (Ahern et al.,

2007; Harris & McElrath, 2012; Livingston & Boyd, 2010; Madden, 2019; Matthews et al., 2017; Paquette et al., 2018).

In considering the broader environment of substance use research, it is critical to understand the social context of drug use and how PWUD motivations may be informed by drug-related stigma, social isolation, and the search for purpose—in essence, feelings of alienation. Previous work has framed PWUD' motivations to participate in largely instrumental terms, such as accessing the study stipend (Abadie et al., 2019; Bell & Salmon, 2011; Fry & Dwyer, 2001; Park et al., 2012) or otherwise unavailable healthcare or treatment (Timmermans & McKay, 2009). Further, much of this work has been quantitative in nature and may limit the range of motivations that participants can express (Dhalla et al., 2010; Dhalla & Poole, 2014; Young et al., 2015), suggesting that ancillary qualitative research may provide additional depth around participants' underlying motivations (Maher & Neale, 2019). However, research on PWUD motivations to access substance use treatment have highlighted a more robust range of motives (e.g., to improve relationships with friends or family, financial concerns, health concerns, etc.; Malvini Redden et al., 2013; Scorsone et al., 2020; Teruya & Hser, 2010), signaling that RCT enrollment motivations may be more complex and multifaceted than previously thought. In light of this, I aim to investigate the multiple direct and indirect pathways through which the social context of drug use (e.g., stigma, isolation, desire for social connection) shapes motivations to participate in a substance use RCT.

3.2 Methods

As described previously, data for this study are derived from a nested qualitative ancillary study within the multi-site, phase IV, pragmatic OPTIMA trial. Drawing from 115 interviews conducted with 75 participants, the current study explores participant motivations for enrolling in the OPTIMA study. To analyze the interviews, I utilized a flexible coding approach, a qualitative

analysis method suited for large qualitative datasets (Deterding & Waters, 2018). Using nVivo software, I indexed the data with a set of indices that mirrored the content and structure of the interview guide. Then, I further synthesized the data by applying analytic codes within indices pertinent to enrollment motivations, including: housing and living; family relationships; romantic relationships; friendships; drug scene involvement; income generation; and general motivations to participate (e.g., altruism, study stipend, etc.). I used NVivo matrix coding and crosstab tools to understand the saturation of themes and to seek counterexamples (Deterding & Waters, 2018). Through this abductive approach, I am able to incorporate existing conceptualizations of research and treatment motivations and draw from sociological concepts to produce new insights around RCT participation among PWUD (Deterding & Waters, 2018; Tavory & Timmermans, 2014; Timmermans & Tavory, 2012).

3.3 Results

While many participants were motivated by rapid access to substance use treatment, upon further analysis, interviews revealed underlying considerations for enrollment that fell into three general categories. First, participants identified enrollment drivers that reflected more specific, instrumental objectives (i.e., getting money directly through the stipend or indirectly through work after study completion). Second, participant responses suggested motivations that were more altruistic in nature, such as wanting to help others or contribute to scientific research. Finally, participants discussed social motivations and saw the study as a means of reconnecting with and supporting their family or distancing themselves from less beneficial social ties, such as friends in drug scenes.

3.3.1 Instrumental motivations

Study stipends. Considering the existing literature on study stipends as an enrollment motivation (Abadie et al., 2019; Bell & Salmon, 2011; Denny & Grady, 2007; Fry & Dwyer, 2001; Monahan & Fisher, 2015; Neale et al., 2018; Treloar et al., 2010), participants were asked how the stipend factored into their decision to participate. Generally, OPTIMA participants did not consider the study stipend to be their sole motivation for study enrollment, despite many participants experiencing socioeconomic marginalization. For Eric (White man, Calgary), the money was important but less of a priority than reducing opioid use: "[I joined] so I could quit heroin. And get $40 when I came here to do it. Yeah, no, I absolutely needed to quit heroin. It was a life-or-death situation basically." Others remarked that the stipend helped them cover bus fare or other expenses. Steve (White man, Vancouver) noted, "it was a day that I didn't have to grind so hard," where economic pressures were reduced. However, the stipend amount was not so high that it constituted a significant inducement. Justin (White man, Vancouver) commented that, "$40 is—I spend more than that in the first ten minutes of my day. That's maybe one point, one shot of my heroin." In the same way, comparing the stipend to the cost of opioids, Joseph (Indigenous man, Calgary) remarked, "The money's always beautiful. Fuck, sure, man. Is it going to help? That might help me with half a fucking point [of heroin]. So instead of paying for a whole point I'll have to pay for half a point. Or it might get me supper or something. Fucking lunch. But that's—I'm going to do [the study] anyways, right." Like Joseph, many participants described the money as a "bonus," and some did not initially realize they would be paid for their contributions. For instance, Rebecca (Indigenous woman, Sudbury) noted the stipend was "a bonus and I didn't know about that at first. When I said yes [to enrolling], I had no idea. And then [study staff] told me and I'm like, 'damn, this is even getting better.' You know, I'm on a low income, I have no money.

But it didn't encourage me to do it." Relatedly, participants emphasized that they would have enrolled in the study regardless, like Sophie (White woman, Montreal) who commented, "I mean no one is going to spit on money, but honestly, I think I would have done it anyway." Participant views on the study stipend were multi-layered and highlight that for PWUD, there may be more than purely instrumental, economic motivations.

Income generation. To provide further insight on their socioeconomic background, participants were asked about the ways they made money and, in their descriptions, many directly or indirectly linked their study participation to work. A few participants were employed in a formal capacity, but a majority of participants were not employed and were receiving income assistance. Given the low amounts of income assistance across Canada (Laidley & Aldridge, 2020), many of these participants supplemented their income with other work activities, including informal recycling, odd jobs (e.g., shoveling snow, cleaning), part-time "peer" work (e.g., staffing an overdose prevention site; Greer et al., 2020), panhandling, drug dealing, or theft. Among participants not employed fulltime, most expressed a desire to return to the formal workforce, and many couched their study participation as a way to reduce their drug use and access employment. For some, the motivation to work was primarily economic. Thomas (White man, Vancouver) noted that drug use was inconsistent with formal employment: "there's not enough money in the world to fuel a drug addiction, right. I mean it doesn't matter what you [do] but you can't maintain a job while maintaining a drug addiction. You always lose your job, right, no matter what." For others, the cessation of drug use was a condition of employment. For instance, Robert (White man, Calgary) remarked, "as soon as I get totally off the drugs, I go three months without doing any drugs, great, I get tested and get my job back." However, for many the reduction or cessation of drug use in the study was just one small step toward employment. Mark (White man, Vancouver)

explained his situation and enrollment decision-making: “I have a hard time getting work, because I have a record. So, 90% of what I looked up on craigslist were right at the bottom, always, ‘clear background check, clear background check.’ I’m like, ‘pfft.’ So this way I get off the T3s, which is good, because I’ve been taking it for like a year, six or eight a day.” To Mark, reducing his use of Tylenol 3s would overcome one hurdle, though other barriers to employment remained.

Beyond economic stability, participants’ desires to work alluded to a related expectation that work would give them a sense of pride or purpose. Jessica (White woman, Vancouver) expressed pride in the accomplishments of her sister, but framed them in contrast with her own self-evaluation**: “**She’s had two babies and she works for the bank and then I look at myself and I’m like, ‘what does she say about me?’ I mean, I know she’s proud of me and she’s happy I’m alive and all that, but at the same time I wish I was doing better so she could be a little more proud and able to speak better about me.” In describing his motivations for work, Jean-Marc (White man, Montreal) explained that he wanted to pick up extra hours as a peer worker, “not to make more money, but more so to do something else with my life, right now.” Zack (White man, Calgary) similarly recalled, “I’ve had pretty good jobs in the past, where I’ve felt pretty proud to have that job or I felt like I was accomplishing something by going to work.” Other participants described additionally tertiary benefits, such as work boosting their mental health or self-esteem, like Shawn (White man, Toronto), who remarked, “I want to become self-sufficient. I want to buy my own work boots.” These goals, or “approved means,” (Merton, 1938) were described in contrast to the shame participants felt about their current income generation strategies. Robert (White man, Calgary) compared his previous work as a heavy equipment operator to his present situation as, “going from $48.00 an hour to begging for a cheque from Alberta Works.” Ken (Indigenous man, Calgary) described being raised on a farm with a “good work ethic” and felt similarly disappointed

to be accessing income assistance: “being on welfare is going to—I mean, from my understanding it’s there to help people to get them through. And I really don’t want to be, but I’m gonna have to be.” These feelings of shame around unemployment reflected the inverse of normative expectations to work. Participants reiterated these normative expectations and linked them to the study, like Cody (White man, Calgary) who remarked, “I would like to be working. As soon as I get out of the program and I can get back to work, I’m definitely going to. I’d much rather be working.” Similarly, Amanda (White woman, Calgary) linked the study treatment to work:

> I’ve been told [stabilizing on suboxone] will happen fairly quickly for the most part, and even with that you get carries faster so I’ll be able to work and go to school and everything. It would be really great. I feel like for me to be completely healthy and happy with life, I definitely need to be working or in school or doing something. I can’t not work anymore.

Here, Amanda links health and happiness with work and the cessation of substance use, highlighting that feelings of shame around not working may be compounded by internalized drug stigma. By making direct or indirection connections between study enrollment, reducing their substance use and work, participants’ narratives reflected elements of strain theory and normative conceptions around legitimate versus illegitimate work, as well as finding a sense of purpose to reduce feelings of alienation. Participant narratives point specifically to their identification of the steps required to uphold normative expectations around drug use and work, and directly linked their participation to instrumental notions around accessing treatment, economic incentives, and opportunities for employment.

3.3.2 Altruistic motivations

While access to the study treatment and its social and economic benefits were among the primary motivations for participation, participants also expressed altruistic motivations. These altruistic motivations can be categorized by the perceived beneficiary of their decision to

participate, as participants reasoned that their contributions could benefit the PWUD community, scientific research, or offer a hybrid or dual benefit to themselves and others.

Benefit to the PWUD community. OPTIMA participants were motivated by the prospect of making a meaningful contribution to the broader community of PWUD. Sam (Indigenous man, Vancouver) explained his reason for enrolling: "honestly, a big part of it was a feeling that I might be able to contribute in a positive way towards—kind of an end goal of there being better resources and better things in place." Jason (White man, Vancouver) described his motivation to contribute as superseding other motivations:

> I know how valuable the information from programs and stuff can be, so I mean why not do something that uses my trials and tribulations of getting clean to make someone else's a little bit easier? I have no problem with that. I don't mind sitting down talking to them for 20 minutes every couple of weeks. I mean, if they want to kick me 40 bucks, hey, that's cool. But it's not about the money. It's about more honestly trying to get the information out there. Like trying to make it better, just to make treatment better for people and make it more successful.

Here, Jason draws on his experience working in the harm reduction field and observing the evaluation of such programs, and he recognizes the value of his contribution to research, relative to the burden of attending follow-up appointments. Related to Jason's quote, some participants perceived the study to be a sort of small positive outcome from their previous negative experiences or that it could prevent someone from experiencing the same hardships. As Cody (White man, Calgary) expressed,

> I just feel that maybe if I can help provide some information about addiction, like through my experiences with it, then maybe I can provide some help down the road to somebody else or just helpful for the whole situation, just for the addiction research in general. So just seemed like a positive thing to do. Kind of take a negative situation and put a little bit of a positive spin on it.

Cody's statement reflects a common sentiment in which OPTIMA participants felt their contribution would somehow help PWUD in the future. However, most participants did not know

or explicitly state how the study results would benefit other PWUD, and instead expressed more vague ideal outcomes (e.g., reduced treatment wait times). In some instances, participants seemed to overstate the potential impact of the study, like Joseph (Indigenous man, Calgary), who remarked:

> I feel like I'm participating in other people's lives. I feel like I'm participating in putting the finger on the motherfucker that needs to be held accountable for Oxycontins, for fentanyl. The government just can't keep fucking signing off on things and blaming it on addicts. They can't keep letting these big money companies roll through us and hand out fucking pills like they're fucking M&Ms and then blame the addict, lock the addict up.

Joseph believed that his contribution would help to hold pharmaceutical companies accountable for their role in the overdose crisis. But given the objective of the RCT to produce clinical evidence for treatment, these perceptions may be inaccurate and result in Joseph's disappointment with the extent of the study's impact, as reflected in previous findings with people with substance use disorders (Jaffe et al., 2021b). Still, participants' perceptions around improving the lives of PWUD were meaningful and may ultimately contribute to feelings of mattering or social solidarity.

Contribution to research. Many participants expressed that one of their driving motivations was a desire to contribute to scientific research and ensure the success of the study. Several participants recognized the value in their unique perspectives as people with lived experience but felt that they were often overlooked or ignored in healthcare settings. Andrew (White man, Toronto) noted a common narrative about PWUD, that "the only information out there are stats on how many people died, how many people got on methadone or suboxone and, there's not…there's not a lot." As Andrew observed, the most widely discussed data points surrounding substance use are overdose statistics, with a dearth of information about other life experiences among PWUD. Other participants felt their participation would help to ensure the generalizability or accuracy of the study data. For instance, Greg (White man, Calgary) remarked

on the appropriateness of PWUD in the study sample: “Where are you going to get your information from better than when people that are there? Living in their shoes like me, right?” Sam (Indigenous man, Vancouver) believed that through his participation, he could contribute “good data”:

> This might sound bad [but] giving some thought to who else might be participating in the study. I wanted to make sure that there was some, I guess, good data getting put in, or honest data, I don’t know. You know, in the community of addicts there are some “less desirables,” and some that go out of their way to intentionally make trouble or to mess with things… It’s just I wanna make sure that we’re not getting represented by the bad apple of the group.

Other participants wanted to contribute to the representativeness of the data by offering what they perceived to be alternative perspectives. For instance, Tammy (Indigenous woman, Calgary) hoped for adequate gender representation in the data: “I wanted to be able to tell you how it is on a woman’s side with respect of the drug itself, how it directs our lives as women, right? As a woman it’s different and it’s difficult.” The variety of different perspectives were important to participants. In another example, Deborah (Indigenous woman, Sudbury) was asked why she remained in the study after stopping the medication and responded, “Because I don’t like not completing things and I believe that it’s important to get an all-around. Like somebody who goes off of the medication [as] opposed to somebody who stays on the medication. It’s good to get different perspective when you’re doing a study like this.” Deborah and several others seemed to intuitively understand that their participation would help to counteract selection effects related to the characteristics of participants who were able to remain in the study or on the study medication. Through their enrollment, these participants felt like not only were they making a meaningful contribution, but that their contributions would offer a diverse and representative array of perspectives, thus supporting the success of the trial.

Complex altruism. Other participants expressed more of a complex or hybrid altruism in which they felt they and others would receive mutual benefit. As Olivier (White man, Montreal) framed it, "It's like win-win. I receive the help that I want to quit drugs and at the same time, I help for future programs that could help other people in that situation. I didn't even realize that they gave you money. When I knew that, I was like, 'wow!'" For Olivier, altruism and treatment access were of equal value and had more influence on his decision than the study stipend. As Emily (White woman, Vancouver) remarked, "Yeah, [the stipend] was a motivator, but either way, I have nothing else better to do. I like to talk, and it feels good because I can't talk about this with anyone else." Several participants reiterated this point, that the opportunity for self-expression was rare and a benefit in itself. As Sam (Indigenous man, Vancouver) explained:

> I have an opinion about a lot of things and being able to actually give my opinion in a way that I'm being listened to, and that there might be something that comes of it. Or just to give input into something that might make a difference or that has meaning, is kind of a nice feeling. Just my life choices have not provided me an outlet in my life. You know, kind of the... [sighs] the druggie lifestyle and stuff as kind of a simpleton, you know, there's not a lot of intellect involved with drug use.

Sam felt that while he had opinions to share, he lacked meaningful interactions in his daily life and the study gave him an outlet for expression, indicating a potential psychological benefit. Anthony (Mixed race man, Calgary) also spoke of the dual benefit of making a contribution as well as having his views heard and remarked that the study "helps people get an idea of how users function and think and it's a voice for people who feel like they don't have one. Like when they feel like people just don't give a shit really. It's awesome because everybody can give their opinion and their thoughts and try and make services better." In essence, Anthony felt the chance to engage in discussion and to contribute to a larger project would afford participants immediate benefit. However, these secondary benefits became a reason that some participants were disappointed their study involvement was coming to an end. Patrick (White man, Toronto) tried to continue his

participation: “I asked [staff] if I can continue doing it, but I don’t think I can. This study’s helped a lot and you build relationships with people, right? I built a relationship with [staff]. It’s coming here and just talking with him, just chilling out and expressing all this shit is kind of helpful.” Similarly, when Amanda (White woman, Calgary) was asked how she felt about completing the study, she shared that she would miss talking with the staff, and that she was “kind of sad in a way that it’s over. Like doing the study and stuff. So I guess sad, but I’m kind of happy because at least some of the research will be put to use and stuff now.” Though Amanda recognized that these particular study benefits were ending, she was encouraged by the idea of her contributions benefiting others.

Through their aspirations to help other PWUD or contribute to a broader scientific project, OPTIMA participants revealed altruistic motivations. Among marginalized or socially isolated PWUD in particular, study participation may provide some sense of purpose, connection, or assign additional meaning to otherwise difficult past experiences (e.g., “a positive spin”). For those with enrollment motivations reflecting a hybrid altruism, participants realized their desire to make a contribution as well as access benefits in the form of treatment or beneficial interactions with clinical staff.

3.3.3 Social Motivations

As participants discussed the important relationships in their lives, many participants connected these relationships to their substance use and decision to enroll/seek treatment. For PWUD who felt disconnected from their families or isolated from friends, study participation was viewed as a way to reconnect or to reciprocate the care and support that had been given them. Participants felt that by enrolling in the study, adhering to the treatment, and reducing their

substance use, they could fulfill normative role expectations to loved ones while distancing themselves from other social ties in drug scenes.

Responding to loss and (re)building social ties. For PWUD, the social context of drug use was imbued with feelings of grief and loss. Participants spoke about feeling isolated due to the loss of friends to overdose, particularly those in British Columbia and Alberta where the unregulated opioid supply is almost entirely fentanyl mixed with varying adulterants (Bouchard et al., 2020). In some ways, the shrinking of their social circles and the looming presence of death motivated participants to access the study and treatment. Mary (Indigenous woman, Vancouver) remarked: "I didn't know it was a study because I was looking for help anyways. I was trying to get off the fentanyl. Because it's dangerous. I kept reading about everybody overdosing. I'm hearing people talk about it and it's a scary thing." Other participants witnessed this transformation in their neighborhoods, like Paul (White man, Vancouver):

> I've noticed that the number of friends that I have has declined in the last three years. Because a lot of people are missing. Like not missing, they've just died. It's just crazy. I remember when I was younger, it'd take five years for somebody that you knew to die. And now it seems like every other week somebody else is dying. It's just kind of – it wears on your mind a little bit. I don't know if you can get PTSD from it, but I bet you I have that from that alone.

As Paul illustrates, this combination of missing friends, death, and grief made participants feel alone and likely had detrimental impacts on participants' mental health. Jason (White man, Vancouver) explained, "my closest friends all died the [last] couple years so it's like I don't have that inner circle anymore. I just don't. And I've got some other close friends, but they live in different cities and different provinces and countries, but my base here is gone. I don't have that support network." In addition to feelings of grief and loneliness, participants in drug scenes had repeated stressful experiences witnessing overdoses and reversing overdoses themselves. Chris (White man, Vancouver) recalled, "I had one weekend where I had to help like six or seven people

in a row that had overdosed and it's pretty scary sometimes." Donna (White woman, Calgary) assisted in overdose response in a similar capacity and noted: "There's a lot of people that aren't with us now, you know? But maybe this [study] could have helped. I fucking saved eleven people last year alone. Without naloxone. Just as a basic rescuer." As a witness to overdose death, Donna wondered whether access to treatment or a study like OPTIMA could have prevented some of these deaths, which may be interpreted in some sense as survivor guilt. As these interviews reveal, the social context of drug use is linked to its inherent physical risks, and for PWUD participants in drug scenes, the dwindling social ties were a stark reminder and motivation to seek treatment.

For many OPTIMA participants, family social ties were also severed, due to conflict or drug-related stigma. Donna (White woman, Calgary) attributed her loss of familial connection and conflict to the disclosure of substance use: "Yeah, I've outed myself out to all my family about the fentanyl. A lot of them have turned their backs on me, won't even talk to me. One wants to tune me up with a baseball bat." Another participant, Sebastien (White man, Montreal), who experienced drug-related incarceration, recalled his strained family relationship upon leaving prison: "When I got out of there, [my father] didn't seem too enthusiastic to come see me. I decided to cut my ties again. So that causes me pain. It's a source of a bit of anxiety. I know I really disappoint him." For many participants experiencing estrangement from their families, study participation and consequent drug use cessation were perceived as a way to rebuild familial ties. For instance, Michael (Indigenous man, Vancouver) wanted to return home to his family upon the cessation of opioid use: **"**I want to go back to [hometown], where I'm from and I'm not going home this way. I'm going home clean." Similarly, Lisa (Indigenous woman, Vancouver) predicted she would reconnect with her family upon reducing her opioid use: **"**I don't talk to my mom very much anymore because of the drug use. I kind of cut her off. She misses me. She tells me to come

home but I can't while I'm doing drugs. I really want to stop." Social signals from loved ones reinforced this motivation. In her exit interview, Lisa described increasing communication with her family during the study: "I've told them I've been coming to the [study location], and they just said, 'Good. Keep up the good work. Maybe we might be able to see each other this summer.'" Both Lisa and her family linked the reduction or cessation of drug use to a potential visit and reconnection.

Some participants who were parents spoke about the study and treatment as a way to reunite with their children who were living elsewhere or who were separated from them by social or legal systems. When asked why she enrolled in the trial, Tracy (Indigenous woman, Calgary) equated the study with treatment: "Well, [treatment is] court ordered. That's why. To get my kids back." Even for participants who lived with their children, there remained underlying fears about losing their children. Megan (Indigenous woman, Toronto) initially felt that enrolling in the study might make someone "look at me like I'm not fit to care for my daughter" and recalled, "I was just really scared for them to call [child services] basically. So that was my biggest worry for [the study] to release information to them. But personally, I feel for them to collect information for a research thing, I think that's great. I think that that will help people in the long run and just to better the future." For participant parents who use drugs, engaging with health and social service institutions was taking a risk, particularly for racialized women who have historically been subjected to greater state scrutiny and harm (Baskin et al., 2015; Robertson et al., 2021). While many participants linked their substance use to strained relationships, it remains to be seen whether study participation or changes to their drug use patterns would fulfill their expectations for reconnection.

Receiving and reciprocating care. Other participants felt that study participation would support or improve existing relationships through facilitating reciprocal support or trust. Eric

(White man, Calgary) expressed a sense of commitment to his sibling, recounting that he enrolled, "because my brother was really worried about me. Just wanted the best for me and stuff so I owed it to him to try and quit… He helped me out a lot and pulled me out of the gutter about a million times. So yeah, I owed it to him to try and get better." In another instance, Cody (White man, Calgary), explained the emotional and accountability support he received from his mother: "I'm out on bail, so I have bail conditions. So, to live with [my mom] I have to follow those bail conditions very strictly, and there's zero tolerance. Yeah, it affects my use in a good way. I mean she's trying to keep me sober and I'm trying to stay sober." Participants in romantic relationships also felt supported by their partners in both instrumental and emotional ways and saw study enrollment as a way to save a relationship or to compensate for previous hardships. Robert (White man, Calgary) described his girlfriend as previously attempting "anything to help me get off drugs. I mean, she was getting to the point where there was not much more she could do with it" but that after enrolling in the study, she felt "just happy that I'm trying something new." Alain (White man, Montreal) reflected on his relationship where, "in 8 years, there were a few points where I could have easily done either something really foolish or something a bit irreparable, no matter to what extent, whether it be in terms of criminality, in terms of my relationship at home. I could have lost everything. My girlfriend, she weathered the storm." For Alain, study enrollment was an end to the metaphorical storm (i.e., problematic substance use, legal entanglements, potential interpersonal conflict), through which his partner navigated and supported him. Emotional support was also evident in instances where participants described their partners as their sole confidants, or when both partners were simultaneously seeking to reduce or cease their substance use. As Cody also explained: "Yeah [my girlfriend's] totally going through very similar situation as me. We're both clean. We're both sober. So yeah, we both support each other." There were also five sets of

participant partners (10 participants) who were interviewed—a study circumstance that generally seemed to benefit participants. If enrolled simultaneously, participant partners could attend follow-up appointments together, remind each other to take their medication, and provide emotional support throughout the duration of the trial.

For parent participants, the ability to provide support was a key concern. Most notably, parent participants were concerned that without opioid treatment they would become "another statistic" and die from drug poisoning, leaving their children behind. As parents, the threat of overdose was a very real concern and Sam (Indigenous man, Vancouver) framed his participation in the context of this crisis and his role as a father:

> Every time you hear sirens, you know, it's probably someone dying or overdosing. And in the past 10 years I've lost a significant amount of my friends to overdose. I recently lost someone that was very important to me, my best friend. And I'm just kind of waking up to the reality that it's not a matter of "if," it's a matter of "when." You know, get a bad hit and end up dead and I don't want to leave that for my daughter to deal with.

As someone who had acutely experienced overdose loss, Sam worried that if he did not reduce his drug use his daughter would experience the same grief. Similarly, Greg (White man, Calgary) invoked overdose in framing his motivation: "I'm still on the right side of the lawn when I wake up in the morning, so let's do something about it now while I still can. I mean I can't do nothing if I'm buried six feet under, right. I don't want my kids to [say], 'Oh, dad overdosed. He didn't make it this time.'" Greg's comment reflects both concern for his children and for how he will be remembered upon his death and frames his study participation as a proactive measure to address these concerns.

Fulfilling social roles. As participants connected their relationships to substance use and the decision to enroll/seek treatment, a final underlying motivation emerged as relating to the desire to fulfill social roles and expectations. For instance, participants who were parents spoke

about enrolling to reduce their substance use and meet some parental standard. Andrew (White man, Toronto) explained how his children encouraged him:

> They're a motivator for me to do better in life. They really are. I've never reached towards drugs because of my kids. It's the opposite. My kids are my rock and what keeps me true and pure and going in life. It's the one thing I do have going for myself regardless of everything else that's out of fucking whack. Like you can ask anybody, I'm an amazing father. I go above and beyond what other fathers don't do, you know what I mean? I try to spend as much time with my kids as possible.

Andrew's positive self-evaluation of his parenting skills, regardless of his substance use, may help to counteract internalized drug stigma. In a similar way, Michael (Indigenous man, Vancouver) was partially motivated by the news of a grandchild: "That's half the reason why I want to get off this. Like I want to be in my baby's life and my grandbaby. I want him to know he can come to my house and not worry about using drugs, right. … I got nine months to help myself before I can help him." OPTIMA participants with romantic partners also described normative role expectations. As Jean-Marc (White man, Montreal) explained, **"**We're definitely trying to create a life for ourselves, with our two dogs and everything. That keeps me on the straight and narrow." For Jean-Marc, the study treatment was a step toward strengthening a partnership and building a home, to signal a specific cultural definition of success. For Jessica (White woman, Vancouver), who was in a newer relationship, internalized drug stigma emerged when she was around her boyfriend:

> I hate that he sees me using the needles. I'll be in the bathroom with the door shut and he'll come in and I'll have blood up and down my legs and it's a mess. I think it's so gross and disgusting and it's not where I want to be. It's not what I want him to see me. I don't like him feeling comfortable watching me use a needle, so I get really nervous when he's around. I'll be like, "can you please leave the washroom because I can't do this with you here." I'm like, "just because I want to stop doing this and I don't want you to see me doing this," and this and that. "It isn't the person I want to be when I'm around you," right. So I'm using him to be the reason to want to stop too, to be my reward in the end of it, that kind of thing.

Jessica wanted her boyfriend to see her in a particular light, not using opioids, but she ultimately reframed this as further motivation to participate and reduce her drug use. For participants with partners who did not use drugs, drug-related stigma shaped their willingness to confide in their partners about substance use and study enrollment. Susan (White woman, Vancouver) recalled her conversation when she told her boyfriend about the study and treatment: "he just thinks it's another pill. 'Oh, same thing. You're going to get hooked on that. How long are you going to take those for?' And I just said, 'I don't know. The rest of my life, if it works, right?'" Andrew (White man, Toronto) experienced similar treatment stigma and remarked that his girlfriend, "didn't really understand it. I tried explaining it to her. She just didn't want to hear it. She just thought [the study treatment was] just another outlet for me to get some type of other drug into my system. And it's not like that at all." Ultimately, because of this absence of support, Andrew ended the relationship. While role expectations generally shape behavior in a way that reduces alienation (Thoits, 2011), for many of these participants, internalized drug stigma and the underlying assumption that one cannot use opioids and be a "good" family member, parent, or partner may place undue pressure on their success in the study.

While participants desired to fulfill some social roles, they also felt the need to transition from other social roles, particularly with friends in drug scenes—environments where people are actively using and selling drugs. As Michael (Indigenous man, Vancouver) remarked: "People, places and things change. I don't see half of my friends that I used to see before, and they're thinking I'm ignoring them, but it's not that I'm ignoring them; I'm just trying to do the right thing." In this instance, the "right thing" was severing friendship ties. Eric (White man, Calgary) remarked on his strategy to avoid drug scenes: "They avoid me. I avoid them. You know, I see them once in a while. It's like 'hey, what's up. See you later.' And just keep going. Yeah, misery

loves company, so I just try to stay away from them." Other participants anticipated challenges around creating distance from drug scenes. Ken (Indigenous man, Calgary) described being tempted by his former dealer: "I didn't even pay for those drugs. They were all free. I think they were just trying to reel me back in because I was a good customer. I did spend a lot of money on them when I was using." Other participants similarly worried about instances in which avoiding old friends was difficult, as described by Patrick (White man, Toronto), who recalled a recent situation:

> So [my friend's] funeral was yesterday. And these guys offered me drugs. We're all kind of friends, so there'd be addicts there. In my mind, I'm like, "I don't want to do this unless I'm going to shoot it, but at the same time I don't want to shoot it, because if I shoot it, I'm just going to start the same shit over again." So I smoked it. I know in the back of my mind it's not going to do anything to me, because if I smoke it, it's not enough to get past the suboxone. And one or two puffs will make these guys happy, but it pissed me off because I knew I was going to piss dirty today, and I was clean for like three weeks.

In this scenario, Patrick describes feeling pressure to use drugs and fulfill the expectations of his friends but also felt frustrated, knowing that when his urine was tested for the study, the results would not accurately reflect his previous efforts to reduce his drug use. For participants who left drug scenes upon enrolling in the study, the loss of friendships could also be a significant adjustment. As James (Indigenous man, Vancouver) remarked: "I'm lonely, but happy. Because you don't do nothing anymore, right, so I do a lot of home stuff now. I try to stay away from people. That helps too, right. So that's what I'm doing right now. [Interviewer: Staying away from people entirely?] Well, no, just the wrong people. It could get me in the wrong place so no, not worth it." Like James, Greg (White man, Calgary) described his changing social milieu and how it felt to exit drug scenes:

> Well, it was easier to become a part of society when I wasn't using. So, being on the methadone I was mingling with other people that are—I wasn't hanging around the same people, right? So it put you back into normal society, taking the

> methadone, right? When I'm not taking the methadone, I'm using drugs with people that are using drugs.

Notably, Greg differentiates PWUD from "normal society," a statement that both alludes to a desire for social connection and integration, as well as reinforces stigmatizing narratives of PWUD as "not normal" or "deviant." Though these participants felt leaving their friends was difficult, they also recognized that severing these social ties could reduce their drug use and improve their adherence to the study medication. While some participants were motivated to enroll in the study as a means of fulfilling social roles, which may increase self-esteem or sense of self-efficacy (Thoits, 2011), other participants recognized that some social roles and social scenes could be detrimental to their efforts in OPTIMA to reduce their drug use and meet broader life goals.

3.4 Discussion

The aim of this chapter was to understand how the broader social context around substance use (e.g., drug-related stigma, alienation, search for meaning or purpose, etc.) may inform PWUD participants' underlying motivations for enrolling in an RCT. To date, scholars have focused heavily on instrumental (e.g., economic) motivations for research participation among PWUD, largely in response to ethical concerns about undue inducement and moralistic concerns about financially subsidizing drug use (Anderson & McNair, 2018; Festinger et al., 2005, 2008; Fry et al., 2006). Fortunately, these efforts have resulted in a general understanding that PWUD should be sufficiently compensated in cash in exchange for their time, energy, data, and shared knowledge (Abadie et al., 2019; Collins et al., 2017; Festinger et al., 2008; Greer et al., 2018). However, amidst these endeavors to ensure the ethical conduct of research with PWUD, less attention has been given to more intrinsic motivations for study enrollment. In light of the drug-related stigma and marginalization experienced by PWUD, I argue that RCT participation may be one way through which they alleviate feelings of alienation (i.e., detachment from society and social ties),

either indirectly by reducing their drug use and strengthening social connections or purposeful activity (e.g., work) or directly through their involvement in this scientific endeavor.

3.4.1 Instrumental motivations

While some participants were motivated by the study stipend offered, others emphasized that the study stipend was just one factor in their decision-making and that primarily they wanted to reduce their drug use, for reasons expressed in further detail below. The amount of money was framed as a "bonus," enough to reduce their daily burden of income generation or encourage them to attend but not significant enough to solely induce enrollment, especially when viewed alongside the cost of opioids in the unregulated market. Other participants said they would enroll without compensation, which speaks to the perceived importance or benefit of study participation but may also speak to some social desirability bias, as expressing purely economic motivations may be viewed as less acceptable or distasteful. PWUD may be more attuned to these normative expectations because of existing biases around PWUD as untrustworthy and financially motivated (Bell & Salmon, 2011; Treloar et al., 2016). Surprisingly, more than a few participants recounted how they did not realize there would be a stipend until they enrolled, demonstrating the degree to which the study treatment alone was motivating. In sum, financial compensation in this study was important and one culturally acceptable means of economic gain, particularly for socioeconomically marginalized PWUD, but it was not the sole or even primary consideration.

Instrumental enrollment motivations were also reflected in participants' responses in indirect ways through discussions of work and income generation. Most OPTIMA participants were receiving some form of income assistance and despite the critical role of assistance in their survival, many demonstrated the presence of internalized stigma around the receipt of state benefits and expressed a desire to work. These findings are supported by previous research on

public perceptions of income assistance recipients, who are framed as lazy, unwilling to work, and undeserving—perceptions that are commonly internalized to produce complex configurations of shame and normative aspirations (Maki, 2011; Reutter et al., 2009). In some participants' minds, drug use was not conducive to formal employment, so study participation was viewed as a way to reduce their substance use so they could return to work. Work was not only perceived as a way to generate income but also as an activity that would give them a sense of accomplishment, pride, or self-sufficiency. These expressions around wanting or needing to work reflect cultural norms where working for income is the ideal and employment serves an integrative, social role (Brand, 2015; Durkheim, 1984; Jahoda, 1982; Kalleberg, 1977; Merton, 1938). Though the reduction or cessation of substance use may allow PWUD more flexibility for work, some forms of medications for opioid use disorder may also pose barriers to employment (Richardson et al., 2012), and so whether study participation and treatment facilitates or hampers future employment remains to be seen.

Given the risks and stigma associated with informal, prohibited, or illegal income-generating activities (Boyd et al., 2018; Jaffe et al., 2018; Richardson et al., 2014, 2015), it follows that participants would express career goals that would proffer economic benefit, security, or distance from drug scenes. However, their intrinsic desires around work to feel pride, meaning, or a sense of purpose highlights the degree to which participants aspired for culturally defined "legitimate" economic engagement (Kalleberg, 1977; Merton, 1938). Both the material realities of living in poverty and the normative pressure for employment produced desire for change, which manifested through participants' narratives around how their personal capabilities would change because of their participation. In sum, instrumental motivations play a significant role in shaping research participation among PWUD, but they may be more complex and wider ranging than

previously considered. Study stipends may initially pique the interest of potential participants or incentivize follow-up attendance, but they remain one of many enrollment considerations, including aspects of participation that have longer-ranging impacts on their economic stability and wellbeing.

3.4.2 Altruistic motivations

Participants in the OPTIMA study expressed altruism, in that they were motivated by the belief that their contribution would benefit research and future PWUD. Previous research has noted PWUD have altruistic motivations to participate in research, but these motivations are often described in general terms (e.g., to "help others"; Neale et al., 2018; Treloar et al., 2010), or in terms of willingness to participate in a hypothetical trial (Fry et al., 2006; Yakovenko et al., 2019). However, since altruism is a socially desirable trait, participants may freely express altruistic motivations regarding hypothetical trials, but this may differ from motivations in actual trials (McCann et al., 2010). In this study, there were several perceived beneficiaries of participants' altruistically motivated enrollment, including communities of PWUD, scientific research, and a hybrid mix of PWUD communities and themselves. Participants' desire to benefit communities of PWUD suggests linkages to previous scholarship on "drug user activism" as a motivating factor to participate in research (Fry & Dwyer, 2001). In Canada, and in Vancouver particularly, there are long histories of drug user community organizing and research (Boyd et al., 2017; Jozaghi et al., 2018; Small et al., 2006; Wild et al., 2017), and so some PWUD may have a greater sense of research literacy and desire to accurately represent communities of PWUD (e.g., "I wanted to make sure that there was some…good data"). Given the active research programs and mobilization around drug use and drug policy in Canada (Priest et al., 2019; Wild et al., 2017), PWUD may feel a greater sense of connection or obligation to this community (i.e., a "disease constituency";

Epstein, 2016) than populations in other trial contexts that may not be characterized by long histories of community solidarity and activism. It was also noteworthy how many study participants perceived scientific research as worthwhile or impactful, in light of previous research on PWUD's mistrust research institutions (Abadie et al., 2018; Bell & Salmon, 2011; Fisher et al., 2008; Treloar et al., 2016). Of course, there may have been selection effects where distrusting PWUD did not enroll in the study to begin with, but even PWUD participants with previous negative experiences in healthcare or research lauded the study and its aims and felt a desire to contribute. Further, in the shadow of the War on Drugs and the ongoing overdose crisis, this desire to help other PWUD may reflect "altruism born of suffering," in which adversity or traumatic events (e.g., an unprecedented level of overdose death) are associated with altruistic acts and subsequent posttraumatic growth (Vollhardt, 2009). For instance, previous work has highlighted how criminalized people are altruistically motivated to participate in research, as well as by the opportunity to "speak with researchers, interact with new faces, and be treated with respect" (Hanson et al., 2015, pp. 362–363). OPTIMA participants similarly highlighted the benefits of having an expressive outlet in their hybrid altruistic motivations, along with accessing treatment and making a contribution. This hybrid, complex altruism in which study participation is described as mutually beneficial highlights implications for enrollment, that while people may intend to contribute and do good for others, in practice actual study enrollment is unlikely without some sort of perceived personal benefit (McCann et al., 2010). Taken together, participants' expressions of altruistic motivations reflected themes of social solidarity (e.g., with the broader community of PWUD), feelings of purpose or existential meaning (e.g., contributing to a larger project via research), and a complex amalgamation of non-economic benefits and sense of contribution

(Bykov, 2017; Durkheim, 1984; Jeffries et al., 2006; McCann et al., 2010; Simmons, 1991; Thoits, 1983).

3.4.3 Social motivations

Given broader cultural stigma toward drug use and resulting social dynamics (Granfield & Cloud, 2001; Hawkins et al., 2019), previous research has highlighted how some PWUD feel socially isolated or alienated from society (Ahern et al., 2007; Cole et al., 2011; Gryczynski et al., 2013; Haritavorn, 2019; March et al., 2005; Sibley et al., 2020). Reflecting these findings, many OPTIMA participants described social losses, both friends due to overdose as well as strained relationships with family due to drug-related events (e.g., criminal justice involvement; child protective services involvement). To rebuild their social ties, some participants sought to enroll in the study with the motivating belief that the cessation of drug use would enable them to reconnect with their families or children. The social expectations for the study (e.g., to be reunited with children) are notable, especially when contrasted with the more mundane study objectives to produce generalizable results, and may have implications for participants' subsequent reflections or satisfaction with the study (Jaffe et al., 2021b). Additionally, participant narratives highlighted the potentially complex dynamics between PWUD and the people who cared for them. After their loved ones helped them navigate opioid use or treatment (e.g., "she weathered the storm"), OPTIMA participants were eager to repay their kindness by reducing their substance use in the study. Parent participants expressed intense worry about overdose death and the care of their children left behind and anticipated shame should such a tragedy occur (e.g., "I don't want my kids to say, 'Oh, dad overdosed'"). Through participants' enrollment and desire to reconnect with and care for loved ones, the RCT can be conceptualized as a potential indirect mechanism for building social connection (Berkman et al., 2000; Thoits, 1983).

Beyond seeking connection and support, participants' narratives reflected aspirations to fulfill social roles (e.g., parent, sibling, partner, etc.). Underlying these social goals were normative role expectations about the perceived obligations and behaviors expected of them (Thoits, 1983). For instance, participants held normative beliefs about what it meant to be a "good" parent, sibling, or adult child, which generally implied that substance use was inconsistent with performing these roles. However, not all relationships were of equal importance or salience for participants. In discussing their friendship networks, many participants believed they needed to distance themselves from friends who were still using drugs, after realizing certain social settings and social cues would trigger their substance use, which has been reflected in previous research (Kirst, 2009; Pettersen et al., 2019; Rhodes, 2009; Villalonga-Olives & Kawachi, 2017). Further, engagement in "normal society" was seen as contradictory to engagement in drug scenes and thus, participants strived to create distance from drug scenes, as a social risk mitigation strategy (Draus et al., 2015b; Granfield & Cloud, 2001; Latkin et al., 1999; McDonald et al., 2011). However, the disruption of these friendships may inadvertently lead participants to increased social isolation, which could produce further feelings of alienation and negative mental health outcomes (Seeman, 1959; Umberson et al., 2010). These feelings may be amplified among PWUD living in drug scenes grieving the loss of friends to overdose, and given the strength of these friendship ties (Ivsins et al., 2019) as well as the associations between socioeconomic inequality, neighborhood disorder, greater social isolation (Kawachi & Kennedy, 1997), and feelings of alienation and distress (Ross & Mirowsky, 2009).

3.4.4 Limitations and conclusion

There are challenges to describing and understanding participant motivations for action, illustrated in the ongoing debates among qualitative researchers on the differences between what

participants say they do in interview and what they actually do (Small & Cook, 2021). However, investigations of motive are of central import to sociological research and to in-depth interviewing, as well as in research on trial enrollment decision-making in RCTs (e.g., studies on "deliberation" versus "implementation" mindsets; Jansen, 2014). First, in expressing their motivations to enroll, participants may be subject to "single motive bias" or the tendency to report a single motivation versus the concurrent, multiple motivations that exist (Small & Cook, 2021). To address this, interviewers asked probing questions to ascertain other motivations and reiterated stated motivations for participant confirmation. Interviewers also expressly asked participants about linkages between life events and enrollment decisions (e.g., "Did this experience with 'event X' play a role in your decision to join the study? How so?"). Second, participants in this study may express therapeutic misconceptions in which they conflated research with treatment, therefore making it difficult to distinguish between a participant's motivation for seeking treatment versus participating in research. However, the treatments are available to participants outside of the study, without randomization, so there is likely some draw to participating in research. It should also be noted that enrollment motivations are further complicated by the varying degrees of efficient access to medication, as highlighted in the following chapter. A third limitation is that participants' motivations may reflect a social desirability bias, in particular around cultural norms related to substance use, altruistic acts, conventional employment participation, and downplaying economic motivations (i.e., study stipend). Still, interview responses are informative in that they demonstrate the pervasiveness of norms around desire to work and appear as a "good" person who does good for others. Additionally, interviewers engaged in several strategies designed to reduce such biases, including reducing ego threat (Small & Cook, 2021) by framing questions in a nonjudgmental way. For instance, questions around the study stipend were framed to assume the stipend was a

valid consideration, for instance, “how did you feel about the study stipend? Was it enough?” Fourth, this chapter is not an exhaustive discussion of all of the reasons that people choose to enroll. Although accessing treatment was a key motivation, it bears repeating from the introductory chapter that both study treatments are technically available to participants outside of the study context, and thus treatment access may have played less of a role than participants in earlier phase RCTs. However, this chapter highlights that motivations to participate are multi-faceted and unique for stigmatized illnesses and other people experiencing alienation and marginalization.

People who use drugs are subjected to intense stigma surround their drug use (Kulesza, 2013; Kulesza et al., 2016; Rhodes et al., 2005; Room, 2005), which can lead to feelings of social isolation or barriers to purposeful work and meaningful social roles (Ahern et al., 2007; Cole et al., 2011; Gryczynski et al., 2013; Haritavorn, 2019; March et al., 2005; Sibley et al., 2020). This broader social context of substance use points to the potentially greater significance of research participation for PWUD than other study populations (Jaffe et al., 2021a), and by exploring this context, the current analysis makes some key contributions. First, this analysis supports more complex theorization around involvement in research and incorporating such complexity into understandings of knowledge production, as well as taking appropriate caution in the interpretation of study results. Second, this analysis emphasizes the importance of applied research nested within actual trials rather than relying solely on measures of willingness to participate in hypothetical RCTs (Buchbinder et al., 2004; Park et al., 2012; Uhlmann et al., 2015; Yakovenko et al., 2019). Finally, these results call for broader considerations of enrollment decision-making beyond purely instrumental motivations, to include those focused on the desire for economic stability, a sense of mattering or purpose, and social connection—motivations that may have central relevance for the design of future RCTs and recruitment of PWUD in the field of substance use research.

4 "Trying to get down here when the dealer's closer": Place, politics, and pragmatic trial participation

In the conduct of randomized controlled trials (RCTs), medical sociologists have highlighted the difficulties and potential unintended consequences of standardization in medicine across settings, as healthcare contexts remain far from standardized (Montgomery, 2017; Pearce et al., 2015; Timmermans & Epstein, 2010). In response to critiques about the lack of generalizability of RCTs across such contexts, particularly in early phase trials (Gibbons, 1999), a proliferation of pragmatic RCTs has emerged in health research (Rushforth, 2015). Compared to early phase RCTs that seek to create "ideal," hyper-controlled study environments (Williams & Fisher, 2018), pragmatic trials aim to replicate clinical practice settings in which the administration of the treatment or intervention reflects what would occur in typical clinical interactions. However, while pragmatic trials assess feasibility to generate "real world" evidence, they are still characterized by processes of standardization across contexts (Montgomery, 2017; Pearce et al., 2015; Timmermans & Epstein, 2010), and therefore "what the real world is made of is a question needing more granular and transparent treatment" (Montgomery 2017, p. 40). Emerging pragmatic trials for substance use may be considerably impacted by place and context, considering the local climate and public attitudes around drug use (Eibl et al., 2017; Morin et al., 2017; Small et al., 2006), the status of drug use as criminalized and/or medicalized across jurisdictions (Hansen & Roberts, 2012; Kolla & Strike, 2021), and variations in treatment resources and drug policies (Priest et al., 2019; Socías & Ahamad, 2016). In his research on early HIV/AIDS trials, Epstein (1997) spoke to the consequences of ignoring the broader settings in which RCTs are conducted, observing that "clinical trials do not occur in a vacuum and when the environment in which trials are conducted and interpreted is so contentious, then these experiments, rather than settling controversies, may instead reflect and propel them" (Epstein, 1997, p. 716). In the contentious area

of substance use research, neglecting the social and political dimensions of the context in which RCTs are conducted may result in critical misinterpretation of study results and participants' experiences, with implications for the development of drug policies and treatment practices. However, comparative analyses of trial experiences across multiple sites are rare, particularly in the field of substance use research. Without understanding RCT experiences as locally situated, researchers may fail to appreciate the different mechanisms through which place-based effects impact knowledge production, ranging from initial support for the conduct of drug research, through the recruitment and retention of a representative study sample, to the broader generalizability of trial results. Considering this knowledge gap and these implications, I analyzed interview data with 75 participants enrolled in a pragmatic RCT conducted across four Canadian provinces to understand the ways in which place, treatment access, and policy contexts shape participant perceptions and experiences.

4.1 Background

4.1.1 Place and health research

In his seminal work, Gieryn (2000) highlights the key distinctions of place, as a space that has a geographic location, takes material form, and that is embedded with meaning and values. To Gieryn, a place manifests when "ordinary people extract from continuous and abstract space a bounded, identified, meaningful, named, and significant place," and that in this way, places are continuously created (Gieryn, 2000, p. 471). Health sociologists have expanded this work to explore how place shapes wellbeing through composition (i.e., residents and their connections and interactions; Macintyre et al., 2002), such as social disorder (Ross & Mirowsky, 2009; Shoff & Yang, 2012), as well as context (i.e., features of a place), such as neighborhood characteristics (Robert, 1999; Weden et al., 2008), neighborhood social capital (Carpiano, 2007; Veenstra et al.,

2005), or the built environment (Martin et al., 2015). Others have argued for a relational approach to place and health (Veenstra & Burnett, 2014) in which places have dynamic and fluid boundaries, are connected by nodes within networks, subjectively understood, and imbued with social meaning (Cummins et al., 2007). People are not bound to particular geographical areas but move between spaces and within networks and, thus, the "processes and interactions" (Cummins et al., 2007, p. 1828) may be as important or greater than contextual and compositional effects on well-being. Relational approaches have been applied to a range of empirical studies, including the health impacts of spatial stigma (Keene & Padilla, 2014), how "enabling places" promote recovery from mental illness (Duff, 2012), and the ways in which "social rules" shape access to neighborhood health resources (Bernard et al., 2007). Through these compositional, contextual, and relational analytical approaches, health sociologists have contributed rich understandings of the multifaceted linkages between place and wellbeing.

Clinical trial research can also be shaped by localized processes and interactions. For instance, a wealth of research has explored the relationship between RCT participation and participants' trust in physicians, in researchers, and in healthcare institutions (Abadie et al., 2018; Fisher, 2008; Hall et al., 2001, 2006; Hurd et al., 2017; Jaffe et al., 2021b; Kerasidou, 2016; Sherber et al., 2009). Qualitative analysis of multisite trials may be a particularly effective way to explore situated processes and interactions across research settings (Jenkins et al., 2018). One qualitative study of a multisite insulin trial found that individual, social, and institutional factors influenced the way study staff enacted a particular protocol, highlighting how study data can vary by site (Lawton et al., 2012). On a macro level, policy features can also structure the conduct of a clinical trial. In her work on socioeconomically marginalized volunteers in Phase 1 clinical trials, Fisher (2013) argues that disproportionate focus has been placed on individual-level decision-

making and undue inducement at the micro-level of the study. Instead, study participation should be understood in terms of the broader social and economic context and the structural violence that shapes research participation, which she defines as "structural coercion" (Fisher, 2013). Previous research in the United States has also identified how a lack of access to health insurance and substance use treatment may frame clinical trials as a treatment option (Timmermans & McKay, 2009), which may reduce the voluntariness of participants' trial enrollment. In study settings where participants are without insurance or access to medical treatments, deploying the RCT as a "safety net," where enrollment is directly linked to healthcare access may be ethically tenuous and indicative of patterns of structural coercion that are worthy of further inquiry (Burke, 2014; Fisher, 2013; Joseph & Dohan, 2012). In sum, place-based analysis of clinical trial research is critically important for understanding both micro-level study dynamics and the broader research context that shapes processes of knowledge production.

4.1.2 Considerations of place in substance use research

As context has been increasingly incorporated into health research, substance use research has also experienced a shift toward contextual and environmental understandings of problematic substance use, in tandem with a decreasing focus on individual risk-oriented approaches. Rhodes' Risk Environment Framework (2002) has been employed as an analytic heuristic for studying ecological features of the drug risk environment, including physical, social, policy, and economic elements that position people at greater risk for drug-related harm (Cooper & Tempalski, 2014; Rhodes, 2002, 2009; Rhodes et al., 2003). Building on this structuralist framework, social scientists have sought to incorporate understandings of place and place-making into studies of drug use through investigations of local social and spatial dynamics (Cooper & Tempalski, 2014; Draus et al., 2015a; Duff, 2007, 2011; Keane, 2011; Showalter, 2020). For instance, using a relational

approach (Cummins et al., 2007), researchers have explored "drugscapes" as socially constructed areas of the urban environment, occupied by the stigmatized "other" engaging in drug use and trade (Tempalski & McQuie, 2009). There have also been detailed investigations into the relationships between place/space and substance use treatment (Cooper et al., 2020; Duff, 2012; Sultan & Duff, 2021) and harm reduction services (Kolla & Strike, 2021). Previous analyses have explored people who use drugs' (PWUD's) place-making around hospitals and pharmacies, which they construct as sites of surveillance and regulation (Harris & McElrath, 2012; McNeil et al., 2014; Paquette et al., 2018; Szott, 2014), as well as sites of conflict with hospital regulations, security guards, and other patients (Markwick et al., 2015; Strike et al., 2014). PWUD living in economically depressed urban areas may encounter territorial stigma or the "blemish of place," that follows them as they seek health and social services (Collins et al., 2016; Keene & Padilla, 2014; McNeil et al., 2015; Wacquant, 2007, p. 67). Others have illustrated how urban spaces and places are not always defined by drug- and health-related risk, that they can be sources of wellbeing and social connection (Ivsins et al., 2019), and where PWUD develop survival strategies for navigating the city (Curtis et al., 2018).

In addition to these meso-level place effects on drug use and wellbeing, characteristics of local policy, politics, and public support can also impact drug treatment and research. Despite a policy of universal healthcare coverage for essential health services, the availability, access, and coverage for medications for opioid use disorder (MOUD) varies significantly across Canadian provinces (Eibl et al., 2017; Priest et al., 2019). In most jurisdictions, methadone is provided free of charge for people receiving income assistance or through supplemental prescription programs, but there are gaps among those who are not eligible for low income-based prescription coverage programs but cannot afford medication (Socías & Ahamad, 2016). Some provinces have sought to

remedy these issues with a patchwork of approaches, like the British Columbia (BC) government which started providing MOUD coverage to all those making under $42,000 per year, which ultimately improved retention and reduced treatment interruptions (Hongdilokkul et al., 2021). Still, substance use disorder treatment is far from universally available across Canada (Eibl et al., 2017), and as previous analysis in other contexts have shown (Gartry et al., 2009; Timmermans & McKay, 2009), differential access to MOUD can impact the design and governing elements (e.g., where and how treatments can be dispensed and accessed) of substance use RCTs as well as participants' willingness to enroll, amidst a dearth of alternative treatment options.

Additionally, social and political factors can inform the extent to which drug use is medicalized or criminalized in a given context (Hansen & Roberts, 2012) and thereby impact the climate in which research is conducted and drug treatment is provided. In the United States, highly controlled substances (e.g., cannabis, diacetylmorphine, etc.) are difficult to study given the barriers related to regulatory (e.g., drug procurement), legal (e.g., contradiction with local laws), ethical (e.g., risk of prosecution of participants) and social (e.g., stigma toward investigators/participants) aspects involved in research (Andreae & Einstein, 2016). As a result, a "Catch-22" has emerged in which substances are highly controlled and considered to have no therapeutic value because they cannot be studied for their therapeutic value (Andreae & Einstein, 2016). Such policies around drug use, research, and treatment have been characterized as an exemplar of morality policy, or "policymaking that involves clashes of core values about the legitimacy of providing certain kinds of services to a target population" (Bowen, 2012; Wild et al., 2017, p. 10).

These locally constructed political and policy decisions can determine the allocation of resources for harm reduction, prevention, treatment, or criminal enforcement (Cooper &

Tempalski, 2014; Gieryn, 2000; Kolla & Strike, 2021; Morin et al., 2017; Tempalski et al., 2007). In the US, access to syringe exchange programs and drug treatment varies considerably nationwide, but availability and access to these programs has been demonstrated to be associated with policy support not with demonstrated need (Friedman et al., 2007; Tempalski et al., 2007, 2020). In Canada, supervised consumption sites were established in Vancouver 14 years before they opened in Toronto, a difference that has been attributed to a confluence of public support, variations in political support for supervised consumption regionally and nationally under different governments and, eventually, greater levels of support from law enforcement in Vancouver compared to those in Toronto (Hayle, 2018). Such advances in drug policy in BC have consequently attracted additional funding for drug research, which in turn has garnered more support for novel interventions and greater access to emerging treatments for PWUD (Tempalski et al., 2007; Wild et al., 2017). In combination with individual and social characteristics (e.g., drug use patterns, stigma, etc.), these place-based institutional and policy features may directly or indirectly structure participants' clinical trial experiences, including their motivations to enroll, acceptability of the study treatment, and adherence to the study medication. To understand the ways in which these place effects impact RCT participant experiences and in consideration of the increasing demand for novel drug treatments (Pérez-Mañá et al., 2013) and the growing number of substance use RCTs across jurisdictions (Tai et al., 2021), in this analysis I ask, how do meso- and macro-level features of place shape dimensions of substance use RCTs as experienced by enrolled participants?

4.2 Methods

While the OPTIMA parent trial is described in the introductory chapter, there may be additional characteristics related to the physical study site as well as the policy context that are of

key relevance to this chapter. In contrast to early phase trials conducted in isolated settings (Williams & Fisher, 2018), this phase IV multi-site pragmatic trial embedded the study sites in urban centers. The physical research sites ranged from a newly constructed $469.5 million-dollar skyscraper in Montreal, housing a range of health research studies, to a teaching hospital founded in 1894 in Vancouver, recognized for more specialized care, including HIV/AIDS and the care of socioeconomically marginalized populations. The sites were also distributed across four provinces, each with their own provincial guidelines around MOUD treatment, treatment coverage, and funding priorities for treatment, harm reduction initiatives, or recovery programs (Eibl et al., 2017; Priest et al., 2019). These local policies are constantly in flux, as new governments gain control, as medical guidelines change, and with shifting public support for initiatives that seek to address the toxic drug supply killing a growing number of Canadians every year (Eibl et al., 2017). As these policies and politics change over time, nested qualitative research within substance use RCTs may be particularly well-suited for the study of place-based differences, as this method may be able to incorporate understandings of context and relevance for local populations (Jenkins et al., 2018; Mannell & Davis, 2019).

As described earlier, qualitative interview data was derived from 75 participants (n=115 interviews) enrolled in the OPTIMA study (Socias et al., 2018). There were 24 participants from the Vancouver site, 20 in Calgary, 16 in Montreal, 12 in Toronto, and three in Sudbury. All interviews were transcribed verbatim, and interviews conducted in French were professionally translated into English. I used nVivo qualitative analysis software to analyze the interviews and employed a flexible coding approach (Deterding & Waters, 2018). First, I indexed the data, using the interview guide as an initial structure. Then, I further synthesized the data by analyzing relevant indices and applying analytic codes. This analysis focused specifically on meso- and macro-level

features of participants study enrollment: initial experiences at the study site; experiences in attending follow-ups; perspectives of the local substance use treatment and healthcare contexts; experiences with accessing the study treatment; and participants' structural critiques (e.g., criticism of policies) when they rose organically during interview.

4.3 Results

4.3.1 Meso-level: Navigating study spaces

The study site. With the exception of the Sudbury site that catered to participants from rural locations, many participants remarked on the centrality of the study sites and how conducive the location was for attending follow-ups because the sites were "right downtown and I'm always here anyways" (Tim, White man, Calgary). Many participants were already familiar with these sites and associated them with previous positive healthcare experiences. The Toronto site seemed to have the greatest name recognition, likely due to an institutional history of providing mental health care since 1850 when it was first established as a psychiatric asylum. As Patrick (White man, Toronto) describes, "Everyone knows about [study site]. I mean, it's the center for addiction recoveries. It's Toronto's number one place for recovery, right?" Several participants described being referred there by their doctor or recommended they go there by family or friends. The study site retained widespread recognition in the community and its connection with other affiliated service may have instilled confidence in study participants, as well as participants' broader social network, potentially resulting in greater social support for participants. While this institutional recognition had several benefits noted by participants, including reputational trust and prestige within their personal networks, the close association between the clinic and substance use and mental care could also lead to stigma that deters potential participants. As Andrew (White man, Toronto) recounted: "When I tell people I'm coming down here, they're like, 'Dude, what the

fuck's wrong with you?' I said [Laughs], 'What the fuck's wrong *with you*? There's all different forms of mental illness, man.'" While the Toronto clinic had name recognition for treating substance use and mental health, the other sites were embedded in healthcare clinics or hospitals that treated an array of conditions, and these participants may have benefitted from greater confidentiality around the nature of their health concerns while attending study follow-ups. As these data highlight, a site's reputation and participants' previous experiences there could potentially shape perceptions and expectations before the trial even begins.

Other participants remarked on particular interactions between physical and institutional components of space and the social dynamics surrounding the study sites. For instance, Keith (White man, Toronto) expresses his less favorable views on the neighborhood in euphemistic terms: "[it] was interesting where [study site] is physically located in Toronto, in that general area of the city is a little questionable. [Chuckle] So if you're walking in that area, yeah, it's a little unique—you encounter unique people. So I would say that is interesting." In a more direct tone, a Calgary participant, Nick (White man), remarked, "This place is shady as hell. I had never been to the [study site] before I came here either, so it's just been an entirely eye-opening experience." For these participants, study sites once associated with healthcare services were also becoming conceptualized as stigmatized "drugscapes" (Tempalski & McQuie, 2009). Relatedly, participants noted the potential challenges of the close proximity to drug use and use-related activities as a result of being located near harm reduction services, like the safe consumption facility on the ground floor of the Calgary site. For Eric (White man, Calgary), the site was a potential trigger for substance use: "There's lots of users and stuff here, right, because of the safe injection site. So I try not to hang out down here. Like the odd time I do run into somebody down there, asks me if I want to get high or, you know. That's about the only bad thing about coming down here."

Additionally, the clinics and hospitals typically had security guards on staff which some participants felt to be a threat, like Justin (White man, Vancouver) who remarked:

> It's not bad, other than the fact that the security guards in this building are just—I think they're bored because I swear to god, they just harass and pick on people. This morning, I actually wanted to come here earlier to go to the [study site] right at 9am 'cause it's faster. I got here quarter to 8am and instead of sitting in the empty hallway, I just sat in the waiting room downstairs. And after about 15 minutes, they come up three strong and kicked me out of the building. Just for sitting there, waiting for [study site] to open.

Given the sites' locations in urban centers and proximity to heavily surveilled drug markets, city police were often nearby, rendering the study site a place of heightened visibility for PWUD. In one instance, Paul (White man, Vancouver) was arrested just after leaving the study site:

> I ended up going to jail, and that was the worst 28 hours of my life…I'm leaving here with my script. And when I got on the SkyTrain, I got caught, arrested on the SkyTrain. [Interviewer: They just came across you, or they knew you…?] No. Someone I knew was outside of [study site] when I got out of here, and they suggested that we take the SkyTrain. So I think what happened was—I found the person in my group of individuals that I hang out with, that they got paid by the Crime Stoppers that day. It had to be.

According to Paul, an acquaintance knew he would be at the study site, and in exchange for compensation gave his location to police who had a warrant for him. Due to his arrest upon leaving the study site, Paul was unable to fill his prescription and subsequently experienced withdrawal in jail. Justin (White man, Vancouver) was also arrested shortly after leaving the study site and was unable to fill his prescription: "I left [study site] and I decided to cross through Robson Square and a bike cop pulled me over. I had the prescription in my pocket. When I got arrested it was Monday morning and I didn't get my methadone until Saturday morning. So that was bad. I was really hurting, really sick." Justin was arrested because he fit a suspect description, and though he was released later that week, he described experiencing severe withdrawal while in jail. Though Paul and Justin were able to get access to methadone again, many PWUD must repeatedly navigate

similar difficult circumstances as they seek medical treatment for a condition that is simultaneously criminalized, often while embodying visible markers of a "territorial stigma" (Wacquant, 2007). As the study spaces largely took place in urban settings in close proximity to "drugscapes," sites were surveilled by police and security which could impact participants in critical ways, ranging from discomfort, as in Nick's case, intimidation, like Eric felt, or increased visibility to police and arrest, like Paul experienced—place effects that could potentially deter participants from attending follow-ups or from accessing study medication.

The pharmacy. While there are challenges around medication adherence for any clinical trial, one of the OPTIMA study treatments required daily witnessed dosing at the pharmacy, a place of regulation and surveillance (Harris & McElrath, 2012). Daily pharmacy attendance was a substantial burden for participants with competing responsibilities and time constraints. Philippe (White man, Montreal) felt that this witnessed dosing component interfered with his family life, as the physical distance between his daughter and his pharmacy was significant: "let's say that I want to go sleep at my daughter's mother's home, because my daughter has to go to school the next day. There, I have to do the round-trip to get access to my bottles. I can't have my bottles. Absolutely everything is fine except that bit! I don't have access to my life now because of that." Similarly, for participants who were working, fitting their daily prescription dispensation into their schedule posed a significant barrier as some pharmacies did not open until after the start of their workday. Keith (Man, Toronto, race/ethnicity not given), interviewed after the start of the COVID-19 pandemic, noted the potential difficulty of medication adherence in regular circumstances: "The fact that I'm working from home makes life easier. But if there was no COVID, being physically at the office, then the pharmacy—I think that would be complicated." For PWUD entrenched in drug scenes, it could be difficult to get to the pharmacy every day, as Eric (White man, Calgary)

noted in describing his major barrier: “Just energy. Yeah, the energy, trying to get down here when the dealer’s closer than here.” Thomas (White man, Vancouver) further detailed the challenges of adhering to a methadone prescription:

> One of the things when you’re addicted to mood altering chemicals is that you’re not very good at getting places on time and stuff, like your focus is on other things. …When I’m forced to go to a pharmacy and pick up my script, sometimes you have to go seven days a week for the first little while until your doctor deems that you can have carries. And on the weekends, they’re only open till noon and so you end up missing a day and when you miss that day, generally speaking, you go out and get something else to replace the methadone that you’ve missed. So the next day you’re not all mentally there and so maybe you don’t make that day either. Before you know, you missed three days and your prescription’s cancelled, and you got to get a new script. So it’s kind of like a license to fail.

As Thomas highlights, integrating pharmacy visits into daily life could be difficult, especially for those not attuned to the clinic’s organization (e.g., operating hours), or governing procedures (e.g., number of permitted missed doses). Other participants felt frustrated with both the burden of daily dosing as well as the witnessed dispensation, like Nick (White man, Calgary), who found this regimen to be, “[a] serious pain in the ass. Well for somebody like me, who is used to getting a month worth of pills at one time and having them delivered to my house, and then having to go to a pharmacy every single day and get the third degree from these people and have to do random piss tests.” As described in Chapter 2, naïve participants without previous MOUD experiences were likely to find such medication restrictions to be especially burdensome. However, some participants on suboxone were eventually able to gain more flexible access. Amir (Middle Eastern man, Vancouver) describes this transition, “In the beginning, it was a little bit tough. One time I have to go every day for the pharmacist to witness me, even Sundays. That was very tough in the beginning but now I’m good. Imagine Sundays go—some pharmacies they are not even open. But I had to come all the way down to one in Vancouver. Now they know me.” While Amir initially had to commute each day from a suburb to access his prescription, he eventually built trust with

his pharmacist and doctor and was able to acquire take-home doses of suboxone. Many participants found that the relational aspects they had with spaces and activity spheres (e.g., work, caregiving) of their day-to-day lives were interrupted or interfered with the need to both attend pharmacies to obtain treatment and adhere to strict pharmacy regulations. In essence, as spaces of both medical care and medical control, the pharmacy had the capacity to positively or negatively impact study experiences.

Participants' experiences within pharmacy spaces were also shaped by the local features of the healthcare environment, including MOUD availability and acceptability and treatment stigma. While study staff aided participants in finding a convenient pharmacy, participants across sites described varying availability of the study medication as not all pharmacies carried MOUD. Participants with MOUD experiences in different Canadian cities were especially attuned to site-specific differences. For instance, Anthony (mixed race man) in Calgary who had previously lived in British Columbia, remarked: "Here, you have to travel bus, train and walk for half an hour to get to the one place that has [methadone]. The size of Calgary and it's just like, what the hell are you guys thinking? A town in BC has 14 locations where you can get your prescription of methadone and a city this size has two. That's really screwy." In another instance, Sandra (White woman, Vancouver), who moved from Vancouver to Toronto during the study, described the difficulty in transferring her methadone prescription to an Ontario pharmacy: "I went to three different pharmacists and they're like, 'we don't have it at this pharmacy. We don't have it at this pharmacy.' And then finally I went to the one across the street and he said it was mostly because they don't want ex-drug addicts in their pharmacies. They don't want to have to deal with those people." As illustrated by Sandra, treatment-related stigma among pharmacists or pharmacy managers may shape MOUD availability and, consequently, participants' study treatment

adherence. These narratives highlight how the varying availability of MOUD in pharmacies across study locations may affect participants' medication experiences (e.g., being required to travel to a distant pharmacy versus a local pharmacy may deter participants from adhering to medication).

Even within pharmacies that dispensed methadone, some participants perceived treatment stigma from pharmacists. In Montreal, Sophie (White woman) felt her pharmacy options were limited because she had to pick up both her harm reduction supplies and methadone prescription in the same place and risk facing judgement: "Honestly, it's happened that I've been uncomfortable about going to pick them up at my pharmacy. Because Pharmaprix, that's pretty much the only place where there are needles, and that's where I go to pick up my methadone. But when you don't have a choice, you don't have a choice!" Treatment stigma underlying the methadone availability also shaped participants' interactions with pharmacists. After transferring pharmacies, Zack (White man, Calgary) encountered issues with his new pharmacist: "I just thought maybe the pharmacist didn't like me, because I was going to a smaller sort of pharmacy, like a neighborhood pharmacy run by an older gentleman. I just thought maybe they weren't making the [methadone] formula right or they were watering it down, I didn't know. I was sick." Jacques (White man, Montreal) also encountered issues with his pharmacy: "we changed pharmacies at a certain point because there was a problem with the privileges. The pharmacist was stubborn, and she didn't want to give them to [friend in the study] because he was at [homeless shelter]." Both of these participants recalled instances in which they perceived the pharmacists' stigma to directly impact their access to the study medication. Although the pharmacies were not directly affiliated with the OPTIMA study, the interactional and institutional dynamics in pharmacy spaces could directly affect study medication experiences. Further, the varying availability of MOUD at pharmacies

across study locations could affect participants' ability to adhere to study medication, highlighting a fundamental challenge of multi-site, pragmatic trials.

Navigating study spaces. Though participants described challenges related to the study sites and pharmacies, they also employed a range of strategies to navigate these challenges. For instance, while transportation to the clinic or pharmacy was not covered by the study, participants drew on their networks of friends, family, and local resources. Joseph (Indigenous man, Calgary) described relying on Calgary city bus drivers who were sympathetic to PWUD, especially in the winter:

> A lot of the bus drivers understand that, okay, we got an ugly fucking nasty police force here and that guy out there in the fucking snow with no shoes and fucking no jacket, hitchhiking to get fucking somewhere, anywhere, so he's not fucking frostbit frozen dead tomorrow because the police dropped him off—the bus drivers'll pick you up. Or you tell them, "Listen, I have a study in the opioid clinic downtown and I have no money but I have to get there." They're pretty good.

Other participants reduced the number of times they would have to come for follow-ups by strategically scheduling all of their study appointments, pharmacy visits, and other nearby social service or medical visits on the same day. Another participant, Paul (White man, Vancouver), did not seem to view the distance as a barrier at all, and appreciated the structure that his commute to the pharmacy gave to his day:

> I liked going. I like having something to do too. I know I got to be at my pharmacy by 2:00 in the afternoon on the weekends, and I've got to be there by 4:00pm on the weekdays, so that gives me something to do. And it's pretty far out there too, right? Like people are surprised that I go that far to get my methadone. And when I leave, I can walk back downtown, and it's all downhill, and there's all kinds of stuff to do. Like there's a couple of hotels in between and there I stop and see some friends of mine at a [supportive housing facility]. And sometimes I just stay there; it's a shorter distance to my methadone clinic the next day.

Although this perspective was somewhat unique among participants, it was noteworthy how Paul incorporated his daily pharmacy trip into his conceptual assemblage of the city and his friendship

network and then structured his day accordingly. Some resourceful participants were able to overcome more institutional barriers to treatment (e.g., prescribing guidelines, coverage issues) by drawing on their experience and on their networks. For instance, Brian's (Asian man, Vancouver) treatment was jeopardized when his belongings were stolen: "I got my bag stolen and all my IDs gone so I can't [get] my prescription. I have to go to Richmond every day to get my methadone. I tried to go to Shoppers over here but I don't have ID so they won't let me get my prescription here. [Interviewer: So you're going to Richmond every day?] With my dog on the train." Brian remembered that his old pharmacy had a copy of his ID on file and so without identification or transit pass and while carrying a small dog on a 40-minute commute, Brian still managed to access his methadone. Brian later commented that he did not find this process to be onerous because "it's a lot easier doing the methadone. It's a lot of work being a drug addict." To Brian, these institutional barriers paled in comparison to the daily labor of generating income, procuring drugs, and managing drug scenes. As these narratives illustrate, while some place features could impede study participation, many PWUD could draw on an assemblage of resources embedded in places and spaces that facilitated study participation (Ivsins et al., 2019).

4.3.2 Macro-level: Treatment context

As a pragmatic trial, the OPTIMA study aimed to reflect real-life treatment settings, but across Canada these treatment settings seemed to vary in critical ways. It should be noted that, generally, participants recognized that Canada had more progressive drug policies than other countries. Martin (White man), who moved back to Montreal after living in the United States remarked, "I'm happy that cities like Montreal and Vancouver and even Toronto have been so positive on wanting to find help for people like me." Participants also appreciated Canada's universal healthcare system, even if not all of their healthcare interactions were positive. Jacob

(White man, Toronto) remarked: "I think Canada's awesome. The fact that we've got free healthcare. When you actually go in and see and experience it—yeah, no regrets on paying taxes." However, the social climate around drug use varied across provinces, which was especially apparent to participants who had lived in different Canadian cities. For instance, Joseph (Indigenous man, Calgary) felt that both government policies and intensifying stigma were making it harder for PWUD to survive in the city:

> And this [Mayor's] got no room for fucking addicts. I just see what he's done and he's eliminated any survival for addicts in this city. You can't even find a warm vent blowing out of a building. Like he's turned people—people hate fucking addicts in this city like I've never seen anywhere. Oh my God. They'll kick rocks at you and they'll fucking swear at you. They'll spit on you if you're panhandling. But it's okay for you to do to me because I'm an addict. That's Calgary. … Living in Vancouver, or Edmonton, or Toronto as an addict is doable. Here, I don't know how many fucking people die every week. A huge issue is that everybody knows that it's Alberta. It's got the oil, it's got to be rich. There's money there. People are still flocking to this place in droves, addicts included, and they don't realize they're running full tilt into a fucking 500-degree oven.

In this quote, Joseph observes an interplay of elements, including the economic and employment context, local drug policies, and shifting social attitudes, that contribute to the marginalization of PWUD and the ongoing overdose crisis. Other participants made similar connections between public policy, public perceptions and experiences of living with a substance use disorder. Alain (White man, Montreal) felt there was "too much judgement" that shaped the availability of treatment services, and that government had the wrong funding priorities: "Instead of putting 5 million into a large [Ferris] wheel in the Vieux-Port, I would have put it in the [homeless shelter]. That's sort of what I deplore, in our work, our society—people on the street, there are loads, you could have put that money towards them." Although not all participants provided the same sharp critiques of government drug or fiscal policies, their accounts of accessing MOUD across trial sites here and in earlier chapters, demonstrated the impacts of such macro-level features. In contexts

where there are negative public perceptions around drug use and policies divert funds from assistance programs, treatment may become more difficult to access, even in a study setting, as described below.

Medication coverage. While the RCT was situated in a universal healthcare context, gaps in MOUD prescription coverage were apparent, especially in Alberta. Many Alberta participants initially had access to the study treatment through the province's emergency coverage program but lost access when this coverage eventually lapsed. Tim (White man, Calgary) explained his situation: "The emergency coverage was same day and that was good. But then they cut off getting coverage for the next month, because they said I didn't do my 2017 taxes or something, which I still don't understand what that has to do with anything. That was the worst part of it, so I could not get the medication coverage. It was insane." Participants seemed to lose access to income assistance ("Alberta Works") and medication coverage with some regularity, but given that this was a pragmatic trial, participants could remain in the study even without MOUD. Trial staff also helped many participants file their taxes to prove their eligibility for Alberta Works and for MOUD coverage. Joseph (Indigenous man, Calgary) voiced his frustration with this situation:

> Okay, so I'm Canadian. I'm on social assistance. I have a Grade 8 education. But I need to get off this shit and I'm going on methadone. Now you want me to find funding for that methadone? How the fuck am I going to do that? I don't know how to do that. But that was left in my fucking bag and if [study staff] wasn't there, I would have never done it. No fucking way.

Aware of his right to healthcare, Joseph was perplexed as to why and how he would find funding for his methadone. Amanda (White woman, Calgary), who had moved to Calgary from Prince Edward Island, noted the provincial discrepancies in coverage: "[In PEI,] if you go through the government one, all methadone's covered; you don't have to worry about it. And [here], it's expensive, like ten to 15 bucks a day. You may as well just go [be a] drug addict again because

sometimes it's cheaper." Considering these barriers to accessing MOUD, some participants experienced gaps in study treatment and had to substitute with unregulated opioids which ultimately placed them at risk of overdose. Greg (White man, Calgary) pointed out that in clinical practice, such a policy would be unethical: "If you have your medical, they even wean you off the methadone, right? If they know they're going to take it away. So, getting cut off completely, it's—like they were using dope more. Right back to using dope." While study staff and physicians would not have supported the sudden cessation of MOUD, Alberta's policies around income assistance and medication coverage may have produced such an outcome over the course of the study. Participants in other sites did not report such issues with medication coverage, which may speak to either their ability to pay out-of-pocket, or to provincial differences in insurance coverage for people accessing income assistance (Eibl et al., 2017). Just as politics, policy and public support can shape the availability of drug treatment and harm reduction services (Cooper & Tempalski, 2014; Eibl et al., 2017), there are ensuing consequences for the conduct of substance use research, study outcomes across jurisdictions and, most importantly, the safety and wellbeing of study participants.

Treatment access. While Alberta participants experienced issues with treatment coverage during the study, PWUD in other provinces experienced barriers to treatment prior to the start of the study, which shaped their willingness to enroll. In Ontario, Keith (man, race/ethnicity not given) recalled that when he "entered [the study site], I was told that I could either wait a few weeks or months in order to get into the program or I could start this OPTIMA study program which is basically exactly the same thing and you start, like, tomorrow." In Montreal, Edgar (White man) encountered a similar situation and described his relief:

> Everyone was telling me that often, there's a month or month-and-a-half or longer waiting period, it depends on the time of the year. And I know that I went through

> faster because I'd accepted the OPTIMA study. For me, I thought it was excellent because I was fed up with waiting! I couldn't face a month and a half of waiting. Really, I didn't feel good. So, in my case, according to what the clients who I knew were telling me, the amount they waited compared to me, I'm lucky.

Although MOUD is accessible to participants outside of the study, trial enrollment seemed to expedite treatment access, particularly in Quebec where wait times were described by participants as longer. However, even in settings where MOUD can be accessed more quickly, participants pointed out that this is not fast enough for someone experiencing withdrawal or otherwise in distress. Andrew (White man, Toronto), who enrolled in the trial via clinic referral, recalled his initial experience seeking treatment:

> When I called that day, and they said, "Well, you can't come in for another three weeks," I'm like, "In three weeks I could be dead. I want some fucking help." Every treatment center I've called, the same thing. Unless you got 30-grand for a treatment, then you're not getting help. And then the lady goes, "Oh, wait a minute. Are you interested in taking a study?" I said, "A study? I'm not calling for a study." She goes, "Oh, it has to do with an opiate study. I can get you an appointment tomorrow. Somebody just canceled." I'm like, "Yes, sign me in." And then she goes, "Do you want to hear about it?" I said, "No. If it means I'll get some type of treatment through it, yeah, I'm in this study."

Andrew felt somewhat desperate to access treatment and for him, the trial was the most efficient pathway to treatment, with little regard for the study details. While MOUD is technically available to these participants, the severe illness experienced by PWUD in withdrawal, the toxic unregulated opioid supply, and the barriers to efficient MOUD access may indicate a study recruitment and enrollment process that could be characterized as structural coercion (Fisher, 2013), in which broader structural considerations shape the voluntariness of study enrollment.

While participants in Ontario and Quebec described barriers or delays in accessing MOUD, in British Columbia MOUD is considered to be widely accessible in a timely manner. Nevertheless, in the eyes of participants with previous treatment experience, not all medication formulations are considered equal. In 2014, a provincial policy change transferred patients from a

methadone prescription to a different medication formulation, "methadose," without their knowledge or consent. Many patients felt methadose was inadequate and left them with withdrawal symptoms and, as a result, patients returned to the unregulated opioid supply and risked possible overdose (McNeil et al., 2015). In joining the OPTIMA study, some BC participants were interested in potentially accessing the old methadone as their study treatment. Jason (White man, Vancouver) described his previous experience and motivation to enroll: "I tried methadose. It just didn't work for me at all. I was taking a large dose of it and I wasn't even touching my habit. The only one that ever worked for me was methadone. Years ago, I took it and it worked for me, so that's why I decided to do this was because they said they could get me real methadone and I'm willing to give it a shot." Although Jason had hoped he would get access to methadone through the study, in his exit interview he noted the study "had me on Metadol-D actually. It's supposed to be more like old methadone but it's still not and it takes too long to get up to a dose where you can actually start to feel it." In addition to medication formulations, other experienced participants noted the changes in dosing regulations, like Lisa (Indigenous woman, Vancouver) who recalled: "It's hard. I like the way they had it before. Where they would just give me the whole bunch straight up because obviously, I got a high tolerance for dope, right, because I think I've only OD'd once when the fentanyl came out. And I think the doctors should know like that I'm not going to OD from methadone." Several participants in the Vancouver site made similar observations that the potency of the local drug supply was extremely high, but the starting dose of methadone was low. As Brian (Asian man, Vancouver) explained: "It takes a while to plateau, 'cause I was using quite a bit. And then it would stretch out very long. So it took about five to seven days to feel better." It may be that, though starting doses were likely comparable across sites, some Vancouver participants experienced a greater delay in achieving the same level of relief from methadone due

to the potency of the local drug supply and the specific formulation of methadone used in BC (Bouchard et al., 2020). While these participants generally were retained in the study, the accessibility of the treatment did not necessarily indicate sufficient treatment, and participants may have needed to temporarily supplement with unregulated opioids, thereby prolonging their exposure to the toxic drug market.

Social context. In Vancouver, participants' perceptions of the study treatments were also shaped by the local social context around drug use and emerging novel treatments. Decades of activism and advocacy in Vancouver resulted in rapid changes to provincial drug policy, as Brian (Asian man, Vancouver), observed: "Before it was really hard to get on methadone, but now they changed their thinking way, right? The four pillars." After implementation of the "Four Pillars" approach (i.e. pillars focused on harm reduction, prevention, treatment, enforcement) in the early 2000s, Vancouver gained international recognition for its innovations in opioid treatment (Small et al., 2006), of which participants seemed well aware. Michael (Indigenous man, Vancouver) remarked, "[The study physicians], they know what they're doing. That's why I can't wait to be sober, to be one of their success stories. Vancouver is one of the best in the world, man, and that's why people are coming here for it." While Michael was glad to be involved in OPTIMA, other participants were curious about alternate emerging treatments, like injectable opioid agonist treatments ("iOAT"; e.g., hydromorphone, diacetylmorphine), that would fill the "huge gap in treatment services that falls that falls before suboxone and before methadone" (Sam, Indigenous man, Vancouver). Thomas (White man, Vancouver) had a similar perspective on the study design:

> I think there should be basically three options. You have an addiction to something. You can go on methadone, you quit using the stuff and then they take you off it and you live happily ever after. You go on suboxone, you quit using the stuff, they wean you off it and you live happily ever after. If you don't, then they offer you the drug that you're doing, and you can continue to do that for the rest of your life if you want.

In his hypothetical study, Thomas describes a third "safe supply" option, which has generated widespread support among PWUD, researchers, and activists in Vancouver in recent years, as one strategy for combating the ongoing overdose crisis (Ivsins et al., 2020). Since the start of the pandemic, such risk mitigation initiatives have been implemented but this occurred after data collection for the current study was complete. Jason (White man, Vancouver) provided further rationale for safe supply:

> The replacement that I want, yes, it's incredibly hard to get on. Which is kind of bullshit actually because I know that [medical clinic] wants to expand their program too, but fucking BC government is—you know what I mean? Until they do that man, every death is blood on their hands man, as far as I'm concerned. Because they can put an end to it by letting a clean healthy heroin in and putting people on a program. They could end the crisis like that.

In essence, Jason was seeking treatments beyond what was being offered by the study, and reflecting the language of local drug activists, seemed unimpressed with the inaccessibility of novel treatments and safe supply. In some ways, Vancouver's position as a vanguard of harm reduction and substance use research was a motivating factor, but in other instances, prompted additional critique from participants about the (lack of) availability of novel treatments. Largely, these critiques did not arise in interviews with participants at the other sites. One Montreal participant spoke of his time as a participant in North America's first RCT for prescription heroin (Oviedo-Joekes et al., 2009), and a few participants in Calgary mentioned the pilot program for injectable opioid agonist treatment, but that has since been shut down by the provincial government (Omstead, 2020). Across study sites, participants in Vancouver, a site characterized by treatment innovation, were either not specifically motivated by treatment access or expressed broader critiques of the medication, whereas participant responses in other study sites, characterized by less treatment innovation, tended to produce more expressions of appreciation. The contrast

between these perspectives exemplifies how the broader social context of a place can underlie expectations for and perceptions of research.

Across all trial sites, participants spoke to localized characteristics that shaped their enrollment, medication experiences, and expectations and perceptions of the study objectives. Their narratives referenced the research site reputations, physical features of the sites (e.g., location, travel distances, surrounding "drugscapes"), relational and interactional elements within clinics and pharmacies (e.g., witnessed dosing, stigma, police and security interactions), as well as how they managed threats to study retention or medication adherence through a network of resources and strategies. Additionally, participant accounts illustrated the impact of broader policy and politics across provinces related to study medication coverage (Alberta), wait times to access MOUD in regular care (Ontario, Quebec), medication formulation changes or novel harm reduction initiatives (British Columbia) that may have impacted their enrollment, expectations for the study and medication adherence, all highly consequential in the life course of an RCT and study outcomes. Altogether, these results highlight key processes through which features of place may bear effects on the processes of knowledge production.

4.4 Discussion

As a pragmatic RCT, the OPTIMA trial was designed to examine and compare the feasibility and effectiveness of the medications, and both data collection and treatment occurred in clinical settings to reflect clinical practice. In qualitative interviews conducted at the beginning and end of their trial involvement, participants revealed the ways in which the "real world" influenced their enrollment decisions, trial experiences, and study perceptions. Reflecting the ideals of "objectivity" in RCT design, many of these real-world circumstances were not operationalized or measured by the parent study and could not be randomized across study arms.

However, participant narratives revealed how knowledge production processes were socially and spatially embedded, thus shaping individual and trial outcomes. Specifically, study experiences were situated and discussed within both meso-level elements, such as study spaces (e.g., hospitals, clinics) and processes in these spaces (e.g., interactions with pharmacists, security guards), as well as macro-level forces, including provincial policies (e.g., medication coverage) and the treatment context (e.g., access to medication, wait times). Applying such relational and contextual understandings of place and health reinforces the extent to which RCT experiences are locally situated and highlights a fundamental issue of multi-site, pragmatic trials that creates site-specific differences not addressed by randomization protocols.

In describing their initial decision-making around enrollment in the OPTIMA study, some participants described previous positive healthcare experiences at the sites or emphasized how reputational factors were a draw, such as the positive perceptions of the Toronto research institution, which may have boosted participants' trust, willingness to enroll, or levels of external social support. Research sites varied in terms of their positions within institutions (e.g., in outpatient clinic settings, a hospital, a modern research building) and physical characteristics, including location within the city, and geographic centrality to other health and social services, which could at times pose challenges for participants. Still, participants described ways of mitigating these barriers to follow-up or medication adherence, such as strategically drawing upon an assemblage of resources (Ivsins et al., 2019) to navigate the city or avoiding potentially triggering harm reduction services around the study sites. The proximity of the sites to "drugscapes" that were heavily surveilled by police meant that participants were exposed to a certain level of risk (e.g., negative police interactions, arrest) in order to attend study visits or access their medication. While PWUD are medicalized in the study settings, the moment they leave

the building, or even the research office, they may be subjected to harassment, targeting, or arrest. These experiences may be most prominent for people who are socioeconomically marginalized, racialized, or experience territorial stigma (e.g., visible markers of homelessness; known to police in highly surveilled neighborhoods, etc.). Further, the "processes and interactions" within places indirectly affiliated with the study (e.g., hospital, pharmacy) also shaped study experiences, for instance, when participants encountered stigmatizing attitudes or resistance to dispense MOUD from pharmacists, reflecting prior research around the link between intervention stigma and gatekeeping among pharmacists (Cooper et al., 2020; Harris and McElrath, 2012; Madden, 2019; Paquette et al., 2018). As these results demonstrate, place can confer power that becomes embedded, as participants "extract" the research space as a "bounded, identified, meaningful, named, and significant place" (Gieryn, 2000, p. 471) with real consequences for individual health outcomes and for the conduct of trials and the generalizability of study results.

While all Canadians are guaranteed universal healthcare to essential services, these findings demonstrated that timely and continuous access to MOUD varies by province, and that these structural barriers shaped both enrollment and perceptions of the study. In Quebec and Ontario, wait times for MOUD in regular clinical care proved to be such a great obstacle that study participation was perceived as a highly desirable alternative. The underfunded or under-resourced substance use treatment reflects other contexts in which there is employment- or income-dependent health coverage and uninsured participants enroll in clinical trials to access healthcare (Timmermans & McKay, 2009) and may reflect a type of structural coercion (Fisher, 2013), where PWUD who need immediate access (e.g., to avoid physical withdrawal or overdose) enroll in the study for lack of a better option. In western Canada, participants spoke of relatively efficient access to MOUD outside of the study, and thus study enrollment may not be subject to structural

incentives outside the design and operational activities of the study in the same way. However, treatment coverage could be abruptly ended, as was the case in Alberta among people receiving income assistance. While they waited for coverage, some participants were able to pay out-of-pocket while others stopped taking the study medication entirely and began to use unregulated opioids. For these participants, this could be discouraging at best, as they felt they had worked diligently to achieve a stable dose of methadone, and life-threatening at worst, as they were exposed to the unregulated, toxic opioid supply. These structural barriers to treatment create both participant incentives to enroll in RCTs as well as form constraints in participant retention, complicating data comparison across study sites and underscoring the ways that policy and politics are embedded even in "objective" processes of knowledge production. Trial researchers should consider methods to sufficiently measure such structural considerations to understand the practical realities of study participation, particularly for pragmatic trials where real world contingencies have concrete implications for the study data and trial outcomes.

The treatment context and, by extension, the research context are also informed by the broader social context around drug use. As highlighted in a previous chapter, more participants in BC had treatment experience and, as this analysis showed, some experienced disappointment when study enrollment did not ensure access to the "old methadone," and instead they received formulations that they perceived to be less desirable. These data reflects previous research on the change in formulation and associated challenges (McNeil et al., 2015), as well as an ongoing class action lawsuit against the BC Ministry of Health, College of Pharmacists, and makers of Methadose organized in part by BC drug user activist groups seeking to restore access to the old formula and compensation for those hurt by the formulation change (Woo, 2020). Such collective actions contribute to social and policy shifts as people with similar circumstances are clustered

together and place-based networks are formed (Brown et al., 2004; Epstein, 2016; Gieryn, 2000). In British Columbia, drug advocacy and activism continues to be a driving force behind the expansion of treatment and harm reduction services, and around them extensive research networks are formed, positioning the city on the frontiers of substance use research (Hyshka et al., 2017; Wild et al., 2017). Thus, given the range of alternative treatment and/or research options available to BC participants (e.g., slow-release oral morphine, injectable hydromorphone or diacetylmorphine), this group may have had less desire to be randomized to a medication to which they already have efficient access. Conversely, the lack of access to MOUD and other emerging harm reduction initiatives in other provinces may speak to a treatment context informed by public perceptions via "morality policy" where resources are allocated toward abstinence-based treatment models, and away from more stigmatized forms of substance use treatment (Bowen, 2012; Wild et al., 2017). For instance, in Alberta, the conservative government has voiced sharp criticism of harm reduction services, allocated more funding to recovery services (Smith, 2020), and recently closed Calgary's only safe consumption site (Smith, 2021)—politically motivated shifts that may have consequences for the future MOUD treatment landscape in the province. While there is significant public support for "universal" healthcare in Canada (Jedwab, 2019), public and political support for drug treatment varies significantly across provinces (Eibl et al., 2017; Hyshka et al., 2017; Morin et al., 2017; Wild et al., 2017). Woven throughout these findings are key reminders that clinical trials are socially embedded and that in substance use research, studies on MOUD, "rather than settling controversies, may instead reflect and propel them" (Epstein, 1997, p. 716).

4.4.1 Limitations and conclusion

This analysis has some limitations. First, I assessed differences across study spaces and treatment contexts but there may be other critical differences in the study populations. For instance,

more participants in Vancouver may be socioeconomically marginalized, in part due to the patient population of the study site and the site's proximity to downtown, compared to participants in Toronto, where the clinic was further away from the downtown core. Still, these distinctions reinforce the challenges of conducting multisite trials in substance use treatment and the significance of the local context. Second, there were a fair number of participants who were lost to follow-up in the trial and therefore not able to be interviewed at study exit. Thus, these participants likely experienced additional barriers to participation that were not captured in these data but that potentially belie underlying systematic differences related to interactions between participants, the research "place," and study procedures that resulted in loss to follow-up. Third, there are a number of other places and spaces that are indirectly related to study participation (e.g., housing, criminal justice contexts, previous addiction treatment) that may have a role to play in study experiences; these are outside the scope of the current analysis but may be considered in future analyses. Finally, this analysis does not attempt to directly measure the impacts of place on study retention or treatment outcomes. Future analyses may include quantitative trial data with these metrics and mixed methods investigations to understand how participant considerations map onto clinical outcomes (e.g., pharmacy experiences and trial indicators of medication adherence).

While strict protocols, processes of regulation, and randomization in experimental research are designed to mitigate the distribution of unmeasured differences across study arms and study sites, social scientists have called into question the challenges of standardization in medicine across social settings (Lawton et al., 2012; Montgomery, 2017; Timmermans & Epstein, 2010). In substance use research, these challenges may be amplified by the contentious policies, politics, and public conceptions surrounding drug treatment. In this qualitative nested study, participants illustrated how places interact with study processes on meso- and macro-levels in ways that may

be consequential for individual study outcomes and the interpretation of trial results across sites. Most prominent were the structural inequalities in treatment access across sites and the ways in which these inequalities shaped study enrollment. While such contextual influences on participation typically go unmeasured in clinical research, these results illustrate that while place-based and policy factors appear disconnected from the seemingly objective process of medical knowledge production, research processes are, in fact, embedded in complex social and economic contexts.

5 Conclusion

5.1 Summary of findings

Drawing data from a nested qualitative study within a clinical trial, this dissertation aimed to apply sociological understandings of biomedical knowledge production at micro, meso, and macro levels of experimental substance use research. In Chapter 1, I began by contextualizing the study within social scientific perspectives on clinical trial research, relevant findings in substance use research, and critical background information related to drug use and drug treatment, as well as detailing my methodological approach and the organization of the dissertation.

In Chapter 2, I applied sociological understandings of the cultural, social, and symbolic meaning of medications to an experimental context in order to highlight how socially constructed perceptions of treatment can have real, observable impacts on individual trial experiences and study outcomes. I characterized participants in the study on two dimensions: history of treatment (i.e., previous MOUD prescription) and drug cultural experience (i.e., knowledge of and experience with drug effects, drug-related language, drug scenes and treatments). As a result, I used the four possible combinations of these two important dimensions to categorize participants into three groups: experienced participants (treatment and drug cultural experience), semi-experienced (no treatment but cultural experience), and inexperienced participants (neither treatment nor cultural experience). Through this characterization, I was able to move beyond demographics or clinical indicators to demonstrate how participants' accumulated experiences can shape beliefs around medication mechanisms and efficacy, safety and side effects, sources of medication information and expertise, and experienced or internalized treatment stigma. By comparing and contrasting such perceptions across groups, these findings highlight the advantages

and disadvantages of lay expertise in RCT settings for counteracting medication perceptions as well as the implications of cultural and treatment background for RCT recruitment and design.

In Chapter 3, I drew on linkages between sociological concepts related to alienation (e.g., stigma, social isolation, and search for meaning or purpose), drug use, and research participation to frame underlying motivations to enroll in OPTIMA among PWUD. First, informed by a broader context of drug-related stigma and marginalization, my results showed that participants were motivated to enroll in OPTIMA by the desire to reduce their substance use and by instrumental, altruistic, and social motivations. While research on PWUD instrumental motivations generally focuses on study stipends, these results additionally highlight how participants connected their study enrollment to the potential for employment, reflecting both financial incentives as well as normative conceptions around work. Second, participants recounted altruistic motivations to participate that were concentrated around benefit to the PWUD community, benefit to research, and a hybrid benefit to themselves and others. Altogether, these findings emphasize the potential for research to provide social connection or a sense of meaning to otherwise difficult life experiences. Third and finally, participants connected their enrollment to social motivations, including the potential to rebuild social ties, the ability to provide or reciprocate social support, and the fulfillment of normative social expectations (e.g., being a good parent). By linking theoretical understandings of alienation and drug use to research participation, I uncovered complex and multifaceted motivations for research among PWUD that highlight the potentially greater significance of RCT research for PWUD than for other trial populations. This analysis has methodological implications for the conduct of applied research within actual trials, as well as empirical implications to consider broader intrinsic motivations (e.g., stability, meaning, or social connection) for enrollment among PWUD.

In Chapter 4, I investigated how place interacts with knowledge production processes by analyzing the experiences of PWUD participants in OPTIMA trial study sites across four Canadian provinces. Specifically, I compared participant experiences across study contexts to understand how physical spaces (e.g., convenience, centrality to drugscapes, presence of police surveillance) and the interactions within them (e.g., stigma from pharmacists, harassment by security guards) shape study experiences. Additionally, I considered the macro-level forces that impacted the study, such as provincial insurance coverage and availability or access to MOUD, which ultimately created incentives for participant enrollment in the trial (e.g., to access treatment immediately), but also formed barriers to participant retention (e.g., loss of coverage). These fundamental differences in social dynamics, health policies, and local politics have concrete implications for the comparative analysis of study data and outcomes across sites. Through the qualitative analysis of this multisite study, this research illustrates how policy and politics underlie seemingly "objective" research processes, with further consequences for the development of drug policies and treatment practices.

5.2 Limitations

Specific study limitations are included within each chapter that reflect each respective analysis. However, there are several general limitations that are worth addressing. First, while the aim of qualitative research is not generalizability (Jenkins et al., 2018), it should be noted that some findings may have less applicability to other study contexts as the Canadian context is unique on at least two key dimensions related to governance, regulation, and study implementation. In terms of substance use treatment and drug policies, the locus of control generally lies at the provincial level (Priest et al., 2019), whereas in other contexts federal guidelines may take precedence. This may have significant impacts on study standardization and implementation of

multisite trials. Notably, participants in Canada had access to universal healthcare coverage, and while drug treatment coverage may not be included under the umbrella of essential health services, still, participants may not be motivated to enroll and seek medical care to the same degree as demonstrated by RCT participants in other healthcare contexts (Fisher, 2013; Timmermans & McKay, 2009).

Second, there is the limitation of potential selection bias. The study sample is primarily comprised of willing participants in the OPTIMA RCT. While I was able to recruit several participants who later withdrew from the study or failed to initiate treatment, it should be noted that, overall, these data do not reflect the perspectives of those who were never interested in OPTIMA or who did not pass OPTIMA eligibility screening. In effect, participants in this study may be more trusting, willing to engage with health researchers, or willing to be randomized as compared to non-participants (Dennis et al., 2015). Further, there were participants who were lost to follow-up in the OPTIMA trial and thus unable to be interviewed at study exit. Without these interviews, key insights may have been missed around substantial barriers that altogether barred participants from completing the trial.

Third and finally, in the conduct of research around a stigmatized and often criminalized health issue, there are concerns around social desirability bias and response bias. The former is a potential issue when participants underreport less desirable behaviors that contradict social norms (e.g., drug use patterns or practices; Krumpal, 2013). The latter concerns some risk of participants conflating the OPTIMA study with the qualitative study which could result in responses to questions that were more socially desirable or positive in their evaluation of OPTIMA. However, interviewers were unaffiliated with the study team and trained on nonjudgmental interview

approaches and were asked to reiterate to participants that interview recordings or transcripts would not be shared with study staff.

5.3 Implications for clinical research with PWUD

With the growth of substance use research (Tai et al., 2021), results from this dissertation have the potential to provide critical recommendations to inform the ethical conduct of future RCTs testing pharmacotherapies for substance use disorders. These insights center around three areas: the need for a) greater representation and diversity of PWUD populations in RCTs; b) further contextualization around substance use trials; and c) challenges to the dominance of the RCT paradigm, particularly in substance use research.

5.3.1 Representation of PWUD populations in RCTs

As a pragmatic trial, this RCT sought to enroll a more heterogenous sample of PWUD than might be found in early phase trials with more strict and exclusionary eligibility criteria. Interview data shed additional light on the range of participant life experiences, including experiences pertaining to housing and homelessness, social support and social isolation, different forms of income generation, the healthcare system, and criminal justice involvement, among others. However, there were also critical barriers to participation that may point to opportunities to expand access to research to a wider array of participants and thereby further increase the generalizability of study findings. Notably, recruitment efforts could be expanded beyond hospitals and clinics to reach PWUD who are not engaged in medical systems or who have not accessed MOUD in the past. Accessibility may also be increased through additional measures, such as language interpreters, transportation or transit vouchers, home delivery of medication, access to a cell phone or prepaid cell minutes, or home study visits for those with mobility issues or caregiving responsibilities.

With regard to improving retention, telemedicine may be a viable alternative to follow-up visits when participants are unable or unwilling to travel for research follow-up visits (as shown during the COVID-19 pandemic for health care seeking among the general population). While some PWUD do not have access to telecommunication devices or prefer in-person visits, virtual research visits may benefit participants who have employment and caregiving responsibilities, participants who live in rural areas, or participants who relocate. Ultimately, virtual visits improve study retention and allow participation from a broader, more representative swath of the population, thus producing more generalizable results (Eibl et al., 2017).

5.3.2 Contextualizing substance use research

In their work on RCT participation as treatment option, McKay and Timmermans (2009) argue that researchers should avoid making a "bioethical misconception," in which they solely focus on RCT ethical principles while ignoring the broader social context. One example of this has been the substantial debate around the ethics of paying socioeconomically marginalized PWUD to participate in research, largely centered around concerns of undue inducement or moralistic questions about subsidizing drug use (Anderson & McNair, 2018; Denny & Grady, 2007; Festinger et al., 2005, 2008; Fry et al., 2006). While these debates have abated in favor of compensating PWUD fairly for their time and expertise (Abadie et al., 2019; Collins et al., 2017; Festinger et al., 2008; Greer et al., 2018; Treloar et al., 2010), ethical concerns remain that go beyond individual or trial-level factors (Neale et al., 2018), such as the broader overdose crisis in which substance use RCTs take place (Steel et al., 2017). By medical definitions, opioid use disorder is characterized as "chronic," and in some ways PWUD RCT participants are similar to participants in other RCTs that aim to address symptoms of chronic illness. But in other ways, RCTs conducted in the shadow of the overdose epidemic reflect parallels to RCTs that address other immediate,

life-threatening illnesses. For cancer patients facing a terminal diagnosis, a clinical trial may offer a chance to try an experimental, life-saving treatment. In a setting where thousands die each year of drug poisoning from the unregulated toxic drug supply ("'it's not a matter of 'if,' it's a matter of 'when'") and where PWUD repeatedly bury their friends and family ("my closest friends all died the last couple years"), the chance to immediately access MOUD may also appear to be lifesaving. The impact of such an environment on participants' decision-making may be more important than design elements of any individual trial. Indeed, social scientists have pointed to the broader context of inequality and social exclusion that places participants in a vulnerable position, what has been deemed "structural coercion" (Fisher, 2013; Welch et al., 2015). This more constructive framing redirects emphasis on individual trials or specific enrollment processes and places it upon the underlying patterns of structural violence that, for instance, frame study participation as the most viable form of income, the most accessible study treatment, or a way to avoid overdose. While RCT research in addiction medicine continues to expand, as long as drug use remains stigmatized and criminalized, the structural coercion of PWUD participants will persist.

While individual trials cannot be expected to address large-scale structural inequality or the ongoing overdose crisis, there is an individual responsibility for researchers conducting trials with PWUD to be attuned to the social and economic marginalization that shapes participants' wellbeing and, to the extent possible, engage in efforts to reduce such inequities. For example, clinical investigators may be able to leverage their power within the institution to advocate for PWUD participants in health settings (e.g., supporting harm reduction initiatives; Bell & Salmon, 2011; Higgs et al., 2006). As these results highlighted the challenges of participation for socioeconomically marginalized PWUD, efforts can also be made to reduce the study burden by,

for instance, offering transportation vouchers and flexibility in study appointments (Neale et al., 2018) and by creating a welcoming, nonjudgmental research space for a population that disproportionately experiences stigma and discrimination in healthcare settings (Abadie et al., 2018; Bell & Salmon, 2011). After the trial, study staff should ensure the continued wellbeing of participants by preserving their access to the study medication and connecting them with relevant health and social services (Bell & Salmon, 2011; Higgs et al., 2006; Jaffe et al., 2021a; Oviedo-Joekes et al., 2009). Such post-trial support may be an even greater ethical imperative in sites where there are notable barriers to treatment outside the context of the study, as described in chapter four. Finally, consultation with community groups and involving PWUD in the process of designing and implementing the trial would additionally provide critical insights on study-specific strategies to support mutually beneficial study involvement (Barratt et al., 2007; Bell & Salmon, 2011; Bonevski et al., 2014; Neale et al., 2018).

5.3.3 Challenging the RCT paradigm

A final consideration for researchers is to engage in efforts that challenge the epistemic dominance of the RCT in biomedical knowledge production. As this dissertation demonstrates, key contextual factors may have a significant impact on a study above and beyond what can be controlled through randomization and statistical measures. In substance use research, study populations are heterogeneous, with significant variability in drug use patterns, treatment experience, health comorbidities, socioeconomic status, and other factors—all of which have implications for external generalizability (Dennis et al., 2015; Reddon et al., 2020). Further, not all interventions need be tested under conditions of randomization, particularly when working with marginalized populations whose autonomy is revoked or consistently challenged in institutions and everyday interactions. Instead, observational studies can in many cases provide robust

evidence of drug use, treatment, and health data over time, as well as empirical support for policy change (Reddon et al., 2020).

5.4 Future directions and conclusion

I conclude by highlighting three directions for future research. First, future research should consider and incorporate the social positions of PWUD (i.e., race, ethnicity, gender, age, socioeconomic status, health status) into its analyses in order to understand how these factors shape research experiences. While extensive research has explored differences in willingness to participate, trust, and acceptability of trial dimensions between specific groups (Bonevski et al., 2014; Farmer et al., 2007; Hurd et al., 2017; Smirnoff et al., 2018), few analyses have focused on how intersecting social locations such as race and gender shape PWUD's perceptions of medical research. Given the racial and gender politics of MOUD in clinical settings (Fraser, 1997; Hansen & Roberts, 2012; McHugh et al., 2017), exploring treatment and study experiences in research clinic settings would be informative and instructive. Second, future qualitative inquiries could incorporate quantitative trial results through mixed methods analyses to reveal ways the 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. By utilizing quantitative measures on topics that are also asked in qualitative interviews, researchers may be able to explore convergent and divergent findings that generate additional insights into participant RCT experiences (Creswell & Plano Clark, 2017). Third, future research could interview members of groups that contribute to or are involved in the clinical trial endeavor. For instance, interviews with clinical trial staff, including principal investigators, research coordinators, research nurses, and research assistants, could explore both the challenges experienced in research as well as the strategies they employ in working with a hard-to-reach

population and the processes of trust- and relationship-building with PWUD communities (Donovan et al., 2014; Fisher, 2006; Lawton et al., 2012; Rooshenas et al., 2016; Strong et al., 2016). Interviews with social service and healthcare workers that operate research clinics or refer participants to trials could also provide vital insights as informed outsiders. These workers typically have close relationships with communities of PWUD and often serve as either a source of study participants or a source of potential critique. Finally, as indicated in the limitations section, interviews with PWUD who have declined trial participation would provide a more critical appraisal of clinical trial research and highlight potential participants' perceptions of study barriers compared to those PWUD enrolled.

In conclusion, this dissertation offers three empirical analyses of critical aspects of the conduct of medical research with PWUD. While each chapter draws on distinct theories and poses unique questions, taken together this research advances understandings of individual, social, and structural processes that shape RCT participation among PWUD and builds conceptual linkages between sociology, public health, drug policy, and science and technology studies. By applying a sociological lens to understand purportedly "objective" processes of biomedical knowledge production, this research calls into question claims of standardization across differently resourced settings, especially in the study of a population subjected to varying degrees of stigmatization, medicalization, and criminalization. Additionally, this analysis is methodologically innovative by utilizing qualitative methods within a quantitative substance use trial and, by so doing, generates a deeper understanding of the experiences of PWUD beyond standard trial indicators and provides insights into how we might adapt research processes to improve the experiences of marginalized population in research. Finally, this research has direct relevance to ongoing discussions around

the ethics of research with marginalized populations amidst public health crises such as the COVID-19 pandemic, the overdose epidemic, and increasing social inequality.

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