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SLOW RELEASE ORAL MORPHINE VERSUS METHADONE FOR OPIOID USE DISORDER IN THE FENTANYL ERA (PRESTO): PROTOCOL FOR A NON-INFERIORITY RANDOMIZED CLINICAL TRIAL

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Abstract

Background—North America is facing an unprecedented public health crisis of opioid-related morbidity and mortality, increasingly as a result of the introduction of illicitly manufactured fentanyl into the street drug market. Although the treatment of opioid use disorder (OUD) is a key element in the response to the opioid overdose epidemic, currently available pharmacotherapies (e.g., methadone, buprenorphine) may not be acceptable to or effective in all patients. Available evidence suggests that slow-release oral morphine (SROM) has similar efficacy rates as methadone with respect to promoting abstinence, and with improvements in a number of patient-reported outcomes among persons using heroin. However, little is known about the relative effectiveness and acceptability of SROM compared to methadone in the context of fentanyl use. This study aims to address this research gap.

Methods—pRESTO is a 24-week, open-label, two arm, non-inferiority, randomized controlled trial comparing SROM versus methadone for the treatment of OUD. Participants will be 298 clinically stable, non-pregnant adults with OUD, recruited from outpatient clinics in Vancouver, Canada, where the majority of the illicit opioids are contaminated with fentanyl. The primary outcome is suppression of illicit opioid use, measured by bi-weekly urine drug screens. Secondary outcomes include: treatment retention, medication safety, overdose events, treatment satisfaction, psychological functioning, changes in drug-related problems, changes in quality of life, opioid cravings, other substance use, and cost-effectiveness.

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Declaration of Competing Interest

SMM reports having consulted for/advised Sandoz Inc. on an economic model unrelated to the submitted work. All other authors declare no conflict of interests.

Appendix A. Supplementary data

Discussion—pRESTO will be among the first studies to evaluate treatment options for individuals primarily using synthetic street opioids, providing important evidence to guide treatment strategies for this population.

Keywords

Slow-release oral morphine; Methadone; Opioid use disorder; Randomized clinical trial; Fentanyl; Overdose

1. INTRODUCTION

North America is facing an unprecedented public health crisis of opioid-related morbidity and mortality. It is estimated that over 2.5 million Americans have an opioid use disorder (OUD), and that over 47,000 died from an opioid-related overdose in 2018 [1]. Although precise estimates for Canada do not exist, available data suggest that as many as 0.5–1 million Canadians may suffer problematic opioid use, and that there were more than 4500 opioid-related deaths in 2018 in Canada, an increase of over 45% from 2016 [2]. Of note, opioid-related overdose deaths are now one of the leading causes of injury and death in North America [3,4]. While the current opioid crisis is largely attributable to the misuse of prescription opioids, in recent years there has been a dramatic rise in overdose deaths from illicitly manufactured fentanyl (IMF) and related analogs [5,6]. For example, among the more than 47,000 overdose deaths in the United States (U.S.) in 2018, approximately two thirds involved IMF. Some jurisdictions in Canada are experiencing similar rising overdose epidemics, as demonstrated by the over 1500 illicit drug overdose deaths in 2018 in British Columbia (BC; 31 deaths per 100,000 individuals), a 300% increase from 2015, with IMF involved in over 80% of the cases [5].

While the causes of the opioid-related overdose crisis in North America are multifactorial, one of the major drivers is untreated OUD. Indeed, despite the well-established benefits of medications for OUD (MOUD), such as buprenorphine/naloxone or methadone in reducing opioid-related morbidity and mortality [[7], [8], [9], [10]], major individual- and structural-level barriers to uptake of this medication and engagement in OUD care persist [11]. This unmet treatment gap has resulted in substantial numbers of individuals with untreated OUD who continue to be at risk of death and other adverse health outcomes [11].

Due to its relative safety profile [10], buprenorphine/naloxone has emerged as the preferred first-line treatment option in Canada and the U.S. [12,13]. However, buprenorphine/naloxone may not be appropriate for all patients, particularly for individuals with social instability who are at high risk of attrition [14,15]. Although methadone may offer an alternative treatment option in these cases, its safety and toxicity profile (e.g., increased cardiovascular and overdose risk) [16,17], as well as the high potential for drug-drug interactions [18] and patient reported concerns with its side effects [19], further limits its broader use. In addition, while extended-release naltrexone is also available in the U.S., the efficacy of this medication for people with more severe OUD, including those who have not benefitted from oral MOUD is unknown [20].

Comparative effectiveness research that can aid in the identification of viable new therapies that can better account for patients' perceptions, needs, and factors shaping satisfaction with treatment will be critical to improving retention in treatment as well as health and social outcomes [21–23]. In this regard, a number of small studies have explored the potential of slow release oral morphine (SROM) versus methadone, and provided preliminary evidence suggesting similar efficacy rates in suppressing illicit opioid use and retention in treatment [24–27]. In addition, some of these preliminary studies have suggested that SROM may have a superior safety profile (e.g., shorter mean QTc interval) and perform better than methadone in improving patient-reported outcomes, including mental health, alleviation of cravings and withdrawal symptoms, and treatment satisfaction [24–26, 28–30]. Based on this growing evidence base, SROM is increasingly and successfully used in several European countries [31] and Canadian provinces (off-label) [13,32]. However, as identified in three systematic reviews on the topic [25–27], available clinical studies have a number of important limitations including that, among the only four available randomized trials [24,25], these were relatively small, and none involved individuals using illicit fentanyl. Likewise, there are no clinical trials evaluating methadone or other MOUD for people with OUD using fentanyl, and thus questions remain as to how these medications perform in this population, particularly given fentanyl's higher potency compared to other opioids.

To better inform clinical practice in the context of the escalating and evolving opioid epidemic in North America, this study will assess the relative effectiveness, safety, and acceptability of SROM as MOUD compared to methadone in real world outpatient settings. The present manuscript describes the study design of this randomized effectiveness trial, in accordance with recommendations from SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement [33].

2. METHODS

2.1. Study design

2.1.1. Overview—"Repurposing Slow-Release Oral Morphine as a New Oral Alternative for the Treatment of Opioid Use Disorder" (pRESTO) is a 24-week, open-label, two arm, non-inferiority, randomized controlled trial with a parallel design comparing the effectiveness of SROM to methadone in outpatient substance use treatment settings among individuals with OUD (Fig. 1).

Interested individuals will undergo an initial pre-screening assessment to determine general eligibility, and potentially eligible candidates will then be invited to complete the informed consent process. Once written consent is voluntarily given, participants will undergo screening assessments to confirm eligibility. Eligible and consenting participants will be randomized as soon as possible, on a 1:1 ratio to either: a) Methadone supplied as part of standard of care or b) Slow Release Oral Morphine. Both medications will be dispensed via daily witnessed ingestion in designated community pharmacies. Randomization will be stratified by use of medication to manage withdrawal symptoms before treatment can be initiated, using a permuted block design, with blocks of varying sizes.

Once treatment is initiated, participants will be followed for 24 weeks, with research visits every 2 weeks. At the end of the 24-week active treatment period, the research team will ensure that all participants are transitioned to community addiction care with the least possible disruption. A follow-up visit will be conducted 28 weeks after randomization to assess short-term safety after the end of the study, and to determine current engagement in addiction care. Long-term follow up will include confidential data linkages with provincial health administrative databases to monitor health care utilization and outcomes among enrolled participants up to 36 months after randomization.

2.1.2. Study objectives—The primary objective is to compare the relative effectiveness of SROM versus methadone in suppressing illicit opioid use among individuals with OUD. Secondary objectives are to compare other key indicators of treatment success between the two arms, including: retention, safety, overdose events, treatment satisfaction, psychological functioning, quality of life, cravings, other substance use, and cost-effectiveness.

2.1.3. Study sites—In Canada, MOUD are typically prescribed in the context of primary care, and dispensed through community-based pharmacies [34]. In line with this low-threshold model of OUD care, the study will be implemented at outpatient clinics in the lower mainland area of British Columbia. Two sites have initially been selected: (1) the Columbia Street Community Clinic, a comprehensive primary care clinic run by Portland Hotel Society Community Services Society, a non-profit organization located in Vancouver's Downtown Eastside neighborhood, where most fentanyl use is concentrated, and (2) the Rapid Access Addiction Clinic at St. Paul's Hospital, an addiction outpatient clinic co-located within an inner-city hospital in downtown Vancouver. Participants will be able to choose from three community pharmacies located in close proximity to the clinical sites to receive their daily witnessed dose of study drug.

2.1.4. Study population—To ensure diversity and representativeness of the population with OUD and to examine the relative effectiveness of each model of care in different health system environments, recruitment will be done through a number of venues, including primary care clinics, emergency departments, overdose preventions sites and other community venues commonly visited by the target population.

In addition, to maximize representativeness of the broader population with OUD across Canada who may benefit from alternative forms of oral MOUD, this trial has broad eligibility criteria, which are presented in Table 1. In brief, participants will be non-pregnant clinically stable adults with OUD who are not currently on a stable dose of MOUD and are interested in and eligible for treatment with either methadone or SROM as per the British Columbia and Canadian guidelines for the management of OUD [12,13]. Given high rates of contamination of the street drug supply with IMF in BC (>90% for opioids), we expect that most of our study population will be intentionally or unintentionally exposed to fentanyl [35].

2.2. Study interventions

Dosing and administration of both study drugs will be in line with British Columbia and Canadian guidelines for the management of OUD [12,13]. Typically, this involves administration via once-daily directly witnessed ingestion in community pharmacies. Take-home doses may be allowed for stable patients for short periods of time (e.g., weekends, holidays), at the discretion of the study physician. For the purposes of this trial, we have selected three community pharmacies with experience providing MOUD and located in close proximity to the selected clinic sites and patient catchment areas.

2.2.1. Slow-release oral morphine—The use of SROM for the treatment of OUD is off-label in Canada, and is decided on a case by case basis. According to existing provincial and national guidelines, common starting doses are 30 to 60 mg per day [12,13]. Based on expert-led approach, the maximum SROM dose is 200 mg on the first day. Doses are increased by 50–100 mg every 1–2 days until the patient achieves a stable daily dosage (e.g., control of withdrawal symptoms and cravings, without opioid toxicity). Most patients will achieve stabilization with doses between 800 and 1200 mg/day; however, higher doses may be needed for some patients.

2.2.2. Methadone—In Canada, methadone is the recommended pharmacotherapy for individuals with poor response, side effects or contraindications to buprenorphine/naloxone. The starting dose of methadone is based on the level of opioid tolerance, ranging from 5 to 10 mg/day to 30 mg/day [12,13]. Doses are then slowly titrated by 5–10 mg every 3–5 days until a stable dose is achieved. Most patients achieve stabilization with daily doses of 60–120 mg.

2.2.3. Medical management—Participants in both arms will receive medical management through trained study physicians, and as per regular standard practice. Typically, these visits include education on OUD and MOUD, monitoring of efficacy, side effects, and adherence to the assigned MOUD, as well as potential dose adjustments, review of use of opioids and other substances, as well as referrals to other health and social services, as needed and appropriate [36].

2.3. Assessments

The schedule of visits and assessments is presented in Table 2. Screening and baseline assessments gather information on participant socio-demographics, medical, psychiatric, overdose and addiction treatment history, patterns of substance use, health status, motivations for treatment, utilization of health services, and urine drug tests (UDT). In addition, pregnancy and birth control are assessed at screening/baseline and every 4 weeks thereafter for female participants of childbearing potential. Baseline assessments will be conducted immediately before randomization and treatment initiation; there will be only one baseline measurement (as opposed to averaging multiple measurements).

2.4. Outcomes

2.4.1. Primary outcome measure—The primary outcome measure is suppression of illicit opioid use (including fentanyl), measured by the overall percentage of opioid-free

UDT (excluding the assigned MOUD and its metabolites) from weeks 2 to 24 of the trial. UDT will be collected at baseline, and every 2 weeks for the 24-week active treatment period. Missing urine samples will be considered positive for opioids.

2.4.2. Secondary outcome measures—Secondary outcome measures include: (1) retention on the assigned intervention, defined as having both a) an active prescription for the assigned MOUD, and b) a positive UDT result for the assigned MOUD at week 24; (2) safety measured by adverse and serious adverse events; (3) overdose events; (4) treatment satisfaction assessed by the Medication Satisfaction Questionnaire (MSQ) [37]; (5) psychological functioning assessed by PROMIS short form measures for anxiety and depression [38]; (6) drug-related problems, evaluated by the the Addiction Severity Index (ASI) Self-Report Form [39,40]; (7) health-related quality of life assessed by the EQ-5D-5 L [41,42]; (8) opioid craving, measured using a visual analog scale, and (9) use of other substances measured by a combination of UDT results and self-report using the Timeline Follow-Back (TLFB) instrument [43,44]. The schedule of secondary outcome assessments is shown in Table 2.

2.4.3. Long-term outcome measures—Long-term outcomes, including engagement in MOUD, health care utilization and mortality up to 36 months post randomization will be assessed through confidential data linkages with the provincial, centralized health administrative data system, which incorporates databases for prescription drug dispensations, inpatient and outpatient care, and vital statistics.

2.5. Sample size and power calculation

The sample size calculation for the primary outcome is based on testing for non-inferiority in a parallel trial. Being consistent with the existing literature [45], we will compute the proportion of opioid-free UDT for each participant, and the mean of these proportions per treatment group will be derived for the comparison. The methadone arm will have an expected mean of 50% opioid-free UDT test results during the 24-week intervention period [46–51]. Following FDA guidance [52], and based on consultations with addiction medicine experts (i.e., what would be the largest loss in efficacy in suppressing opioid use that would be clinically acceptable, especially if SROM shows superiority in key secondary outcomes) and literature review [24], the non-inferiority margin was set conservatively at 10%. The choice of this margin reflects our willingness to accept a small decrease in effectiveness in suppressing opioid use in return for increased safety, tolerability and other improvements in patient-reported outcomes. Based on the literature, the standard deviation is conservatively expected to be 25% [24]. Given the above assumptions and using a recommended one-sided significance level of 2.5%, a power of 80% [53], and a 1:1 allocation ratio, a total of 198 participants (99 per arm) will be required. Once half of the participants have completed the 24-week study period, following FDA guidance [54], the DSMB will conduct a blinded interim analysis of aggregate data to assess the accuracy of the variance parameter, and whether a sample size re-estimation may be required.

2.6. Statistical analyses

All analyses will adhere to recommendations of the Extension of the CONSORT 2010 Statement for the reporting of non-inferiority and equivalence randomized trials [55], under the intention-to-treat (ITT) principle. A "switch equals failure" approach will be used, where UDTs from participants who discontinue their assigned medication for any reason are considered positive for opioids from that time forward [56]. We will also conduct a per-protocol (PP) analysis that will comprise participants who receive at least one dose of the assigned medication, and analysis adjusted to actual treatment received.

2.6.1. Primary outcome—For each treatment arm, the overall mean and 95% confidence interval of the individual proportion of opioid-free UDT will be calculated. Non-inferiority will be established if the lower limit of the two-sided 95% confidence interval for the mean difference between the SROM and methadone (TAU) arms is greater than −10%. For the primary analysis linear regression will be used, adjusting only for the stratification factor (i.e., use of withdrawal medications). In sensitivity analyses, we will build multivariable models to adjust for known relevant confounders (e.g., gender, Indigenous ancestry) and other covariates that show imbalance across arms (i.e., association with the outcome at $p < 0.1$ levels in bivariate analyses), using a previously utilized stepwise procedure [57]. We will also conduct exploratory analyses using multivariable models to: (1) investigate potential demographic and clinical factors (e.g., participants' treatment preferences) predicting success of each treatment intervention; and (2) assess the possibility of differential treatment effects across subgroups (e.g., exposure to fentanyl, gender, ethnicity) by examining the interaction terms between treatment assignment and subgroup characteristics.

2.6.2. Secondary outcomes—Secondary outcome analyses will use "superiority" hypotheses, where two-sided tests will be performed with a significance level of 5%. For the assessment of secondary outcomes involving repeated measures, generalized linear mixed-effects modeling (GLMM) with random intercepts will be utilized to account for the repeated measurements, adjusting for known relevant confounders and covariates that show imbalance across arms [58].

2.6.3. Missing data—Regarding the handling of missing data, consistent with international standards in substance use disorder trials [59], missing UDT will be considered positive for illicit opioids, and thus there will be no missing data for the primary outcome. In addition, and recognizing that dropout from treatment typically reflects a failure of that particular model of care to engage patients in long-term care, a "switch equals failure" approach will be used, where participants who discontinue their assigned medication for any reason (including switches to the other arm) are classified as failures, and UDT from this time point forward will be considered positive for opioids [60,61]. This approach will allow a better evaluation of the overall effectiveness of each model of OAT in real-world treatment conditions (including efficacy, tolerability, safety profile, and patients' preferences), enhancing the external validity of the study results.

For secondary outcomes, there may be missing data due to missed visits or study dropouts. Our statistical approach (GLMM) assumes that missing data are missing at random. Sensitivity analyses will also be conducted to fully understand the impact of missing data on conclusions, and to examine the stability of our assumption of missing data as random. Multiple imputation techniques will be utilized to handle missing values, and the analysis results based on multiple imputation will be reported [62].

2.6.4. Health economic analysis—We will conduct a comprehensive economic evaluation of SROM compared to methadone, from the healthcare-sector, provincial-policymaker, and societal perspectives. The evaluation will follow well-established guidelines for conducting health-economic analyses alongside clinical trials [63,64]. The healthcare sector perspective includes all medical costs incurred on behalf of the patient, regardless of who is responsible for paying them. The provincial-policymaker perspective includes all costs necessary to inform resource allocation decisions for provincial agencies and the public; therefore, it will include all publicly-funded healthcare costs, and other costs relevant to the province, such as direct costs to the criminal justice system. The societal perspective includes all costs from the healthcare sector perspective, as well as other costs important to the public, such as the direct and indirect (e.g., pain and suffering) costs of crime, lost workplace productivity, etc.

First, we will conduct a microcosting analysis to estimate the costs associated with the implementation of SROM, as well as the costs associated with the day-to-day management of the intervention, using a tailored version of the Drug Abuse Treatment Cost Analysis Program (DATCAP) instrument [65,66]. Healthcare service utilization will be captured using medical records, and through self-report using the Non-study Medical and Other Services (NMOS) form. The NMOS has been used extensively in previous research with similar populations [67–70]. Two measures of effectiveness will be included in the cost-effectiveness analysis. The primary effectiveness measure will be the quality-adjusted life-year (QALY), a measure that combines a person's health-related quality-of-life and the amount of time spent in that health state [64]. The secondary measure of effectiveness will be the abstinent year, measured as the predicted proportion of the year that the participant was abstinent from opioids.

All measures of cost and effectiveness will be obtained using longitudinal multivariable regression, in order to control for potentially confounding factors relevant to the economic analysis that are unbalanced between arms at any given time point. All monetary values will be adjusted for inflation, and measures obtained beyond 12 months of baseline will be discounted for time preference [63,64]. Nonparametric bootstrapping techniques will be used to estimate standard errors and to generate an acceptability curve, which will display the probability that SROM is cost-effective, relative to methadone, at various value thresholds. Finally, sensitivity analyses will be conducted to account for uncertainty in parameter inputs, such as prices.

2.7. Data safety and monitoring

An independent Data and Safety Monitoring Board (DSMB) reviewed the final draft of the protocol and recommended final revisions. The DSMB will also monitor accumulating trial data on a regular basis to ensure participant's safety and adequate trial performance. In addition, an appointed medical monitor will oversee and evaluate all adverse events.

2.8. Approvals and registration

pRESTO has received approvals from the Health Canada Therapeutic Products Directorate and Office of Controlled Substances, and the University of British Columbia/ Providence Health Care Research Ethics Board. The study is registered on Clinicaltrials.gov (NCT03948464).

3. DISCUSSION

There is an urgent need for science-driven solutions with potential for rapid scalability to address the rising opioid epidemic in North America. This is true particularly in the context of the recent escalation of fentanyl use and other highly potent fentanyl derivatives. Alongside continued efforts to expand access to and capacity of methadone- and buprenorphine-based treatment programs, alternative treatment options are needed to improve access to treatment while better addressing the evolving needs of individuals with OUD and optimizing treatment outcomes in this population.

In this context, the rigorous evaluation of SROM as an alternative form of oral treatment for individuals with OUD is particularly timely and relevant. Indeed, the need for alternative evidence-based oral MOUD has consistently emerged as a key issue reported by patient groups, health care providers and other key stakeholders in Canada, the U.S. and elsewhere [31, 71–75]. The goal of this study is to evaluate the relative effectiveness, safety and acceptability of SROM vs. methadone for the treatment of OUD. In doing so, the proposed study aims to address some of the more urgent clinical questions in the context of the worsening opioid epidemic in Canada. First, to confirm previous encouraging preliminary results on the potential of SROM as an effective, safe and acceptable oral form of MOUD. Second, to provide critical and novel information on the clinical utility of SROM-based treatment as a potential alternative treatment option for OUD. Third, to evaluate treatment approaches for the growing and difficult-to-treat population of people who use or are exposed to fentanyl in North America.

Given the lack of clinical studies evaluating different MOUD for individuals exposed to novel synthetic opioids, and the limited evidence to guide strategies for individuals intolerant or not responding to first-line MOUD, the proposed study offers a timely and unique opportunity to address these research gaps, with high potential to inform patient-centered approaches and stepped care strategies in the management of OUD. Importantly, given that SROM is already approved in Canada for pain management, if results from this study confirm its clinical utility as MOUD it may present significant potential to rapidly increase access to an additional form of evidence-based MOUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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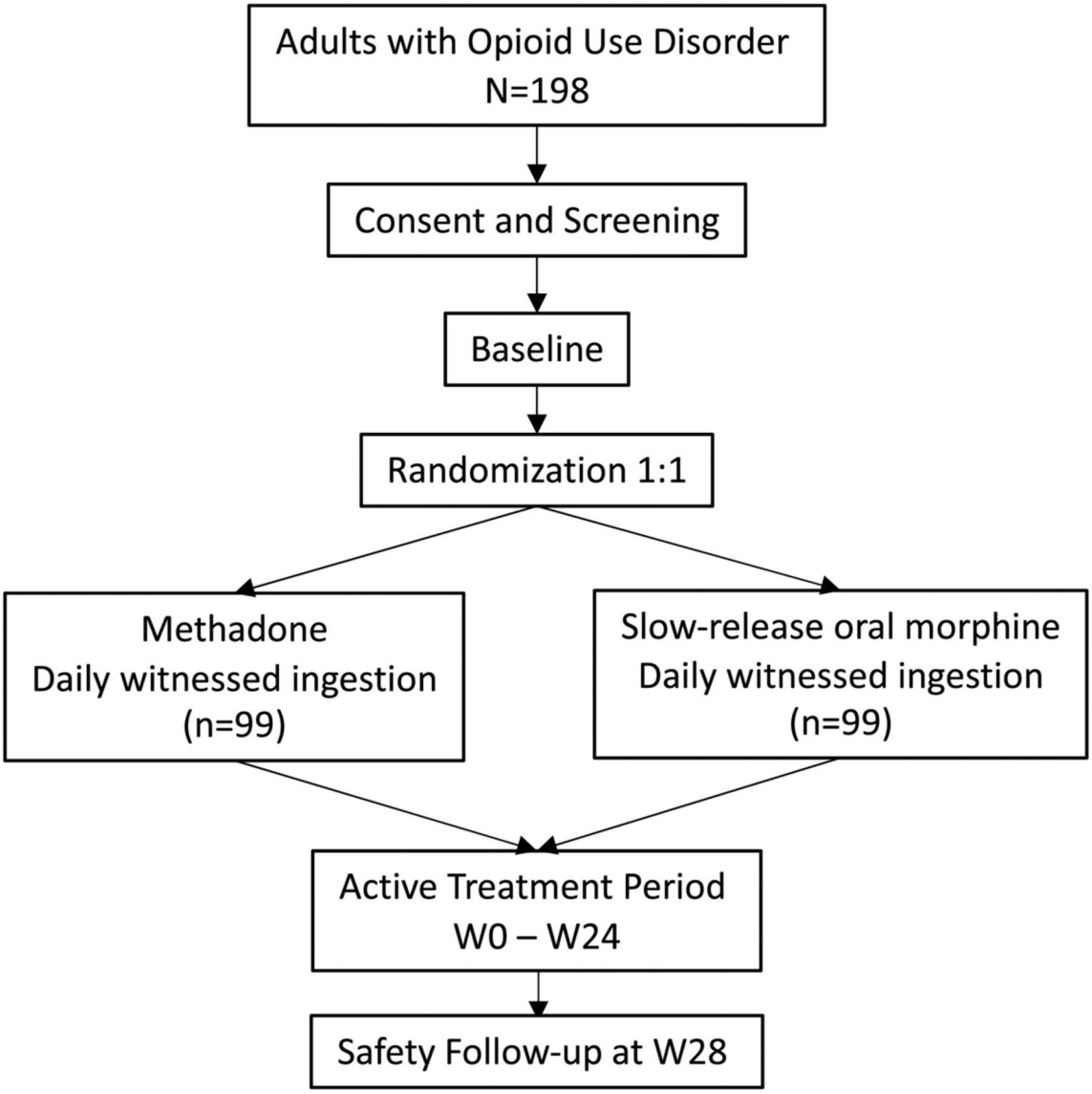

Figure 1.
Study schema

Table 1.

pRESTO eligibility criteria.

Inclusion criteria	
1	Be aged between 19 and 64 years of age, inclusively;
2	Be diagnosed with OUD requiring MOUD, as per DSM-5 criteria and the discretion of the study physician;
3	Be interested in receiving MOUD;
4	Be willing and eligible to be randomized to SROM or methadone as per British Columbia guidelines for the management of OUD;
5	If female:
	a. Be of non-childbearing potential, defined as (i) postmenopausal (12 months of spontaneous amenorrhea and over 45 years of age); or (ii) documented surgical sterilization (i.e., tubal ligation, hysterectomy, or bilateral oophorectomy); or
	b. If of childbearing potential, be willing to use an acceptable method of contraception throughout the study and have a negative pregnancy test at screening;
6	Be able to provide written informed consent;
7	Be willing to comply with study procedures;
8	Be able to communicate in English;
Exclusion criteria	
1	Any disabling, severe, or unstable medical or psychiatric condition that, in the opinion of the study physician, precludes safe participation in the study or the ability to provide fully informed consent, as assessed by medical and psychiatric history, physical examination, vital signs, and/or laboratory tests.
2	Any severe or unstable co-morbid substance use disorder (e.g., delirium tremens, acute alcohol intoxication) that, in the opinion of the study physician, precludes safe participation in the study;
3	Maintenance on buprenorphine at doses of ≥4 mg in the 5 days prior to screening and stable in the opinion of the study physician;
4	Maintenance on methadone at doses of ≥60 mg in the 5 days prior to screening and stable in the opinion of the study physician;
5	Maintenance on slow release oral morphine at doses of ≥250 mg in the 5 days prior to screening and stable in the opinion of the study physician;
6	Pregnant, breastfeeding, or planning to become pregnant during the study period;
7	History of a serious adverse drug reaction, hypersensitivity reaction, or allergy to methadone or SROM;
8	Use of an investigational drug in the 30 days prior to screening;
9	Pending legal action or other reasons that might prevent completion of the study;
10	Current or anticipated need for treatment with any medication that may interact with methadone or SROM (e.g., benzodiazepines, MAOIs used currently or within the past 14 days) and that, in the opinion of the study physician, would be deemed unsafe or could prevent study completion.

OUD, opioid use disorder. MOUD, medication for opioid use disorder. SROM, slow-release oral morphine. MAOI, monoamine oxidase inhibitor.

Table 2.

Schedule of study procedures and assessments.

Assessment	Frequency
General	
Informed Consent Form	SCR
Demographics	SCR
Inclusion/Exclusion criteria	SCR
Locator Form	SCR, then at each study visit
Randomization	BSL
Safety and medical assessments	
DSM-5 Diagnostic Criteria for OUD	SCR
Medical and Psychiatric History	SCR
Targeted Physical Exam & Vital Signs	SCR, EOT
Pregnancy and Birth Control Assessment	SCR, BSL, W 4, 8, 12, 16, 20, EOT
Concomitant medications	SCR, BSL, then W 1 to 24
Adverse Events and Serious Adverse Events	W 1 to 24
Non-fatal Overdose Events	BSL, W 12, EOT
Efficacy and acceptability assessments	
Urine Drug Test (UDT)	BSL, then at each study visit (i.e., every 2 weeks)
Assigned MOUD - Pharmacy Abstraction	W 1 to 24
Medical Satisfaction Questionnaire	W 4, 12, EOT
PROMIS Short Forms for Anxiety and Depression	BSL, W 4, 12, EOT
ASI-Self Report Form	BSL and EOT
Visual Analog Scale for opioid craving	BSL, W 2, 4, 8, 12, 16, 20, EOT
EuroQol-5D-5 L	BSL, W 4, 8, 12, 16, 20, EOT
Non-study Medical and Other Services form	BSL, W 4, 8, 12, 16, 20, EOT
Criminal and Legal Activities form	BSL, W 4, 8, 12, 16, 20, EOT
Timeline Follow Back	BSL, W 4, 8, 12, 16, 20, EOT
Motivations and expectations form	BSL
Health Data Linkages	BSL, M12, M24, M36
Treatment	
Assigned MOUD-Dosing	BSL, then W 1 to 24
Medical Management	BSL, then as clinically needed

SCR, Screening. BSL, Baseline. EOT, End of Treatment. W, week. M, month. OUD, opioid use disorder. MOUD, medication for opioid use disorder.