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The comparative effectiveness of buprenorphine-naloxone versus methadone: a population-based observational study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-036102
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2019
Complete List of Authors:	<p>Piske, Micah; BC Centre for Excellence in HIV/AIDS Thomson, Trevor; BC Centre for Excellence in HIV/AIDS Krebs, Emanuel; BC Centre for Excellence in HIV/AIDS Hongdilokkul, Natt; BC Centre for Excellence in HIV/AIDS Bruneau, Julie; CRCHUM; Universite de Montreal Greenland, Sander; UCLA, Department of Epidemiology and Department of Statistics Gustafson, Paul; UBC, Department of Statistics Karim, Ehsan; UBC, School of Population and Public Health; Centre for Health Evaluation and Outcome Sciences, Providence Health Care McCandless, Lawrence; Simon Fraser University, Department of Statistics and Actuarial Sciences; SFU, Faculty of Health Sciences Maclure, Malcolm; UBC, Department of Anesthesiology, Pharmacology and Therapeutics Platt, Robert; McGill University, Department of Epidemiology, Biostatistics and Occupational Health; Lady Davis Institute for Medical Research Socías, M.; BC Centre on Substance Use; UBC, Department of Medicine, Faculty of Medicine Tsui, Judith; University of Washington, Department of Medicine, Section of General Internal Medicine Wood, Evan; UBC, Department of Medicine, Faculty of Medicine, University of British Columbia Nosyk, Bohdan; British Columbia Centre for Excellence in HIV/AIDS; SFU, Faculty of Health Sciences</p>
Keywords:	Substance misuse < PSYCHIATRY, EPIDEMIOLOGY, PRIMARY CARE, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS

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The comparative effectiveness of Buprenorphine-Naloxone versus Methadone: a population-based observational study protocol

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Word Count: [4027/4000]

Tables: 2

Figures: 1

Supplemental Appendix Tables: 3

Funding statement: This work was supported by a Health Canada Substance Use and Addictions Program Grant No. 1819-HQ-000036.

Competing Interests: None declared.

"All inferences, opinions, and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s)."

Abstract

Introduction: Despite a recent meta-analysis including 31 randomized controlled trials comparing methadone and buprenorphine for the treatment of opioid use disorder, important knowledge gaps remain regarding the long-term effectiveness of different treatment modalities across individuals, including rigorously-collected data on retention rates and other treatment outcomes. Our objective is to determine the comparative effectiveness of methadone versus buprenorphine/naloxone, both overall and within key populations, in a setting where both medications are simultaneously available in office-based practices and specialized clinics.

Methods and analysis: We propose a retrospective cohort study of all adults living in British Columbia (BC) receiving opioid agonist treatment (OAT) with methadone or buprenorphine/naloxone between January 1st, 2008 and September 30th, 2018. The study will draw upon seven linked population-level administrative databases. The primary outcomes include retention in OAT and all-cause mortality. We will determine the effectiveness of buprenorphine/naloxone versus methadone using intention-to-treat and per-protocol analyses – the former emulating flexible-dose trials and the latter focusing on the comparison of the two medication regimens offered at the optimal dose. Sensitivity analyses will be used to assess the robustness of results to heterogeneity in the patient population and threats to internal validity.

Ethics and dissemination: The protocol, cohort creation, and analysis plan have been approved and classified as a quality improvement initiative exempt from ethical review (Providence Health Care Research Institute and the Simon Fraser University Office of Research Ethics). Dissemination is planned via conferences and publications, and through direct engagement and collaboration with entities that issue clinical guidelines, such as professional medical societies and public health organizations

Article Summary

Strengths and limitations of this study

- British Columbia's single-payer system represents an ideal setting for direct comparisons at the population-level and within key subgroups
- An intent-to-treat analysis with both instrumental variable and high-dimensional propensity score matching techniques will emulate trials featuring flexible dosing regimens
- A per-protocol analysis, implemented with G-estimation methods, will provide a direct comparison of the treatment regimens administered at clinical guideline-recommended doses and other guideline-recommended clinical practices
- Potential uncontrolled confounding and other threats to validity will be assessed via a range of sensitivity analyses and bias analysis

1.0 Introduction

Evidence supporting the use of opioid agonist treatment (OAT) for long-term treatment of opioid use disorder (OUD) is well established.¹ Nonetheless, a consensus study report of the National Academies of Sciences, Engineering, and Medicine, with support from the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration, recently highlighted the need for further studies to determine the most appropriate medication for key population subgroups and the comparative effectiveness of different medications over the long term.² The report further noted the refining of treatment protocols for effective use of existing medications as a priority topic. This is due in part to the fact that much of the existing evidence from randomized controlled trials (RCTs) has been generated utilizing protocols not representative of current clinical practice guidelines (which themselves are based on limited evidence) and within restrictive study cohorts over short durations (e.g. ranging from 6 to 52 weeks) that do not account for the chronic nature of OUD. The lack of consistent, high-quality evidence, therefore, continues to challenge informed decision-making when determining the best treatment option for individuals with OUD.

Numerous RCTs have indicated that buprenorphine and methadone are effective treatments for OUD.³⁻⁵ The effectiveness of methadone as a therapeutic treatment for OUD is the most established among the various forms of OAT.⁶ Methadone is a synthetic opioid agonist with high μ -opioid receptor binding affinity,⁷ but has a narrow therapeutic index, long elimination half-life and potential for interactions with alcohol and other drugs; properties which increase its risk of toxicity and other adverse effects.⁸ Buprenorphine is a safe and effective alternative to methadone treatment,⁹ working as a partial agonist with high affinity at the μ -opioid receptor and an antagonist at the κ -opioid receptor. Compared to methadone, buprenorphine features an improved safety profile with shorter induction; a milder side effect profile; milder withdrawal symptoms and fewer drug interactions; decreased risk of overdose due to a partial agonist 'ceiling effect'; and reduced risks of respiratory depression.⁸ Buprenorphine additionally offers a decreased risk of injection, and therefore harms related to diversion when taken in the buprenorphine/naloxone formulation. As a result, most settings have allowed more flexible and take-home dosing schedules earlier in the course of treatment.⁸

Regarding the comparative effectiveness of OAT regimens, evidence from randomized studies is mixed and dependent on whether a fixed or flexible dosing schedule was assigned.⁴ Retention in buprenorphine was less effective than methadone when dosing was flexible (RR:0.83 [0.73,0.95]); however, these differences were not observed when buprenorphine dosages were fixed at

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3 medium (7-16 mg/day) (RR:0.87 [0.69,1.10]) and high (≥ 16 mg/day) doses (RR:0.79 [0.20,3.16]).⁴
4 'Flexible-dose' studies were also conducted where doses were adjusted to individual need;
5 however, several RCTs utilizing such protocols reported maximum dose limits below the
6 recommended effective maintenance or induction dosage for buprenorphine.⁴ Many of the
7 flexible-dose studies yielded equivalent results for buprenorphine compared to methadone;
8 although this finding was not supported in a systematic review integrating earlier studies with
9 more recent trials.⁴ The implications of these findings are unclear as fixed dosing regimens are
10 not recommended in clinical practice. Further, substantial heterogeneity across studies included
11 in this meta-analysis with respect to participant selection and exclusion criteria, disease severity,
12 study design, dosing protocols, observation times and how retention is measured limits
13 generalizability, particularly to key populations excluded from the RCTs. Consequently, there are
14 several factors which limit conclusions drawn from previous studies in the comparative
15 effectiveness between buprenorphine and methadone, and challenge their applicability to clinical
16 practice.
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- 27 1. Restricted participant inclusion criteria in previous RCTs meta-analyzed by Mattick et al.⁴ have
28 resulted in an unrepresentative sample of the population living with OUD included in these
29 studies. People with opioid use disorder (PWOUD) have been observed to have a high
30 prevalence of co-morbid conditions, such as mental health disorders, other substance use
31 disorders, respiratory illness, chronic pain, HCV, and HIV/AIDS.¹⁰⁻¹² We previously reported a
32 high prevalence of mental health disorders (66%), chronic pain (53%), substance use
33 disorders (43%) and alcohol use disorders (20%) in a recent population-based study of
34 PWOUD in British Columbia (BC).¹³ A majority of the RCTs included in the Cochrane review
35 excluded individuals with major psychiatric medical conditions, other serious conditions,
36 previous receipt of OAT, and those with co-dependence on other substances, such as
37 stimulants, alcohol, cannabis and sedatives. Additionally, a vast majority of these studies
38 investigated treatment among heroin users before the era of fentanyl and the dramatic rise in
39 synthetic opioid use. Furthermore, most of the RCTs did not investigate OAT effectiveness
40 among special populations outlined in the American Society of Addiction Medicine (ASAM
41 guidelines), particularly through the exclusion of pregnant women and youth. A prior Cochrane
42 review conducted by Minozzi et al.¹⁴ investigating OAT efficacy in pregnant women with OUD,
43 reported insufficient evidence to draw firm conclusions about the equivalence of the
44 treatments for all outcomes including retention.
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3 2. Limited observation periods afforded by the RCTs included in the Mattick et al. study provided
4 an insufficient timeframe to determine retention and long-term treatment response.¹⁵ The
5 evaluation periods for RCTs in the review ranged from 6 to 48 weeks in the flexible-dose trials,
6 18 to 24 weeks in the low dose RCTs, 13 to 52 weeks in the medium-dose trials and 17 weeks
7 in the one high dose RCT included. The heterogeneity of study periods across these trials
8 limit conclusions on retention. Further challenging conclusions is the variation in the statistical
9 methods that were employed to investigate this outcome.
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15 3. Inconsistencies among RCTs regarding the formulation of OAT administered among
16 participants may influence treatment outcomes due to differences in their bioavailability and
17 effectiveness. Mattick et al. indicate nearly half of the RCTs included in their analysis utilized
18 aqueous ethanol-based buprenorphine solutions, which have been reported to have a higher
19 bioavailability resulting in nearly 50% higher peak plasma levels than marketed tablet forms.⁴
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21 ¹⁶ In other settings such as BC, buprenorphine/naloxone is predominantly available and
22 prescribed in the sublingual tablet formulation. Only three studies included the
23 buprenorphine/naloxone tablet formulation, (as opposed to buprenorphine alone), further
24 limiting available data for this specific OAT option.
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30 4. Buprenorphine's relative inferiority in retention compared to methadone reported in Mattick et
31 al. was suggested to have been influenced by inadequate buprenorphine dosage during
32 induction and maintenance in several of the referenced studies.¹⁷⁻¹⁹ One study noted their
33 buprenorphine doses may have been too low during the induction phase (2-6 mg during the
34 first week) and not increased quickly enough to retain patients, while rapid induction of doses
35 up to 12-16 mg of buprenorphine may be required to maximize retention.¹⁸ Another RCT
36 included in the flexible dosing analysis noted that their buprenorphine upper dose limit of 8
37 mg might have resulted in their high buprenorphine dropout rate.¹⁷ Mattick et al. report
38 equivalent outcomes in retention between buprenorphine and methadone during fixed-doses
39 of buprenorphine above 7mg. Seven of the eleven flexible-dose studies found no difference
40 in retention between methadone and buprenorphine, with mean buprenorphine doses ranging
41 from 9mg to 16mg/day.^{20 21-23 24} The other four flexible-dose studies, which reported
42 methadone's superior retention to buprenorphine, indicated mean buprenorphine doses
43 ranging from 2 mg to 16 mg/day.^{17 18 25 19} These findings may suggest retention is more likely
44 observed at higher buprenorphine dosage even in flexible dosing practice. Whether the same
45 results are observed with the buprenorphine/naloxone formulation will be important to clarify.
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3 5. Over half of the studies investigating retention included in the Cochrane meta-analysis
4 involved a form of individual or group counselling or cognitive behavioral therapy; however,
5 the contribution of this treatment to study outcomes is unclear. Numerous studies have
6 indicated that counselling or psychotherapy does not improve buprenorphine retention;²⁶⁻²⁸
7 however, several studies report contrasting results.²⁹⁻³¹ Given the inconsistency across the
8 studies with respect to adjunct psycho-social intervention, it is unclear how these additions
9 may have affected retention and influenced conclusions from the meta-analysis.
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15 In light of these challenges, observational studies may provide additional clarity on the
16 comparative effectiveness of methadone versus buprenorphine, as well as the impacts of flexible
17 dosing and adjunctive psychosocial interventions. Real-world data can provide a powerful basis
18 to improve health care decision making and offer valuable insights beyond the restricted scope of
19 RCTs.³² However, findings from observational studies on this topic are limited by confounders,
20 particularly those which are time-variant, requiring advanced statistical methods to account for
21 their effects. Nonetheless, decision-makers are increasingly relying on real-world data for
22 evidence on treatment effectiveness and its relevance to specific populations.^{32,33} To this end,
23 methadone has demonstrated better retention relative to buprenorphine/naloxone in
24 observational settings in Australia and the US³⁴⁻³⁶, though selection bias and uncontrolled
25 (residual) confounding may bias these comparisons.⁸ This comparison is challenged by
26 uncontrolled confounding, structural differences in the setting of care (opioid treatment programs
27 for methadone and office-based treatment for buprenorphine in the US) and the mechanism by
28 which PWOUD are selected, or select themselves into one form of treatment over another.
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38 Buprenorphine/naloxone was made the recommended first-line treatment for OUD in 2017 in BC.
39 However, BC's guidelines differ from ASAM and the Substance Abuse and Mental Health
40 Services Administration's^{37 38}, in part due to the conflicting results of the fixed- and flexible-dosing
41 studies as well as differences in medication availability. Specifically, in Canada, methadone is
42 available through primary care physicians and community pharmacies whereas US regulations
43 limit methadone availability to specialized methadone clinics. Additionally, individuals receiving
44 buprenorphine may safely switch to methadone if buprenorphine's clinical effect is insufficient,
45 with one study demonstrating their equal efficacy with a stepped care strategy.³⁹ Furthermore, the
46 improved safety profile of buprenorphine/naloxone and resulting reductions in the potential harms
47 from diversion have prompted reduced restrictions on take-home dosing for this treatment
48 modality.⁸ While this practice may positively influence treatment retention, it was not permitted in
49 the majority of RCTs included in the Cochrane review.
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3 BC is a single-payer system featuring limited co-payment for medications, with both forms of OAT
4 available in office-based settings. The availability of all forms of OAT in office-based settings in
5 BC allows for a direct comparison that is not possible in naturalistic settings in the US given that
6 methadone can be prescribed only in stand-alone opioid treatment programs. BC is also free of
7 waiver policies, patient limits and other policies that are not supported by evidence or employed
8 for other medical disorders.⁴⁰ With a population-based linked administrative dataset featuring daily
9 dispensation data for over 78,000 person-years on methadone and buprenorphine/naloxone, we
10 are uniquely positioned to contribute high-quality, real-world evidence to resolve these issues.
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16 During a period of heightened OUD-related mortality, identifying effective treatment options is
17 critical in bridging the gap between research evidence and evidence-based care for the clinical
18 management of OUD. We propose a retrospective cohort study with both intention-to-treat and
19 per-protocol (or in this case per clinical guideline) analytic strategies to determine the
20 effectiveness of buprenorphine/naloxone versus methadone in achieving sustained retention and
21 delaying hospitalization and mortality. These analytic strategies allow for adequate comparisons
22 to the previous clinical trials, while respecting the underlying data generating process. We aim to
23 determine the comparative effectiveness both overall and within key populations through
24 conducting analyses that reflect real-world practice and adherence to clinical guidelines .
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2.0 Methods

2.1 Study design

The study is a retrospective observational study based on a provincial cohort of all BC OAT recipients from January 1st, 2008 to September 30th, 2018. The study period (**Figure 1**), corresponds to the period in which buprenorphine/naloxone was available for prescription in BC, although we have methadone prescription records since January 1st 1996. The cohort will be defined using a validated list of Drug Identification Numbers specific to OAT medications. OAT episodes will be determined from dispensed prescription database records throughout the study period. The current iteration of the cohort features seven linked population-level administrative databases, including the Medical Services Plan (capturing physician billing records),⁴¹ the Discharge Abstract Database (hospitalizations),⁴² PharmaNet (drug dispensations),⁴³ Vital Statistics (death and their underlying causes),⁴⁴ BC Corrections (capturing incarceration in provincial prisons),⁴⁵ the National Ambulatory Care Reporting System database (capturing all emergency department visits),⁴⁶ and the Perinatal database (maternal and child health for all provincial births).⁴⁷ Additional information on datasets is provided in **Supplementary Appendix Table A1**. Eligibility for inclusion in the study cohort will be individuals with receipt of OAT (either methadone or buprenorphine/naloxone) during the study period. We will apply specific exclusion criteria in sensitivity analyses for comparison with recent RCTs, and to generate evidence accounting for heterogeneity in key populations identified in the ASAM National Practice Guidelines, including pregnant women, individuals with pain, adolescents, individuals with co-occurring mental disorders and individuals in the criminal justice system.⁴⁸ Case-finding algorithms, applied to address possible misclassification in outpatient and hospital ICD-9/10 codes, will be used to attribute other, OUD-related chronic conditions, including mental health conditions, other substance use disorders, HIV, HCV and chronic pain (**Supplementary Appendix Tables A2 & A3**).

2.2 Outcomes

The primary exposure is receipt of OAT (either methadone or buprenorphine/naloxone), which can be measured at daily, weekly or monthly time intervals. The primary outcomes of interest are (i) continuous retention in OAT; (ii) hospitalization and (iii) all-cause mortality. We defined continuous OAT retention as the time interval during which an individual received OAT with no breaks in days dispensed lasting longer than 5 days for methadone and no longer than 6 days for buprenorphine/naloxone. These objective discontinuation criteria were based on BC guidelines recommending resetting starting doses after these durations of non-compliance to ensure safety.⁸

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3 Initiation and subsequent re-initiation of OAT receipt will be determined from medication
4 dispensation records in PharmaNet and all-cause mortality from vital statistics data.
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6 7 *2.3 Follow-up*

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9 Each individual will be followed from OAT initiation until either administrative loss to follow-up or
10 death. To account for out-of-province migration, administrative loss to follow-up will be defined as
11 no health service utilization record in any of the linked databases for at least 66 months prior to
12 the end of study follow-up. The 66-month cut-off was empirically determined based on the
13 distribution of gaps between hospitalization records, physician billing records, and drug
14 dispensations over the entire data extraction timeframe.^{13 49}
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19 *2.4 Analysis plan*

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21 Our aim is to assess the effectiveness of buprenorphine/naloxone versus methadone in achieving
22 sustained retention and delaying mortality, and we propose to conduct intention-to-treat and per-
23 protocol (per-clinical guideline) analyses. An intention-to-treat analysis allowing for flexible dosing
24 schedules as set by prescribing physicians will focus on an individual's outcome at the end of
25 follow-up, adjusting for selection bias. High-dimensional propensity score matching and
26 instrumental variables estimation will control for measured and unmeasured factors that may
27 systematically influence the selection of either buprenorphine/naloxone or methadone. However,
28 in the presence of sub-optimal dosing, the intention-to-treat effect is less meaningful for clinical
29 decision making.⁵⁰ A longitudinal per-protocol analysis, which censors patients once they deviate
30 from the study protocol, will be used to estimate the comparative effectiveness of each medication
31 regimen when offered at the recommended dose per clinical guidelines.⁵¹
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40 *2.4.1 Intention-to-treat approach*

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42 Accounting for factors that may influence which individuals receive buprenorphine/naloxone
43 versus methadone is one of the key challenges for estimating the causal relationship between
44 treatment and outcome in the comparative effectiveness of methadone versus
45 buprenorphine/naloxone. An intention-to-treat approach, allowing for dosing schedules as set by
46 prescribing physicians, therefore emulating a flexible-dose trial, will focus explicitly on adjusting
47 for uncontrolled confounders that influence treatment selection. We propose two complementary
48 estimation strategies – high-dimensional propensity score matching and instrumental variables –
49 based on different assumptions to account for unmeasured confounders that may influence the
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3 selection of either buprenorphine/naloxone or methadone. As these assumptions are not explicitly
4 testable, concordance in findings will strengthen our inferences.
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6 7 *2.4.1.1 High-dimensional propensity score estimation* 8

9 Like covariate adjustment in standard multiple regression, propensity score matching is a means
10 of controlling for potential bias due to measured confounders. The probability of treatment
11 selection is modeled as a function of measured covariates among individuals. Controls are
12 matched to treated individuals based on their estimated propensity score, which is the individual
13 probability of receiving the medication.
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17 Applications with investigator-selected covariates have found this approach controls confounding
18 comparably to traditional multiple regression.⁵² Residual confounding due to unmeasured
19 variables is an obvious limitation of both approaches, however. High-dimensional propensity
20 score (hdPS) is a semi-automated data-driven approach to identify potentially important proxy
21 variables from administrative data for inclusion in propensity score models.⁵³ It identifies
22 covariates collected for billing and routine administrative purposes as proxies for uncontrolled
23 confounders, eliminating those with very low prevalence and minimal potential for controlling bias.
24 In the final hdPS step, propensity score techniques are used to adjust for the selected investigator-
25 specified covariates and proxy variables identified as important by the hdPS algorithm.
26 Comparisons of the performance of the hdPS against investigator-specified propensity scores
27 constructed with health administrative and clinical registry-based data have generally found
28 improved performance, approaching that of clinical registry-based analyses.⁵⁴
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37 *2.4.1.2 Instrumental variable estimation* 38

39 IV methods are a common approach to handling unmeasured confounders, where selection into
40 a treatment group (i.e., those accessing buprenorphine/naloxone compared to methadone) is
41 influenced by factors that may not be observed.⁵⁵ The goal of IV methods is to reduce confounding
42 bias without measuring all factors driving treatment decisions. Typical IV methods require a
43 variable – the ‘instrument’ – that meets three conditions: (1) the instrument is monotonically
44 associated with the treatment; (2) the instrument does not affect the outcome except through
45 treatment (also known as the exclusion restriction assumption); and (3) the instrument does not
46 share any uncontrolled causes with the outcome (is not itself confounded).
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53 Physician preference has been used as an IV in prior comparative effectiveness applications.⁵⁶
54 In a recent analysis on the determinants of treatment selection, we found unexplained (residual)
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3 between-physician variance accounted for 28.4% of the explained variation in the odds of
4 selecting buprenorphine/naloxone whereas the unexplained between-individual variance
5 accounted for 18.5%.⁵⁷ Physician preference will be measured in our application by the
6 prescriber's selection of medication regimen (methadone or buprenorphine/naloxone) for their
7 most recent OAT-naïve clients. This IV will serve as a starting point for our analysis, although we
8 will compare the relative performance of this measure (and similar variations, i.e., preference in
9 the past twenty naïve patients, etc.), with other instruments noted in a recent review.⁵⁶
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14 We will follow current methodological standards for selection, validation and reporting of IVs.⁵⁵
15 Validation entails an empirical assessment of condition 1 above, and we will conduct F-tests from
16 the first-stage regression to support this condition. However, there is less consensus on assessing
17 conditions 2 and 3. In following Swanson and Hernan,⁵⁵ we propose to assess condition 2 using
18 clinical knowledge of a scientific advisory committee to build a case that the instrument does not
19 affect the outcome except through treatment (i.e., that one individual's potential outcomes are not
20 affected by the choice of medication for other individuals). For condition 3, we propose to show
21 empirically that the proposed instrumental variables are not associated with the available
22 covariates listed in **Table 1**.^{55 56 58} We will also consider alternative empirical approaches for
23 assessing conditions 2 and 3, consistent with recommendations of Glymour et al.⁵⁹
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31 The use of IVs is controversial, in part because conditions (2) and (3) listed above are not explicitly
32 testable for unmeasured confounders.⁵⁵ Others have warned of bias amplification if instruments
33 are controlled in a conventional manner,⁶⁰ and counterarguments have been made regarding the
34 use of physician preference as an instrument.⁶¹ The choice between propensity score and IV
35 approaches depends on whether the selection mechanism for treatment is identifiable or not,
36 respectively. While both approaches have faced criticism, concordance in their results will
37 strengthen the inference, while discordance (overall or within a given subgroup) may indicate a
38 need for additional, possibly experimental, studies to validly estimate effects.
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45 *2.4.2 Per-protocol approach*

46 G-methods offer the advantage of controlling for time-varying confounders that may be both acting
47 as confounding and intermediate variables simultaneously.⁶² In this application, a daily dose at or
48 above the minimum effective dosing threshold may be the result of spending sufficient time in
49 treatment to titrate up to this dose, among other considerations (including individual-, prescriber-
50 and facility-level factors). In turn, higher daily dosing is associated with longer retention – the key
51 aspect of the estimation problem requiring G-methods.
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3 G-estimation of structural nested models^{63 64} is most applicable in our setting, because we are
4 explicitly concerned with the comparative effect of methadone versus buprenorphine/naloxone at
5 the optimal dose (≥ 80 mg/day for methadone; ≥ 16 mg/day for buprenorphine/naloxone).^{8 65 66} The
6 interaction between dosage and time-varying factors can obscure the causal effect of treatment
7 on the outcome. G-estimation is a two-step iterative process designed to handle this problem; its
8 objective is to exploit the conditional independence between the exposure and potential outcomes
9 to estimate the model parameters. The unobserved potential outcome is first estimated using an
10 accelerated failure time model, where a known function links the unobserved potential outcome
11 with the observed potential outcome using an unknown effect parameter.^{67 68} An additional model
12 for treatment is then specified, which includes all confounders and treatment history, and the
13 association between treatment and the baseline (control) potential outcome is assessed. This
14 step finds the effect-parameter value that results in the treatment being unrelated to the potential
15 outcome, the G-estimate.

16
17 We will apply G-estimation to the OAT episodes to obtain the treatment effects of methadone and
18 buprenorphine/naloxone on the study outcomes. For each OAT episode, we will specify a model
19 for the levels of OAT dosage to perform G-estimation, and then estimate the potential outcomes
20 with a structural accelerated failure time model.

21 22 23 24 25 26 27 28 29 30 31 *2.4.3 Covariate selection*

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33 While the assumption of no uncontrolled confounding cannot be verified in observational settings,
34 we adjust for all potential confounders available within our linked database.⁶⁹ We identified these
35 covariates by conducting a systematic literature review for articles published up to September 2,
36 2019 to identify factors associated with OAT retention. The following search string was included
37 in PubMed: (“opiate substitution treatment”[MeSH] OR “opioid agonist treatment”[MeSH] OR
38 “buprenorphine”[MeSH] OR “methadone”[MeSH]) AND (“retention”[MeSH] OR
39 “determinants”[MeSH] OR “factors”[MeSH] OR “predictor”[MeSH]). The search was restricted to
40 studies on humans reported in English and published after December 31, 2000 to ensure findings
41 were relevant to current treatment options. A total of 55 articles resulted from this search, which
42 were screened for inclusion. **Table 1** highlights fixed and time-varying individual, contextual and
43 treatment-related factors associated with OAT retention, whether these factors were positively or
44 negatively associated with OAT retention and the quality of the underlying evidence. We specify
45 factors captured (directly or with reasonable proxies) and not captured within our database, with
46 the latter serving as candidates for probabilistic bias analysis. Alternately, machine learning
47 algorithms will be used for covariate selection within the intention-to-treat analysis with high-

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3 dimensional propensity scores, as described above. Additionally, we will consider the flexibility
4 buprenorphine allows for take-home use (which was not permitted in the majority of RCTs
5 included in the Cochrane review).
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8 *2.4.4 Subgroup and Sensitivity analysis*

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10 We will conduct a range of subgroup and sensitivity analyses to assess the robustness of our
11 results and heterogeneity in treatment effects across key client subgroups. We specify a priori
12 targets focusing on cohort restriction, timeline restriction, variable classification and model
13 specification in **Table 2**. Applicable results will be presented in tornado diagrams centered on the
14 baseline relative risk from each analytical strategy. Any post hoc additions to this protocol will be
15 identified as such in final reports.
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20 *3. Ethics and dissemination*

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22 This linked database was made available to the research team by BC Ministries of Health and
23 Mental Health and Addiction as part of the response to the provincial opioid overdose public health
24 emergency, and classified as a quality improvement initiative. Providence Health Care Research
25 Institute and the Simon Fraser University Office of Research Ethics determined the analysis met
26 criteria for exemption per Article 2.5 of the Tri-Council Policy Statement: Ethical Conduct for
27 Research Involving Humans.⁷⁰
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33 This study will follow international guidelines for study conduct and reporting, including
34 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,⁷¹
35 and the administration of the 'Risk of Bias in Non-Randomized Studies – of Interventions'
36 (ROBINS-I) tool to a multidisciplinary scientific advisory committee for ex-post evaluation. Results
37 will be published in peer-reviewed journals electronically and in print.
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41 This study will generate robust evidence on how competing forms of opioid agonist treatment
42 compare in real-world practice over the long term, in the interest of improving retention in these
43 essential⁷² and life-saving⁷³ medications.
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47 **Data sharing**

48 Study datasets: Not available. Statistical code: Available from Dr. Bohdan Nosyk
49 (bnosyk@sfu.ca).
50
51

52 **Contributions**

53

54 MP conducted literature reviews and wrote the first draft of the article. TT, EK, and NH wrote key
55 methodological components of the article and provided critical revisions. JB, SG, PG, MEK, LCM,
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3 MM, RWP, MES, JIT, EW, and BN aided in the methodological development and provided critical
4 revisions to the manuscript. BN conceptualized and secured funding for the study. All authors
5 approved the final draft.
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48
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For peer review only

References

1. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *The Lancet* 2019;393(10182):1760-72.
2. National Academies of Sciences, Engineering, Medicine. Medications for Opioid Use Disorder Save Lives, 2019.
3. Ahmadi J. Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients. *Journal of Substance Abuse Treatment* 2003;24(3):217-20.
4. Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews* 2014(2):CD002207.
5. Johnson RE, Eissenberg T, Stitzer ML, et al. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 1995;40(1):17-25.
6. Dole VP, Nyswander M. A Medical Treatment for Diacetylmorphine (Heroin) Addiction: A Clinical Trial With Methadone Hydrochloride. *JAMA* 1965;193(8):646-50.
7. Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs* 2012;72(2):217-28.
8. British Columbia Centre on Substance Use (BCCSU). A guideline for the clinical management of opioid use disorder, 2017.
9. Johnson RE, Jaffe JH, Fudala PJ. A Controlled Trial of Buprenorphine Treatment for Opioid Dependence. *JAMA* 1992;267(20):2750-55.
10. Sproule B, Brands B, Li S, et al. Changing patterns in opioid addiction: characterizing users of oxycodone and other opioids. *Can Fam Physician* 2009;55(1):68-69.e695.
11. Socias ME, Wood E, Kerr T, et al. Trends in engagement in the cascade of care for opioid use disorder, Vancouver, Canada, 2006–2016. *Drug and Alcohol Dependence* 2018;189:90-95.
12. Nielsen S, Lintzeris N, Bruno R, et al. Benzodiazepine Use among Chronic Pain Patients Prescribed Opioids: Associations with Pain, Physical and Mental Health, and Health Service Utilization. *Pain Medicine* 2015;16(2):356-66.
13. Piske M, Zhou C, Min J, et al. The cascade of care for opioid use disorder: a retrospective study in British Columbia, Canada. *Second review at Addiction* 2019
14. Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev* 2013(12):Cd006318.
15. Farmani F, Farhadi H, Mohammadi Y. Associated Factors of Maintenance in Patients under Treatment with Methadone: A Comprehensive Systematic Review and Meta-Analysis. *Addict Health* 2018;10(1):41-51.
16. Nath RP, Upton RA, Everhart ET, et al. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *Journal of clinical pharmacology* 1999;39(6):619-23.
17. Fischer G, Gombas W, Eder H, et al. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction* 1999;94(9):1337-47.
18. Mattick RP, Ali R, White JM, et al. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction* 2003;98(4):441-52.
19. Petitjean S, Stohler R, Déglon J-J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug and Alcohol Dependence* 2001;62(1):97-104.
20. Johnson RE, Chutuape MA, Strain EC, et al. A Comparison of Levomethadyl Acetate, Buprenorphine, and Methadone for Opioid Dependence. *New England Journal of Medicine* 2000;343(18):1290-97.

- 1
- 2
- 3
- 4 21. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: Interactions and
- 5 clinical management. *The American Journal on Addictions* 2010;19(1):59-72.
- 6 22. Magura S, Lee JD, Hershberger J, et al. Buprenorphine and methadone maintenance in jail
- 7 and post-release: A randomized clinical trial. *Drug and Alcohol Dependence*
- 8 2009;99(1):222-30.
- 9 23. Neri S, Bruno CM, Pulvirenti D, et al. Randomized clinical trial to compare the effects of
- 10 methadone and buprenorphine on the immune system in drug abusers.
- 11 *Psychopharmacology* 2005;179(3):700-04.
- 12 24. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and
- 13 buprenorphine maintenance therapy and predictors of outcome: results from a
- 14 randomized study. *International Journal of Neuropsychopharmacology* 2008;11(5):641-
- 15 53.
- 16 25. Kristensen Ø, Espegren O, Asland R, et al. [Buprenorphine and methadone to opiate addicts--
- 17 a randomized trial]. *Tidsskr Nor Laegeforen* 2005;125(2):148-51.
- 18 26. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone
- 19 versus clonidine for opioid detoxification: findings from the National Institute on Drug
- 20 Abuse Clinical Trials Network. *Addiction* 2005;100(8):1090-100.
- 21 27. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended
- 22 buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase
- 23 randomized controlled trial. *Arch Gen Psychiatry* 2011;68(12):1238-46.
- 24 28. Moore BA, Fiellin DA, Cutter CJ, et al. Cognitive Behavioral Therapy Improves Treatment
- 25 Outcomes for Prescription Opioid Users in Primary Care Buprenorphine Treatment. *J*
- 26 *Subst Abuse Treat* 2016;71:54-57.
- 27 29. Voelker R. App Aids Treatment Retention for Opioid Use Disorder App Aids Treatment
- 28 Retention for Opioid Use Disorder News From the Food and Drug Administration. *JAMA*
- 29 2019;321(5):444-44.
- 30 30. Chen W, Hong Y, Zou X, et al. Effectiveness of prize-based contingency management in a
- 31 methadone maintenance program in China. *Drug Alcohol Depend* 2013;133(1):270-4.
- 32 31. Hser YI, Li J, Jiang H, et al. Effects of a randomized contingency management intervention
- 33 on opiate abstinence and retention in methadone maintenance treatment in China.
- 34 *Addiction* 2011;106(10):1801-9.
- 35 32. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment
- 36 and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special
- 37 Task Force on real-world evidence in health care decision making.
- 38 *Pharmacoepidemiology and Drug Safety* 2017;26(9):1033-39.
- 39 33. Centers for Disease Control and Prevention (CDC). Medication-Assisted Treatment for Opioid
- 40 Use Disorder Study (MAT Study) [Available from:
- 41 [https://www.cdc.gov/opioids/Medication-Assisted-Treatment-Opioid-Use-Disorder-](https://www.cdc.gov/opioids/Medication-Assisted-Treatment-Opioid-Use-Disorder-Study.html)
- 42 [Study.html](https://www.cdc.gov/opioids/Medication-Assisted-Treatment-Opioid-Use-Disorder-Study.html).
- 43 34. Bell J, Trinh L, Butler B, et al. Comparing retention in treatment and mortality in people after
- 44 initial entry to methadone and buprenorphine treatment. *Addiction* 2009;104(7):1193-200.
- 45 35. Burns L, Gisev N, Larney S, et al. A longitudinal comparison of retention in buprenorphine
- 46 and methadone treatment for opioid dependence in New South Wales, Australia. *Addiction*
- 47 2015;110(4):646-55.
- 48 36. Saxon AJ. Commentary on Burns et al. (2015): retention in buprenorphine treatment.
- 49 *Addiction* 2015;110(4):656-7.
- 50 37. American Society of Addiction Medicine. National practice guideline for the use of medications
- 51 in the treatment of addiction involving opioid use. *Journal of Addiction Medicine*
- 52 2015;9(5):358-67.
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

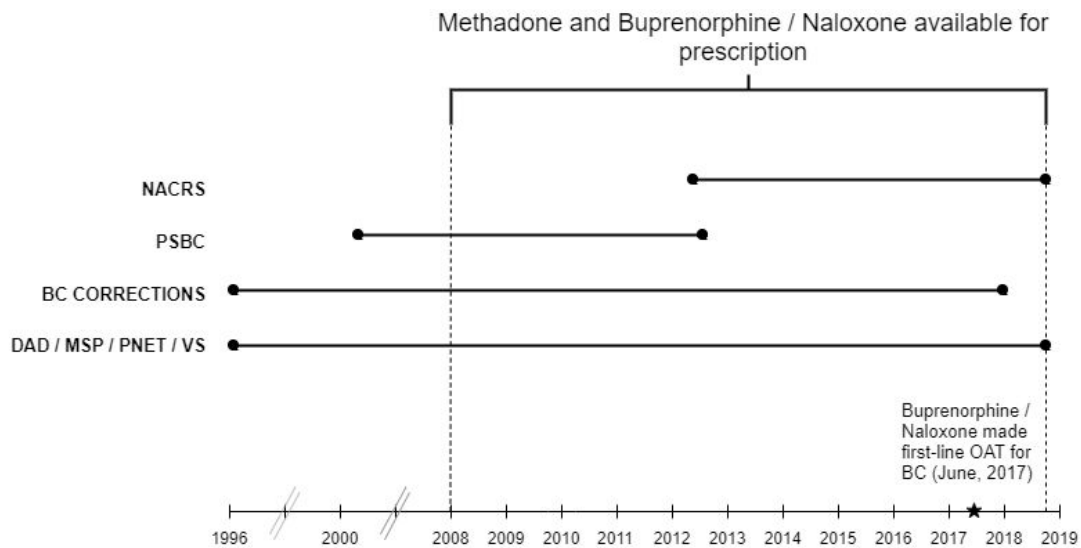
- 1
- 2
- 3
- 4 38. Boyd J, Collins A, Mayer S, et al. Gendered violence & the overdose crisis: A rapid
- 5 ethnographic study of overdose prevention sites in Vancouver, Canada. *Addiction* IN
- 6 PRESS
- 7 39. Kakko J, Gronbladh L, Svanborg KD. A stepped care strategy using buprenorphine and
- 8 methadone versus conventional methadone maintenance in heroin dependence: a
- 9 randomized controlled trial. *Am J Psychiatry* 2007;164(5):797-274.
- 10 40. College of Pharmacists of BC. Opioid Agonist Treatment 2019 [Available from:
- 11 <https://www.bcpharmacists.org/opioid-agonist-treatment>.
- 12 41. British Columbia Ministry of Health [creator] (2018): Medical Services Plan (MSP) Payment
- 13 Information File. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018).
- 14 <http://www.health.gov.bc.ca/data/>.
- 15 42. British Columbia Ministry of Health [creator] (2018): Discharge Abstract Database (Hospital
- 16 Separations). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018).
- 17 <http://www.health.gov.bc.ca/data/>.
- 18 43. British Columbia Ministry of Health [creator] (2018): PharmaNet. British Columbia Ministry of
- 19 Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
- 20 44. BC Vital Statistics Agency [creator] (2018): Vital Statistics Deaths. British Columbia Ministry
- 21 of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
- 22 45. Ministry of Public Safety and Solicitor General (PSSG) [creator] (2018): BC Corrections
- 23 Dataset. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018).
- 24 <http://www.health.gov.bc.ca/data/>.
- 25 46. British Columbia Ministry of Health [creator] (2018): National Ambulatory Care Reporting
- 26 System (NACRS). British Columbia Ministry of Health [publisher]. Data Extract. MOH
- 27 (2018). <http://www.health.gov.bc.ca/data/>.
- 28 47. Perinatal Services BC [creator] (2018): British Columbia Perinatal Data Registry. British
- 29 Columbia Ministry of Health [publisher]. Data Extract. MOH (2018).
- 30 <http://www.health.gov.bc.ca/data/>.
- 31 48. The American Society of Addiction Medicine (ASAM). The ASAM National Practice Guideline
- 32 For The Use of Medications in the Treatment of Addiction Involving Opioid Use, 2015.
- 33 49. Pearce L, Min J, Piske M, et al. Opioid substitution treatment and risk of mortality during an
- 34 opioid overdose public health emergency: A population-based retrospective cohort study.
- 35 *Second review at The BMJ* 2019
- 36 50. Herenan M, Hernandez-Dias S. Beyond the intention-to-treat in comparative effectiveness
- 37 research. *Clin Trials* 2012;9:48-55.
- 38 51. Murray EJ, Hernan MA. Adherence adjustment in the Coronary Drug Project: A call for better
- 39 per-protocol effect estimates in randomized trials. *Clin Trials* 2016;13(4):372-8.
- 40 52. Shah BR, Laupacis A, Hux JE, et al. Propensity score methods gave similar results to
- 41 traditional regression modeling in observational studies: a systematic review. *Journal of*
- 42 *Clinical Epidemiology* 2005;58(6):550-59.
- 43 53. Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment
- 44 in studies of treatment effects using health care claims data. *Epidemiology (Cambridge,*
- 45 *Mass)* 2009;20(4):512-22.
- 46 54. Austin P, Fangyun Wu C, Lee D, et al. Comparing the high-dimensional propensity score for
- 47 use with administrative data with propensity scores derived from high-quality clinical data.
- 48 *Statistical Methods in Medical Research* 2019:096228021984236.
- 49 55. Swanson SA, Hernán MA. Commentary: How to Report Instrumental Variable Analyses
- 50 (Suggestions Welcome). *Epidemiology* 2013;24(3):370-74.
- 51 56. Davies NM, Smith GD, Windmeijer F, et al. Issues in the Reporting and Conduct of
- 52 Instrumental Variable Studies: A Systematic Review. *Epidemiology* 2013;24(3):363-69.
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
- 2
- 3
- 4 57. Homayra F, Hongdilokkul N, Piske M, et al. Determinants of selection into buprenorphine/naloxone among people initiating opioid agonist treatment in British Columbia. *Second review at Drug and Alcohol Dependence* 2019
- 5
- 6 58. Davies NM, Smith GD, Windmeijer F, et al. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology* 2013;24(3):363-9.
- 7
- 8 59. Glymour MM, Tchetgen Tchetgen EJ, Robins JM. Credible Mendelian randomization studies: approaches for evaluating the instrumental variable assumptions. *Am J Epidemiol* 2012;175(4):332-9.
- 9
- 10 60. Ding P, VanderWeele TJ, Robins JM. Instrumental variables as bias amplifiers with general outcome and confounding. *Biometrika* 2017;104(2):291-302.
- 11
- 12 61. Hernán MA, Robins JM. Instruments for Causal Inference: An Epidemiologist's Dream? *Epidemiology* 2006;17(4):360-72.
- 13
- 14 62. Hernan MA, Robins JM. Causal Inference. 2020 ed: Boca Raton: Chapman & Hall/CRC.
- 15 63. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. *New England Journal of Medicine* 2017;377(14):1391-98.
- 16
- 17 64. Murray EJ, Hernan MA. Improved adherence adjustment in the Coronary Drug Project. *Trials* 2018;19(1):158.
- 18
- 19 65. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *Journal of addiction medicine* 2015;9(5):358-67.
- 20
- 21 66. Naimi AI, Cole SR, Kennedy EH. An introduction to g methods. *Int J Epidemiol* 2017;46(2):756-62.
- 22
- 23 67. Naimi AI, Richardson DB, Cole SR. Causal Inference in Occupational Epidemiology: Accounting for the Healthy Worker Effect by Using Structural Nested Models. *American Journal of Epidemiology* 2013;178(12):1681-86.
- 24
- 25 68. Hernan MA, Cole SR, Margolick J, et al. Structural accelerated failure time models for survival analysis in studies with time-varying treatments. *Pharmacoepidemiol Drug Saf* 2005;14(7):477-91.
- 26
- 27 69. VanderWeele T. Principles of confounder selection. *European Journal of Epidemiology* 2019;34
- 28
- 29 70. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Tri-council policy statement: Ethical conduct for research involving humans. . 2010
- 30
- 31 71. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61(4):344-9.
- 32
- 33 72. World Health Organization. WHO Model Lists of Essential Medicines, 2019.
- 34
- 35 73. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *Bmj* 2017;357:j1550.
- 36
- 37 74. Weinstein ZM, Kim HW, Cheng DM, et al. Long-term retention in Office Based Opioid Treatment with buprenorphine. *Journal of substance abuse treatment* 2017;74:65-70.
- 38
- 39 75. Yang F, Lin P, Li Y, et al. Predictors of retention in community-based methadone maintenance treatment program in Pearl River Delta, China. *Harm Reduct J* 2013;10:3.
- 40
- 41 76. Pickens RW, Preston KL, Miles DR, et al. Family history influence on drug abuse severity and treatment outcome. *Drug Alcohol Depend* 2001;61(3):261-70.
- 42
- 43 77. Gerra G, Leonardi C, D'Amore A, et al. Buprenorphine treatment outcome in dually diagnosed heroin dependent patients: A retrospective study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2006;30(2):265-72.
- 44
- 45 78. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
2
3 randomized study. *The international journal of neuropsychopharmacology*
4 2008;11(5):641-53.
- 5 79. Manhapra A, Rosenheck R, Fiellin D. Opioid substitution treatment is linked to reduced risk
6 of death in opioid use disorder. *BMJ* 2017(357):j1947.
- 7 80. Apelt S, Scherbaum N, Soyka M. Induction and Switch to Buprenorphine-Naloxone in opioid
8 dependence treatment: Predictive Value of the First Four Weeks. *Heroin Addiction and*
9 *Related Clinical Problems* 2014;16:87-98.
- 10 81. Dayal P, Balhara YPS. A naturalistic study of predictors of retention in treatment among
11 emerging adults entering first buprenorphine maintenance treatment for opioid use
12 disorders. *J Subst Abuse Treat* 2017;80:1-5.
- 13 82. Cox J, Allard R, Maurais E, et al. Predictors of methadone program non-retention for opioid
14 analgesic dependent patients. *J Subst Abuse Treat* 2013;44(1):52-60.
- 15 83. Lee CS, Liebschutz JM, Anderson BJ, et al. Hospitalized opioid-dependent patients: Exploring
16 predictors of buprenorphine treatment entry and retention after discharge. *Am J Addict*
17 2017;26(7):667-72.
- 18 84. Haddad MS, Zelenev A, Altice FL. Integrating buprenorphine maintenance therapy into
19 federally qualified health centers: real-world substance abuse treatment outcomes. *Drug*
20 *Alcohol Depend* 2013;131(1-2):127-35.
- 21 85. Ruger JP, Chawarski M, Mazlan M, et al. Cost-effectiveness of buprenorphine and naltrexone
22 treatments for heroin dependence in Malaysia. *PLoS one* 2012;7(12):e50673.
- 23 86. Lions C, Carrieri MP, Michel L, et al. Predictors of non-prescribed opioid use after one year of
24 methadone treatment: an attributable-risk approach (ANRS-Methaville trial). *Drug Alcohol*
25 *Depend* 2014;135:1-8.
- 26 87. Degenhardt L, Conroy E, Day C, et al. The impact of a reduction in drug supply on demand
27 for and compliance with treatment for drug dependence. *Drug and Alcohol Dependence*
28 2005;79(2):129-35.
- 29 88. Gryczynski J, Mitchell SG, Jaffe JH, et al. Leaving buprenorphine treatment: patients' reasons
30 for cessation of care. *Journal of substance abuse treatment* 2014;46(3):356-61.
- 31 89. Bao YP, Liu ZM, Epstein DH, et al. A meta-analysis of retention in methadone maintenance
32 by dose and dosing strategy. *Am J Drug Alcohol Abuse* 2009;35(1):28-33.
- 33 90. Bell J, Trinh L, Butler B, et al. Comparing retention in treatment and mortality in people after
34 initial entry to methadone and buprenorphine treatment. *Addiction* 2009;104(7):1193-200.
- 35 91. Morgan JR, Schackman BR, Leff JA, et al. Injectable naltrexone, oral naltrexone, and
36 buprenorphine utilization and discontinuation among individuals treated for opioid use
37 disorder in a United States commercially insured population. *Journal of substance abuse*
38 *treatment* 2018;85:90-96.
- 39 92. VanderWeele T, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-
40 Value. *Ann Intern Med* 2017;167:268-74.
- 41 93. Government of British Columbia. Alternative Payments Program. [Available from:
42 [https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-](https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-compensation/alternative-payments-program)
43 [compensation/alternative-payments-program](https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-compensation/alternative-payments-program).
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Tables and Figures

Figure 1. Study-specific dates, databases and their data extraction period



Abbreviations (data extraction time window): OAT: opioid agonist treatment; BC: British Columbia, Canada; BC Corrections (Jan. 1, 1996 – Dec. 31, 2017); DAD: Discharge Abstract Database (Jan. 1, 1996 – Sep. 30, 2018); MSP: Medical Services Plan (Jan. 1, 1996 – Sep. 30, 2018); NACRS: National Ambulatory Care Reporting System (Apr. 1, 2012 – Sep. 30, 2018); PNET: PharmaNet (Jan. 1, 1996 – Sep. 30, 2018); PSBC: Perinatal Services British Columbia (Mar. 10, 2000 – Aug. 14, 2012); VS: Vital Statistics (Jan. 1, 1996 – Sep. 30, 2018).

Table 1. Potential confounding variables affecting opioid agonist treatment retention

Covariate	Association†	Quality of evidence ^a (source)	Available?
Individual-related characteristics			
<i>Demographics</i>			
Age	+ MET retention	Level I ¹⁵	Yes
Marital status (married)	+ MET retention	Level I ¹⁵	No
Employment status (employed)	+ MET retention	Level I ¹⁵	Yes ^{^*}
Gender (female)	+ MET retention	Level I ¹⁵	Yes
Duration of treatment	+ MET retention	Level I ¹⁵	Yes
Ethnicity (Hispanic or African American)	- BUP retention	Level II ⁷⁴	No
Living in rural area	- MET retention	Level II ⁷⁵	Yes
Family history of addiction	- MET retention	Level II ⁷⁶	No
Homelessness	- MET/BNX retention	Level II ¹¹	Yes ^{^*}
Incarceration	- MET/BNX retention	Level II ¹¹	Yes
History of overdose	Risk factor for overdose	Level III ¹	Yes [*]
<i>Concurrent conditions</i>			
Psychiatric comorbidity: major depression	+ BUP retention	Level II ⁷⁷	Yes ^{***}
Schizophrenia	- BUP retention	Level II ⁷⁷	Yes ^{***}
Personality disorders	- BUP retention	Level II ⁷⁷	Yes ^{***}
Severe withdrawal at beginning of treatment	- BUP retention	Level I ⁷⁸	No
Hepatitis C virus	+ BUP retention	Level II ¹¹	Yes ^{***}
Other substance use disorders	- BUP retention	Level II ⁷⁹	Yes ^{***}
Severe chronic pain	Risk factor for overdose	Level III ¹	Yes ^{***}
Respiratory disease	Risk factor for overdose	Level III ¹	Yes ^{***}
Cocaine use upon admission to OAT	- BNX retention	Level II ⁸⁰	No
Past-month injection drug use	- BNX retention	Level II ⁸¹	No
<i>Medication history</i>			
Use of sedatives within past 30 days of OAT	- BUP retention	Level II ⁸²	Yes
Previous receipt of BUP	+ BUP retention	Level II ⁸³	Yes
Receipt of psychiatric medication ^b	+ BUP retention	Level II ⁸⁴	Yes
Receiving high opioid prescription doses ^c	Risk factor for overdose	Level III ¹	Yes
<i>Health care utilization</i>			
Emergency department visits	- BUP retention	Level II ⁷⁹	Yes
Psychiatric hospitalizations	- BUP retention	Level II ⁷⁹	Yes
Treatment-related & contextual factors			
<i>Service provision</i>			
OAT in integrated care	+ BUP retention	Level I ⁸⁵	Yes
Behavioral therapy	+ BUP/MET retention	Level I ^{29 31}	Yes [*]
Positive relationships with service staff	+ MET retention	Level II ⁸⁶	No
<i>Contextual factors</i>			
Poor availability and quality of heroin in drug supply	+ MET/BUP retention	Level II ⁸⁷	No
<i>OAT dosing</i>			
Insufficient BUP maintenance dose ^d	- BUP retention	Level II ⁸⁸	Yes
Sufficient BUP maintenance dose ^e	+ BUP retention	Level I ⁴	Yes
High MET maintenance dose ^f	+ MET retention	Level I ⁸⁹	Yes
Flexible-dose strategies (compared to fixed dosing)	+ MET retention	Level I ⁸⁹	Yes

Abbreviations: OAT: opioid agonist treatment; iOAT: injectable opioid agonist treatment; BUP: buprenorphine; MET: methadone; BNX: buprenorphine/naloxone. † Significant factors identified in studies. + positive association; - negative association. ^ Plan I / C/ G / Coverage (low-income Pharmacare coverage program); * proxy variable. ** factor not captured in datasets to be included in bias analysis. *** concurrent condition identified via ICD-9/10 diagnostic codes. a. Quality of evidence ratings: Level I: systematic reviews, meta-analyses, and randomized controlled trials; Level II: cohort studies, case control studies, case studies; Level III: case reports, ideas, editorials, opinions (source: Cochrane review library <https://consumers.cochrane.org/levels-evidence>); b. anti-depressant, anti-anxiety, anti-psychotic and mood stabilizing medications; c. >90 morphine equivalents; d. Maximum of 8mg/day; e. Fixed dosing at medium (7-15 mg/day) or high doses (≥16mg/day; f. ≥60mg/day.

Table 2. Proposed subgroup and sensitivity analyses

Proposed sensitivity analysis	Rationale	Application	
1. Sample restriction			
Pregnant women	To assess heterogeneity in the key populations identified in The American Society of Addiction Medicine national practice guidelines. ⁴⁸	All	
PWOUD with pain		All	
Adolescents		All	
PWOUD with mental health disorders ^a		All	
Individuals in the criminal justice system		All	
PWOUD with history of PO prescription prior to diagnosis		May provide indirect evidence of treatment effect for those who primarily misuse PO.	All
PWOUD in regions with highest fentanyl concentrations ^b	May provide indirect evidence of treatment effect for those who primarily misuse fentanyl.	All	
PWOUD receiving care in Community Health Centres ^c	Assesses heterogeneity of treatment effect across clinical settings.	All	
PWOUD receiving care in stand-alone physician practices ^d		All	
2. Timeline restriction			
Buprenorphine/naloxone as first-line OAT in BC ^e	To account for potential influence of this BC policy change on OAT selection. ⁸	All	
3. Variable classification			
Episode discontinuation: 7 days	Alternative discontinuation thresholds have been defined at 7 and 14 days in other studies ^{90,91} as opposed to discontinuation thresholds of 5 days for methadone and 6 days for buprenorphine/naloxone. ⁸	All	
Episode discontinuation: 14 days		All	
Secondary outcome: Drug-related hospitalizations		Treating hospitalizations by other causes as competing risks may provide a more direct effect of exposure on outcome.	All
Secondary outcome: Drug-related deaths		Treating deaths by other causes as competing risks may provide a more direct effect of exposure on outcome.	All
Application of alternate clinical guidelines	Pertaining to both minimum effective daily doses and policies surrounding dose carries. To be executed to tailor PP analyses to other settings.	PP	
Allowing for medication switching ^f	To account for individuals receiving buprenorphine who switch to methadone if withdrawal symptoms are not alleviated. ³⁹	PP	
4. Model specification			
Bias analysis	To measure the association necessary to explain the observed treatment-outcome association attributable to unmeasured factors identified in Table 1. ⁹²	All	
Determining the association between instrumental variables and covariates	To empirically verify that our instrumental variables do not share common observed causes with the outcomes.	ITT-IV	
Leveraging prior causal assumptions	To determine whether the data are compatible with prior valid assumptions of residual confounding of positive residual confounding.	ITT-IV	
Over-identification tests	To assess performance of multiple IVs.	ITT-IV	

Abbreviations: PWOUD: people with opioid use disorder; ITT-IV: intention-to-treat instrumental variable; PP: per-protocol; BC: British Columbia; OAT: opioid agonist treatment; PO: prescription opioid.

a. Conditions outlined in Supplementary Appendix Tables A2 & A3. b. Restricted to the lower mainland Vancouver area after April 1st, 2016 (declaration of public health emergency); c. Physicians practicing in community health centers are remunerated on the province's 'Alternative payment plan'⁹³ as opposed to as indicated by the absence of physician billing record supporting OAT pharmacy dispensations; d. as indicated by prescription renewals from single physicians with low (<20 clients) OAT treatment loads; e. From June 5th, 2017 onwards. f. Allowing continuous OAT episodes to account for switching from buprenorphine/naloxone to methadone, as indicated by BC guidelines. If prescribed doses (during switching) do not follow BC guidelines, the observation will be censored in per-protocol analysis. We note that medication switches are intended to be captured within baseline ITT analyses.

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Supplementary Appendix

Table A1. Databases used for cohort construction

Database	Description	Generating process	Key content	Limitations
PharmaNet	All prescriptions for drugs and medical supplies dispensed from pharmacies including hospital outpatient dispensations.	Electronically submitted by pharmacists dispensing medications in real time. Required for reimbursement.	Drugs dispensed (using DIN/PIN* number), date of dispensation, quantity and duration of prescription, billing information, prescriber code and drug costs.	Records of drugs dispensed within physician private practice incomplete. Third party paid amounts not explicit. Practitioner IDs in PharmaCare are not linkable to practitioner IDs in PharmaNet. No provincial health information standards authority to ensure data quality (disbanded in 2003). PharmaNet does not capture: <ul style="list-style-type: none"> • Medications administered to hospital in-patients • Antiretroviral medications dispensed from the Centre of Excellence in HIV / AIDS at St. Paul's Hospital • Chemotherapy agents dispensed by the BC Cancer Agency • Medications purchased without a prescription may not be on PharmaNet (e.g., over the counter medications, herbal products, vitamins) • Medication samples dispensed at a physician's office (some are entered by physicians with PharmaNet access) https://www2.gov.bc.ca/assets/gov/health/forms/5431save.pdf
Discharge Abstract Database (DAD)	All hospital discharges, day surgery, transfers, and deaths of inpatients. Data of BC residents treated at hospital out of province, and out-of-province residents treated within BC hospitals included.	Data files grouped into fiscal years by separation date (not admission date). Each hospital submits electronic records of patient visits to the provincial government which cleans and then submits the records to the Canadian Institute for Health Information (CIHI). CIHI regularly conducts re-abstraction to ensure data quality.	Hospitalization dates, most responsible diagnosis (ICD 9/10-CA code) and up to 24 additional diagnostic codes, 25 procedure codes using CCI/CCP procedure/ intervention codes [†] , transport method, transfers, primary physician responsible for stay, condition specific resource intensity weights, inpatient grouping. Hospital number, level of care, admission date/time, admission category, readmission, and transfer codes, discharge date/time, discharge,	Visits to emergency department, abortion procedures, outpatient care (e.g. x-rays and blood work) excluded.

			disposition, length of stay, stay by level of care.	
Medical Services Plan (MSP) Database	All medically necessary services provided by fee-for-service practitioners covered by the province's universal insurance program: Medical Services Plan (MSP).	Majority of billing records submitted electronically by practitioners' offices for reimbursement purposes. Diagnosis codes accurate only to 3 rd digit.	Medically necessary services including laboratory and diagnostic procedures (x-rays, ultrasounds), and dental and oral surgery performed in hospital. Up to 5 diagnoses codes included (ICD-9-CA). Service date, fee item, diagnostic codes, practitioner code, service costs and location.	Inconsistent 'shadow billing' of services provided for no charge referrals, in Primary Health Care encounters claims, or by nurse practitioners. Insurance Corporation of British Columbia (ICBC) or WorkSafeBC claims; abortion services; and services provided through alternative payment plans (e.g. salaried, sessional, and service agreement contracts) excluded. Most current year of MSP payment data is 5-10% incomplete, with up to 6 month lag in billings filed.
Vital Statistics (VS)	All deaths registered in the province.	Data is checked against nationally uniform vital registration and statistics standards.	Date of death (year and month), location, underlying cause of death (ICD-9-CA and ICD-10-CA), and nature of injury codes.	Excludes abortions and out-of-province deaths of BC residents. Non-specific information on overdose deaths, drug type not indicated.
National Ambulatory Care Reporting System Database	All hospital-based and community-based ambulatory care including day surgery, outpatient and community-based clinics emergency departments	Data is collected directly from participating facilities or from regional health authorities or ministries of health.	ED records, day surgery, clinic submissions from several jurisdictions, patients' presenting complaint, and ED discharge diagnosis	There is no clear indicator of diseases and the level of the patient's type of separation from the ambulatory care service after registration to that service is not organized.
BC Corrections	The Provincial Health Officer compels Corrections Data from the Ministry of Public Safety and Solicitor General.	The Ministry of health receives inmate client file, inmate event file and inmate event movement files from the Public Safety and Solicitor General. The Ministry of Health Data Provisioning Team anonymizes client	Inmate events: incarceration in/out dates from BC corrections; Inmate moves: movements during incarceration from BC corrections	Ministry data for personal health numbers that are not in the cohort but that are associated with a Corrections Client ID that is also associated with a personal health number in the cohort are not provided, but all the Corrections data will be provided. All "youth" files excluded.

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		ID and personal health numbers and provides an anonymized version of the Client File that contains anonymized IDs.		
Perinatal Database	Perinatal Services BC houses the provincial perinatal database, which consists of data collected from obstetrical facilities as well as births occurring at home attended by BC Registered Midwives.	Perinatal data is collected from facilities throughout the province and imported into the central BC Perinatal Data registry. Installation hospitals have the same software as the central system, and send data on a periodic basis to the provincial database. The non-installation hospitals have their databases maintained at the central office. Data from the Canadian Institute for Health Information (CIHI) and matched files from the British Columbia Vital Statistics Agency complement the data elements. Participation in the registry is not mandatory.	Mother: admission date, discharge date, first contact with physician/midwife date, number of births in current pregnancy, number of antenatal visit in the current pregnancy, gestational age at delivery (in week), mode of delivery, health authority, local health authority (LHA), health service delivery area (HSDA), transfer in/out to another facility, HIV testing flag, Hepatitis B testing flag, substance use flag, mental illness flag, prior still birth, prior low weight baby flag, prior neonatal death, postpartum infection, HSDA, HA, LHA, Institute transferred from/to, admission date, discharge date, institute where mother delivered, first ultrasono date, gestational age at first U/S, ICD code for diagnoses, gestational age at delivery. Baby: admission date, discharge date, HA, HSDA, LHA, birth weight, gestational age at birth, blood culture test, urine culture test, breast feeding	Substance use flag is available only from March 2008- August 2014.

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			<p>initiation, institution to which baby was transferred from the current episode of care, Baby's length of stay for admission expressed in hour, where the baby was discharged to, or the status of the baby at the time of discharge, location where baby received care.</p>	
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*DIN: Drug Identification Number; PIN: Product Identification Number; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada. † Coding structures used by the Canadian Institute of Health Information (CIHI); ‡ A standardized code picklist for presenting complaint developed by CIHI.

Table A2. ICD-9/10-CA and drug identification numbers used to draw initial cohort

Database	Code no.*	Description
PharmaNet	999792, 999793, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 67000008, 67000007, 67000005, 67000006, 67000004, 67000003, 67000001, 67000002	DIN/PIN for methadone as OAT
PharmaNet	2242962, 2242963, 2242964, 2295695, 2295709, 66999994, 66999995, 66999996, 2408090, 2408104, 2424851, 2424878, 2453908, 2453916, 2468085, 2468093	DIN/PIN for buprenorphine/naloxone as OAT
PharmaNet	22123349, 22123346, 22123347, 22123348	DIN/PIN for slow-release oral morphine
PharmaNet	22123357, 66123367, 2146126, 22123340	DIN/PIN for injectable OAT
PharmaNet	999776	DIN/PIN for Narcotic compound
MSP/DAD	304	ICD-9-CA for drug dependence
MSP/DAD	305.2-305.9	ICD-9-CA for non-dependent abuse of drug
MSP/DAD	E850-E854, 969.4-969.7, 965	ICD-9-CA for drug poisoning
MSP/DAD	292, 305, 648.3, 751, 752, 753, 760, 779.5,	ICD-9-CA for cohort creation
MSP/DAD/VS/NACRS/PSBC	T40, T42.4, T43.6, Z50.3, Z71.5, Z72.2, P04.4, P96.1	ICD-10-CA for cohort creation
MSP/DAD/VS/NACRS/PSBC	F11-F16, F19	ICD-10-CA for abuse of drug
MSP/DAD/VS/NACRS/PSBC	X42, X62, Y12	ICD-10-CA for drug poisoning
MSP fee item	39,15039,13013,13014	Fee item for OAT

DAD: Discharge Abstract Database; MSP: Medical services Plan; VS: Vital statistics; NACRS: National Ambulatory Care Reporting System; PSBC: Perinatal services British Columbia; *PharmaNet database: Drug Identification Numbers (DIN)/Product Identification Numbers (PIN) used for identification; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada.

Table A3. Identification of concurrent chronic conditions

Diseases	Diagnosis code	References
MH	ICD-9-CA from DAD and MSP: 295-298,300,301, 308, 309, 311, 314, 317, 318, 319, 76071; ICD-10-CA from DAD/NACRS/VS/PSBC: F20-F25, F28-F34, F38-F43, F48, F60-F61, F69, F70-F73, F78, F79, F90, Q86.0; MSP additional diagnostic code 50B	(1), (2), (3), (4), (5), (6)
HIV	ICD-9-CA from DAD and MSP: 042-044, 079.53, 795.8, V08; ICD-10-CA from DAD/NACRS/VS: B20-B24, B97.35, F02.4, O98.7, Z21; MSP fee item: 13015, 13105, 33645, 36370	(7), (8)
HCV	ICD-9-CA from DAD and MSP: 70.41, 70.51, 70.44, 70.54, 70.7; ICD-10-CA from DAD/NACRS/VS: B17.1, B18.2, B19.2; DIN/PIN: 2370816, 2371448, 2371456, 2371464, 2371472, 2444755, 2451131, 2467550, 2432226, 2436027, 2447711, 2416441, 2418355, 2467542, 2456370, 2371553	(9),(10),(11), (12)
ODD	ICD-9-CA from DAD and MSP: 304.0, 304.7, 305.5, 965.0, E850.0-E850.2 ICD-10-CA from DAD/NACRS/VS/PSBC: F11, X42 & (T40.0-T40.4 or T40.6), X62 & (T40.0-T40.4 or T40.6), Y12 & (T40.0-T40.4 or T40.6) MSP fee item: 39,15039,13013,13014 DINPIN from Pharmanet: 999792, 999793, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 67000008, 67000007, 67000005, 67000006, 67000004, 67000003, 67000001, 67000002, 2242962, 2242963, 2242964,2295695, 2295709, 66999994, 66999995, 66999996, 2408090, 2408104, 2424851, 2424878, 2453908, 2453916, 2468085, 2468093, 22123349, 22123346, 22123347, 22123348, 22123357, 66123367, 2146126, 22123340, 999776	(1), (13), (15),(16)
AUD	ICD-9-CA from DAD and MSP: 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 655.4, 760.71, V65.42; ICD-10-CA from DAD/NACRS/VS/PSBC: F10, Z50.2, Z71.4, Z72.1, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, Q86.0; DIN: 2293269, 2158655, 2213826, 2444275, 2451883,2534, 2542, 2041375, 2041391, 66124089, 66124085, 66124087	(13), (14)
SUD	ICD-9-CA from DAD and MSP: 292, 304.1-304.6, 304.8, 304.9, 305.2-305.4, 305.6-305.9, 648.3,655.5, 760.73,760.75,779.5, 967, 969.4,969.6,969.7,970, E851, E852,E853.2,E854.1,E854.2, E854.3; ICD-10-CA from DAD/NACRS/VS/PSBC: F12-F16, F19, P04.4, P96.1, T40.5,T40.7, T40.8, T40.9, T42.4, T43.6, X42, X62, Y12, Z50.3, Z71.5, Z72.2	(1), (13), (15),(16)
Chronic pain	ICD-9-CA from DAD and MSP: 338.2, 338.4, 307.80, 307.89, 338.0, 719.41, 719.45-719.47, 719.49, 720.0, 720.2, 720.9, 721.0-721.4, 721.6, 721.8, 721.9, 722, 723.0, 723.1, 723.3-723.9, 724.0-724.6, 724.70, 724.79, 724.8, 724.9, 729.0-729.2, 729.4, 729.5, 350, 352-357, 344.0, 344.1, 997.0, 733.0, 733.7, 733.9, 781; ICD-10-CA from DAD/NACRS/VS: F45.4, G89.0, G89.2, G89.4, M08.1, M25.50, M25.51, M25.55-M25.57, M43.2-M43.6, M45, M46.1, M46.3, M46.4, M46.9, M47, M48.0, M48.1, M48.8, M48.9, M50.8, M50.9, M51, M53.1-M53.3, M53.8, M53.9, M54, M60.8, M60.9, M63.3, M79.0-M79.2, M79.6, M79.7, M96.1, G50, G52 - G64, G82, G97, M89, R29	(2), (17), (18)

ODD: opioid use disorder; MH: mental health; HCV: hepatitis C; AUD: alcohol use disorder; SUD: substance use disorder other than ODD and AUD; DAD: Discharge Abstract Database for hospitalization; MSP: Medical Service Plan for physician billing; NACRS: National Ambulatory Care Reporting System; VS: Vital Statistics database in British Columbia; PSBC: Perinatal Services British Columbia; DIN: drug identification number from PharmaNet; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada..

References

1. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical care*. 2005;43(11):1130–9.
2. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE. A chronic disease score with empirically derived weights. *Med Care*. 1995;33(8):783–95.
3. British Columbia. Ministry of Health. Guide to the MENTAL HEALTH ACT. British Columbia. Ministry of Health; 2005.
4. Fraser Health. MENTAL HEALTH ACT: fraserhealth; 2018 [Available from: <http://www.fraserhealth.ca/health-info/mental-health-substance-use/mental-health-act/>].
5. British Columbia. Ministry of Health. Psychiatric Medications Plan (Plan G) 2018 [Available from: <https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/psychiatric-medications-plan-plan-g>].
6. Health Quality Ontario. Hospital admissions for a mental illness or an addiction 2017 [Available from: <http://indicatorlibrary.hqontario.ca/Indicator/Detailed/Mental-health-addiction-admissions/EN>].
7. Nosyk B, Colley G, Yip B, Chan K, Heath K, Lima VD, et al. Application and validation of case-finding algorithms for identifying individuals with human immunodeficiency virus from administrative data in British Columbia, Canada. *PloS one*. 2013;8(1):e54416.
8. IAS-USA. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2016 Recommendations of the International Antiviral Society–USA Panel 2016 [Available from: <https://www.iasusa.org/content/antiretroviral-drugs-treatment-and-prevention-hiv-infection-adults-2016-recommendations>].
9. Robert P Myers MM, Hemant Shah, MD MScCH HPTE, Kelly W Burak, MD MSc, Curtis Cooper, MD, and Jordan J Feld, MD MPH. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. *Canadian Journal of Gastroenterology & Hepatology*. 2015;29(1):19-34.
10. BC Centre for Disease Control. Communicable Disease Control Hepatitis C August 2016. 2016.
11. Hepatitis C Treatment Information Project. THE FOUR CLASSES OF HEP C TREATMENT DAAS 2018 [Available from: <http://www.hepctip.ca/daas/>].
12. Hepatitis C Education and Prevention Society. Current Treatments as of August 2017 2017 [Available from: <http://hepcbc.ca/current-treatments/>].
13. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend*. 2009;105(1-2):9–15.
14. National Collaborating Centre for Mental Health. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. 2011.
15. British Columbia. Ministry of Health. B.C.'s Mental Health and Substance Use Strategy 2017.
16. Antoine B. Douaihy TMK, and Carl Sullivan. Medications for Substance Use Disorders. *Soc Work Public Health*. 2013;28(0):264-78.
17. Doctors of BC. Improving Chronic Pain Management in BC. 2017.
18. Jason W. Busse SC, David N. Juurlink, D. Norman Buckley, Li Wang, Rachel J. Couban, Thomas Agoritsas, Elie A. Akl, Alonso Carrasco-Labra, Lynn Cooper, Chris Cull, Bruno R. da Costa, Joseph W. Frank, Gus Grant, Alfonso Iorio, Navindra Persaud, Sol Stern, Peter Tugwell, Per Olav Vandvik and Gordon H. Guyatt. Guideline for opioid therapy and chronic noncancer pain. *Canadian Medical Association Journal*. 2017;189(18): E659-E66.

BMJ Open

Comparative effectiveness of Buprenorphine-Naloxone versus Methadone for treatment of opioid use disorder: a population-based observational study protocol in British Columbia, Canada

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-036102.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Apr-2020
Complete List of Authors:	<p>Piske, Micah; BC Centre for Excellence in HIV/AIDS Thomson, Trevor; BC Centre for Excellence in HIV/AIDS Krebs, Emanuel; BC Centre for Excellence in HIV/AIDS Hongdilokkul, Natt; BC Centre for Excellence in HIV/AIDS Bruneau, Julie; CRCHUM; Universite de Montreal Greenland, Sander; UCLA, Department of Epidemiology and Department of Statistics Gustafson, Paul; UBC, Department of Statistics Karim, Ehsan; UBC, School of Population and Public Health; Centre for Health Evaluation and Outcome Sciences, Providence Health Care McCandless, Lawrence; Simon Fraser University, Department of Statistics and Actuarial Sciences; SFU, Faculty of Health Sciences Maclure, Malcolm; UBC, Department of Anesthesiology, Pharmacology and Therapeutics Platt, Robert; McGill University, Department of Epidemiology, Biostatistics and Occupational Health; Lady Davis Institute for Medical Research Siebert, U; Harvard University T H Chan School of Public Health, Socías, M.; BC Centre on Substance Use; UBC, Department of Medicine, Faculty of Medicine Tsui, Judith; University of Washington, Department of Medicine, Section of General Internal Medicine Wood, Evan; BC Centre on Substance Use; UBC, Department of Medicine Nosyk, Bohdan; British Columbia Centre for Excellence in HIV/AIDS; SFU, Faculty of Health Sciences</p>
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Epidemiology
Keywords:	Substance misuse < PSYCHIATRY, EPIDEMIOLOGY, PRIMARY CARE, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS

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Comparative effectiveness of Buprenorphine-Naloxone versus Methadone for treatment of opioid use disorder: a population-based observational study protocol in British Columbia, Canada

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Word Count: [4027/4000]

Tables: 2

Figures: 1

Supplemental Appendix Tables: 3

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3 **Funding statement:** This work was supported by a Health Canada Substance Use and
4 Addictions Program Grant No. 1819-HQ-000036. The funding source was independent of the
5 design of this study and did not have any role during its execution, analyses, interpretation of the
6 data, writing, or decision to submit results. All authors had full access to the results in the study
7 and take responsibility for the integrity of the data and accuracy of the analysis.
8

9 **Competing Interests:** None declared.
10

11 **Disclosure:** "All inferences, opinions, and conclusions drawn in this study are those of the
12 authors, and do not reflect the opinions or policies of the Data Steward(s)."
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Abstract

Introduction: Despite a recent meta-analysis including 31 randomized controlled trials comparing methadone and buprenorphine for the treatment of opioid use disorder, important knowledge gaps remain regarding the long-term effectiveness of different treatment modalities across individuals, including rigorously-collected data on retention rates and other treatment outcomes. Evidence from real-world data represents a valuable opportunity to improve personalized treatment and patient-centered guidelines for vulnerable populations and inform strategies to reduce opioid-related mortality. Our objective is to determine the comparative effectiveness of methadone versus buprenorphine/naloxone, both overall and within key populations, in a setting where both medications are simultaneously available in office-based practices and specialized clinics.

Methods and analysis: We propose a retrospective cohort study of all adults living in British Columbia (BC) receiving opioid agonist treatment (OAT) with methadone or buprenorphine/naloxone between January 1st, 2008 and September 30th, 2018. The study will draw upon seven linked population-level administrative databases. The primary outcomes include retention in OAT and all-cause mortality. We will determine the effectiveness of buprenorphine/naloxone versus methadone using intention-to-treat and per-protocol analyses – the former emulating flexible-dose trials and the latter focusing on the comparison of the two medication regimens offered at the optimal dose. Sensitivity analyses will be used to assess the robustness of results to heterogeneity in the patient population and threats to internal validity.

Ethics and dissemination: The protocol, cohort creation, and analysis plan have been approved and classified as a quality improvement initiative exempt from ethical review (Providence Health Care Research Institute and the Simon Fraser University Office of Research Ethics). Dissemination is planned via conferences and publications, and through direct engagement and collaboration with entities that issue clinical guidelines, such as professional medical societies and public health organizations

Article Summary

Strengths and limitations of this study

- British Columbia's single-payer system represents an ideal setting for direct comparisons at the population-level and within key subgroups
- An intent-to-treat analysis with both instrumental variable and high-dimensional propensity score matching techniques will emulate trials featuring flexible dosing regimens
- A per-protocol analysis, implemented with G-estimation methods, will provide a direct comparison of the treatment regimens administered at clinical guideline-recommended doses and other guideline-recommended clinical practices
- Potential uncontrolled confounding and other threats to validity will be assessed via a range of sensitivity analyses and bias analysis

1.0 Introduction

Evidence supporting the use of opioid agonist treatment (OAT) for long-term treatment of opioid use disorder (OUD) is well established.¹ Nonetheless, a consensus study report of the National Academies of Sciences, Engineering, and Medicine, with support from the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration, recently highlighted the need for further studies to determine the most appropriate medication for key population subgroups and the comparative effectiveness of different medications over the long term.² The report further noted the refining of treatment protocols for effective use of existing medications as a priority topic. This is due in part to the fact that much of the existing evidence from randomized controlled trials (RCTs) has been generated utilizing protocols not representative of current clinical practice guidelines (which themselves are based on limited evidence) and within restrictive study cohorts over short durations (e.g., ranging from 6 to 52 weeks) that do not account for the chronic nature of OUD. The lack of consistent, high-quality evidence, therefore, continues to challenge informed decision-making when determining the best treatment option for individuals with OUD.

Numerous RCTs have indicated that buprenorphine and methadone are effective treatments for OUD.³⁻⁵ The effectiveness of methadone as a therapeutic treatment for OUD is the most established among the various forms of OAT.⁶ Methadone is a synthetic opioid agonist with high μ -opioid receptor binding affinity,⁷ but has a narrow therapeutic index, long elimination half-life and potential for interactions with alcohol and other drugs; properties which increase its risk of toxicity and other adverse effects.⁸ Buprenorphine is a safe and effective alternative to methadone treatment,⁹ working as a partial agonist with high affinity at the μ -opioid receptor and an antagonist at the κ -opioid receptor. Compared to methadone, buprenorphine features an improved safety profile with shorter induction; a milder side effect profile; milder withdrawal symptoms and fewer drug interactions; decreased risk of overdose due to a partial agonist 'ceiling effect'; and reduced risks of respiratory depression.⁸ Buprenorphine additionally offers a decreased risk of injection, and therefore harms related to diversion when taken in the buprenorphine/naloxone formulation. As a result, most settings have allowed more flexible and take-home dosing schedules earlier in the course of treatment.⁸

Regarding the comparative effectiveness of OAT regimens, evidence from randomized studies is mixed and dependent on whether a fixed or flexible dosing schedule was assigned.⁴ Retention in buprenorphine was less effective than methadone when dosing was flexible (RR:0.83 [0.73,0.95]); however, these differences were not observed when buprenorphine dosages were fixed at

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3 medium (7-16 mg/day) (RR:0.87 [0.69,1.10]) and high (≥ 16 mg/day) doses (RR:0.79 [0.20,3.16]).⁴
4 'Flexible-dose' studies were also conducted where doses were adjusted to individual need;
5 however, several RCTs utilizing such protocols reported maximum dose limits below the
6 recommended effective maintenance or induction dosage for buprenorphine.⁴ Many of the
7 flexible-dose studies yielded equivalent results for buprenorphine compared to methadone;
8 although this finding was not supported in a systematic review integrating earlier studies with
9 more recent trials.⁴ The implications of these findings are unclear as fixed dosing regimens are
10 not recommended in clinical practice. Further, substantial heterogeneity across studies included
11 in this meta-analysis with respect to participant selection and exclusion criteria, disease severity,
12 study design, dosing protocols, observation times and how retention is measured limits
13 generalizability, particularly to key populations excluded from the RCTs. Consequently, there are
14 several factors which limit conclusions drawn from previous studies in the comparative
15 effectiveness between buprenorphine and methadone, and challenge their applicability to clinical
16 practice.
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1. 27 Restricted participant inclusion criteria in previous RCTs meta-analyzed by Mattick et al.⁴ have
28 resulted in an unrepresentative sample of the population living with OUD included in these
29 studies. People with opioid use disorder (PWOUD) have been observed to have a high
30 prevalence of co-morbid conditions, such as mental health disorders, other substance use
31 disorders, respiratory illness, chronic pain, HCV, and HIV/AIDS.¹⁰⁻¹² We previously reported a
32 high prevalence of mental health disorders (66%), chronic pain (53%), substance use
33 disorders (43%) and alcohol use disorders (20%) in a recent population-based study of
34 PWOUD in British Columbia (BC).¹³ A majority of the RCTs included in the Cochrane review
35 excluded individuals with major psychiatric medical conditions, other serious conditions,
36 previous receipt of OAT, and those with co-dependence on other substances, such as
37 stimulants, alcohol, cannabis and sedatives. Additionally, a vast majority of these studies
38 investigated treatment among heroin users before the era of fentanyl and the dramatic rise in
39 synthetic opioid use. Furthermore, most of the RCTs did not investigate OAT effectiveness
40 among special populations outlined in the American Society of Addiction Medicine (ASAM)
41 guidelines, particularly through the exclusion of pregnant women and youth. A prior Cochrane
42 review conducted by Minozzi et al.¹⁴ investigating OAT efficacy in pregnant women with OUD,
43 reported insufficient evidence to draw firm conclusions about the equivalence of the
44 treatments for all outcomes including retention.
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2. Limited observation periods afforded by the RCTs included in the Mattick et al. study provided an insufficient timeframe to determine retention and long-term treatment response.¹⁵ The evaluation periods for RCTs in the review ranged from 6 to 48 weeks in the flexible-dose trials, 18 to 24 weeks in the low dose RCTs, 13 to 52 weeks in the medium-dose trials and 17 weeks in the one high dose RCT included. The heterogeneity of study periods across these trials limits conclusions on retention. Further challenging conclusions is the variation in the statistical methods that were employed to investigate this outcome.
 3. Inconsistencies among RCTs regarding the formulation of OAT administered among participants may influence treatment outcomes due to differences in their bioavailability and effectiveness. Mattick et al. indicate nearly half of the RCTs included in their analysis utilized aqueous ethanol-based buprenorphine solutions, which have been reported to have a higher bioavailability resulting in nearly 50% higher peak plasma levels than marketed tablet forms.⁴
¹⁶ In other settings such as BC, buprenorphine/naloxone is predominantly available and prescribed in the sublingual tablet formulation. Only three studies included the buprenorphine/naloxone tablet formulation, (as opposed to buprenorphine alone), further limiting available data for this specific OAT option.
 4. Buprenorphine's relative inferiority in retention compared to methadone reported in Mattick et al. was suggested to have been influenced by inadequate buprenorphine dosage during induction and maintenance in several of the referenced studies.¹⁷⁻¹⁹ One study noted their buprenorphine doses may have been too low during the induction phase (2-6 mg during the first week) and not increased quickly enough to retain patients, while rapid induction of doses up to 12-16 mg of buprenorphine may be required to maximize retention.¹⁸ Another RCT included in the flexible dosing analysis noted that their buprenorphine upper dose limit of 8 mg might have resulted in their high buprenorphine dropout rate.¹⁷ Mattick et al. report equivalent outcomes in retention between buprenorphine and methadone during fixed-doses of buprenorphine above 7mg. Seven of the eleven flexible-dose studies found no difference in retention between methadone and buprenorphine, with mean buprenorphine doses ranging from 9mg to 16mg/day.^{20 21-23 24} The other four flexible-dose studies, which reported methadone's superior retention to buprenorphine, indicated mean buprenorphine doses ranging from 2 mg to 16 mg/day.^{17 18 25 19} These findings may suggest retention is more likely observed at higher buprenorphine dosage even in flexible dosing practice. Whether the same results are observed with the buprenorphine/naloxone formulation will be important to clarify.

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3 5. Over half of the studies investigating retention included in the Cochrane meta-analysis
4 involved a form of individual or group counselling or cognitive behavioral therapy; however,
5 the contribution of this treatment to study outcomes is unclear. Numerous studies have
6 indicated that counselling or psychotherapy does not improve buprenorphine retention;²⁶⁻²⁸
7 however, several studies report contrasting results.²⁹⁻³¹ Given the inconsistency across the
8 studies with respect to adjunct psycho-social intervention, it is unclear how these additions
9 may have affected retention and influenced conclusions from the meta-analysis.
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15 In light of these challenges, observational studies may provide additional clarity on the
16 comparative effectiveness of methadone versus buprenorphine, as well as the impacts of flexible
17 dosing and adjunctive psychosocial interventions. Real-world data can provide a powerful basis
18 to improve health care decision making and offer valuable insights beyond the restricted scope of
19 RCTs.³² However, findings from observational studies on this topic are limited by confounders,
20 particularly those which are time-variant, requiring advanced statistical methods to account for
21 their effects. Nonetheless, decision-makers are increasingly relying on real-world data for
22 evidence on treatment effectiveness and its relevance to specific populations.^{32,33} To this end,
23 methadone has demonstrated better retention relative to buprenorphine/naloxone in
24 observational settings in Australia and the US³⁴⁻³⁶, though selection bias and uncontrolled
25 (residual) confounding may bias these comparisons.⁸ This comparison is challenged by
26 uncontrolled confounding, structural differences in the setting of care (opioid treatment programs
27 for methadone and office-based treatment for buprenorphine in the US) and the mechanism by
28 which PWOUD are selected, or select themselves into one form of treatment over another.
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38 Buprenorphine/naloxone was made the recommended first-line treatment for OUD in 2017 in BC.
39 However, BC's guidelines differ from ASAM and the Substance Abuse and Mental Health
40 Services Administration's^{37 38}, in part due to the conflicting results of the fixed- and flexible-dosing
41 studies as well as differences in medication availability. Specifically, in Canada, methadone is
42 available through primary care physicians and community pharmacies, whereas US regulations
43 limit methadone availability to specialized methadone clinics. Additionally, individuals receiving
44 buprenorphine may safely switch to methadone if buprenorphine's clinical effect is insufficient,
45 with one study demonstrating their equal efficacy with a stepped care strategy.³⁹ Furthermore, the
46 improved safety profile of buprenorphine/naloxone and resulting reductions in the potential harms
47 from diversion have prompted reduced restrictions on take-home dosing for this treatment
48 modality.⁸ While this practice may positively influence treatment retention, it was not permitted in
49 the majority of RCTs included in the Cochrane review.
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3 BC is a single-payer system featuring limited co-payment for medications, with both forms of OAT
4 available in office-based settings. The availability of all forms of OAT in office-based settings in
5 BC allows for a direct comparison that is not possible in naturalistic settings in the US, given that
6 methadone can be prescribed only in stand-alone opioid treatment programs. BC is also free of
7 waiver policies, patient limits and other policies that are not supported by evidence or employed
8 for other medical disorders.⁴⁰ With a population-based linked administrative dataset featuring daily
9 dispensation data for over 78,000 person-years on methadone and buprenorphine/naloxone, we
10 are uniquely positioned to contribute high-quality, real-world evidence to resolve these issues.
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16 During a period of heightened OUD-related mortality, identifying effective treatment options is
17 critical in bridging the gap between research evidence and evidence-based care for the clinical
18 management of OUD. We propose a retrospective cohort study with both intention-to-treat and
19 per-protocol (or in this case per clinical guideline) analytic strategies to determine the
20 effectiveness of buprenorphine/naloxone versus methadone in achieving sustained retention and
21 delaying hospitalization and mortality. These analytic strategies allow for adequate comparisons
22 to the previous clinical trials, while respecting the underlying data generating process. We aim to
23 determine the comparative effectiveness both overall and within key populations through
24 conducting analyses that reflect real-world practice and adherence to clinical guidelines.
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2.0 Methods

2.1 Study design

The study is a retrospective observational study based on a provincial cohort of all BC OAT recipients from January 1st, 2008 to September 30th, 2018. The study period (**Figure 1**), corresponds to the period in which buprenorphine/naloxone was available for prescription in BC, although we have methadone prescription records since January 1st 1996. The cohort will be defined using a validated list of Drug Identification Numbers specific to OAT medications. OAT episodes will be determined from dispensed prescription database records throughout the study period. The current iteration of the cohort features seven linked population-level administrative databases, including the Medical Services Plan (capturing physician billing records),⁴¹ the Discharge Abstract Database (hospitalizations),⁴² PharmaNet (drug dispensations),⁴³ Vital Statistics (death and their underlying causes),⁴⁴ BC Corrections (capturing incarceration in provincial prisons),⁴⁵ the National Ambulatory Care Reporting System database (capturing all emergency department visits),⁴⁶ and the Perinatal database (maternal and child health for all provincial births).⁴⁷ Additional information on datasets is provided in **Supplementary Appendix Table A1**. Eligibility for inclusion in the study cohort will be individuals with receipt of OAT (either methadone or buprenorphine/naloxone) during the study period. As of the most recent data update, September 30th, 2018, our study cohort (individuals initiating OAT after January 1st, 2008) consisted of 47,563 individuals with an average duration of follow-up of 60 months (from first OAT dispensation to death, administrative censorship, or the end of study follow-up period).

We will apply specific exclusion criteria in sensitivity analyses for comparison with recent RCTs, and to generate evidence accounting for heterogeneity in key populations identified in the ASAM National Practice Guidelines, including pregnant women, individuals with pain, adolescents, individuals with co-occurring mental disorders and individuals in the criminal justice system.⁴⁸ Case-finding algorithms, applied to address possible misclassification in outpatient and hospital ICD-9/10 codes, will be used to attribute other, OUD-related chronic conditions, including mental health conditions, other substance use disorders, HIV, HCV and chronic pain (**Supplementary Appendix Tables A2 & A3**).

2.2 Outcomes

The primary exposure is a binary indicator for receipt of at least one dispensation of OAT (either methadone or buprenorphine/naloxone). Retention can then be measured at daily, weekly or monthly time intervals. The primary outcomes of interest are (i) length of continuous retention in

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3 OAT; (ii) hospitalization and (iii) all-cause mortality. If a prescription was supplied for more than
4 one day of OAT medication, we assumed that the individual received OAT for the duration of days
5 that the medication was prescribed. We defined continuous OAT retention (OAT episode) as the
6 time interval during which an individual received OAT with no breaks in days dispensed lasting
7 longer than 5 days for methadone and no longer than 6 days for buprenorphine/naloxone. These
8 objective discontinuation criteria were based on BC guidelines recommending resetting starting
9 doses after these durations of non-compliance to ensure safety.¹¹ Our data do not capture OAT
10 receipt in inpatient settings, and therefore we assumed that those who started OAT prior to their
11 hospitalization were retained in treatment throughout the duration of their hospitalization. Initiation
12 and subsequent re-initiation of OAT receipt will be determined from medication dispensation
13 records in PharmaNet and all-cause mortality from vital statistics data.
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21 *2.3 Follow-up*

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23 Each individual will be followed from OAT initiation until either administrative loss to follow-up or
24 death. To account for out-of-province migration, administrative loss to follow-up will be defined as
25 no health service utilization record in any of the linked databases for at least 66 months prior to
26 the end of study follow-up. The 66-month cut-off was empirically determined based on the
27 distribution of gaps between hospitalization records, physician billing records, and drug
28 dispensations over the entire data extraction timeframe.^{13 49}
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33 *2.4 Analysis plan*

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35 Our aim is to assess the effectiveness of buprenorphine/naloxone versus methadone in achieving
36 sustained retention and delaying mortality, and we propose to conduct intention-to-treat and per-
37 protocol (per-clinical guideline) analyses. We will report the comparative effectiveness as a
38 relative risk in order for our results to be comparable with clinical evidence from RCTs. An
39 intention-to-treat analysis allowing for flexible dosing schedules as set by prescribing physicians
40 will focus on an individual's outcome at the end of follow-up, adjusting for selection bias. High-
41 dimensional propensity score matching and instrumental variables estimation will control for
42 measured and unmeasured factors that may systematically influence the selection of either
43 buprenorphine/naloxone or methadone. However, in the presence of sub-optimal dosing, the
44 intention-to-treat effect is less meaningful for clinical decision making.⁵⁰ A longitudinal per-protocol
45 analysis, which censors patients once they deviate from the study protocol, will be used to
46 estimate the comparative effectiveness of each medication regimen when offered at the
47 recommended dose per clinical guidelines.⁵¹
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2.4.1 *Intention-to-treat approach*

Accounting for factors that may influence which individuals receive buprenorphine/naloxone versus methadone is one of the key challenges for estimating the causal relationship between treatment and outcome in the comparative effectiveness of methadone versus buprenorphine/naloxone. An intention-to-treat approach, allowing for dosing schedules as set by prescribing physicians, therefore emulating a flexible-dose trial, will focus explicitly on adjusting for uncontrolled confounders that influence treatment selection. We propose two complementary estimation strategies – high-dimensional propensity score matching and instrumental variables – based on different assumptions to account for unmeasured confounders that may influence the selection of either buprenorphine/naloxone or methadone. As these assumptions are not explicitly testable, concordance in findings will strengthen our inferences.

2.4.1.1 *High-dimensional propensity score estimation*

Like covariate adjustment in standard multiple regression, propensity score matching is a means of controlling for potential bias due to measured confounders. The probability of treatment selection is modeled as a function of measured covariates among individuals. Controls are matched to treated individuals based on their estimated propensity score, which is the individual probability of receiving the medication.

Applications with investigator-selected covariates have found this approach controls confounding comparably to traditional multiple regression.⁵² Residual confounding due to unmeasured variables is an obvious limitation of both approaches, however. High-dimensional propensity score (hdPS) is a semi-automated data-driven approach to identify potentially important proxy variables from administrative data for inclusion in propensity score models.⁵³ It identifies covariates collected for billing and routine administrative purposes as proxies for uncontrolled confounders, eliminating those with very low prevalence and minimal potential for controlling bias. In the final hdPS step, propensity score techniques are used to adjust for the selected investigator-specified covariates and proxy variables identified as important by the hdPS algorithm. Comparisons of the performance of the hdPS against investigator-specified propensity scores constructed with health administrative and clinical registry-based data have generally found improved performance, approaching that of clinical registry-based analyses.⁵⁴

2.4.1.2 *Instrumental variable estimation*

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3 IV methods are a common approach to handling unmeasured confounders, where selection into
4 a treatment group (i.e., those accessing buprenorphine/naloxone compared to methadone) is
5 influenced by factors that may not be observed.⁵⁵ The goal of IV methods is to reduce confounding
6 bias without measuring all factors driving treatment decisions. Typical IV methods require a
7 variable – the ‘instrument’ – that meets three conditions: (1) the instrument is monotonically
8 associated with the treatment; (2) the instrument does not affect the outcome except through
9 treatment (also known as the exclusion restriction assumption); and (3) the instrument does not
10 share any uncontrolled causes with the outcome (is not itself confounded).
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16 Physician preference has been used as an IV in prior comparative effectiveness applications.⁵⁶
17 In a recent analysis on the determinants of treatment selection, we found unexplained (residual)
18 between-physician variance accounted for 28.4% of the explained variation in the odds of
19 selecting buprenorphine/naloxone whereas the unexplained between-individual variance
20 accounted for 18.5%.⁵⁷ Physician preference will be measured in our application by the
21 prescriber’s selection of medication regimen (methadone or buprenorphine/naloxone) for their
22 most recent OAT-naïve clients. This IV will serve as a starting point for our analysis, although we
23 will compare the relative performance of this measure (and similar variations, i.e., preference in
24 the past twenty naïve patients, etc.), with other instruments noted in a recent review.⁵⁶
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31 We will follow current methodological standards for selection, validation and reporting of IVs.⁵⁵
32 Validation entails an empirical assessment of condition 1 above, and we will conduct F-tests from
33 the first-stage regression to support this condition. However, there is less consensus on assessing
34 conditions 2 and 3. In following Swanson and Hernan,⁵⁵ we propose to assess condition 2 using
35 clinical knowledge of a scientific advisory committee to build a case that the instrument does not
36 affect the outcome except through treatment (i.e., that one individual’s potential outcomes are not
37 affected by the choice of medication for other individuals). For condition 3, we propose to show
38 empirically that the proposed instrumental variables are not associated with the available
39 covariates listed in **Table 1**.^{55 56 58} We will also consider alternative empirical approaches for
40 assessing conditions 2 and 3, consistent with recommendations of Glymour et al.⁵⁹
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48 The use of IVs is controversial, in part because conditions (2) and (3) listed above are not explicitly
49 testable for unmeasured confounders.⁵⁵ Others have warned of bias amplification if instruments
50 are controlled in a conventional manner,⁶⁰ and counterarguments have been made regarding the
51 use of physician preference as an instrument.⁶¹ The choice between propensity score and IV
52 approaches depends on whether the selection mechanism for treatment is identifiable or not,
53 respectively. While both approaches have faced criticism, concordance in their results will
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3 strengthen the inference, while discordance (overall or within a given subgroup) may indicate a
4 need for additional, possibly experimental, studies to validly estimate effects.
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2.4.2 Per-protocol approach

G-methods including marginal structural modelling, use of the parametric G-formula (or G-computation) and G-estimation of structural nested models offer the advantage of controlling for time-varying confounders that may be acting as both a confounder and intermediate variable, simultaneously.⁶² In this application, a daily dose at or above the minimum effective dosing threshold may be the result of spending sufficient time in treatment to titrate up to this dose, among other considerations (including individual-, prescriber- and facility-level factors). In turn, higher daily dosing is associated with longer retention – the key aspect of the estimation problem requiring G-methods.

Of the three G-methods listed above, G-estimation of structural nested models is most appropriate in this application,^{63 64} as we are explicitly concerned with the comparative effect of methadone versus buprenorphine/naloxone at the optimal dose ($\geq 80\text{mg/day}$ for methadone; $\geq 16\text{mg/day}$ for buprenorphine/naloxone).^{8 65 66} The interaction between dosage and time-varying factors can obscure the causal effect of treatment on the outcome, which necessitated the use of G-estimation. Specifically, we propose a structural nested accelerated failure time model.⁶⁷ This model postulates that the length of time to the outcome (see Section 2.2) under continuous exposure (treatment type at optimal dose) to be accelerated/decelerated by a factor to the length of time to the outcome if continuously unexposed⁶⁸ (i.e., on MET as opposed to BNX).

Taking as given the assumption of conditional exchangeability, the estimation procedure is a two-step iterative process that exploits the conditional independence between the exposure and potential outcomes. The first step estimates the counterfactual time-to-event outcome under no exposure as a function of observed variables, and the second step finds the G-estimate, the effect-parameter value that results in the treatment being unrelated to the potential outcome.^{67,68} The procedure is repeated at each time step, beginning at the final observation, moving backward until treatment initiation.

We will apply G-estimation on continuous OAT episodes to obtain the treatment effects of methadone and buprenorphine/naloxone, at the optimal dose, on the study outcomes. For each OAT episode, we will specify a model for the levels of OAT dosage to perform G-estimation, and then estimate the potential outcomes with a structural accelerated failure time model. To address for effect modification between time-varying factors, we will follow the setup presented by Vansteelandt & Sjolander.⁶⁹

2.4.3 Covariate selection

While the assumption of no uncontrolled confounding cannot be verified in observational settings, we adjust for all potential confounders available within our linked database.⁷⁰ We identified these covariates by conducting a systematic literature review for articles published up to September 2, 2019 to identify factors associated with OAT retention. The following search string was included in PubMed: (“opiate substitution treatment”[MeSH] OR “opioid agonist treatment”[MeSH] OR “buprenorphine”[MeSH] OR “methadone”[MeSH]) AND (“retention”[MeSH] OR “determinants”[MeSH] OR “factors”[MeSH] OR “predictor”[MeSH]). The search was restricted to studies on humans reported in English and published after December 31, 2000 to ensure findings were relevant to current treatment options. A total of 55 articles resulted from this search, which were screened for inclusion. **Table 1** highlights fixed and time-varying individual, contextual and treatment-related factors associated with OAT retention, whether these factors were positively or negatively associated with OAT retention and the quality of the underlying evidence. We specify factors captured (directly or with reasonable proxies) and not captured within our database, with the latter serving as candidates for probabilistic bias analysis. Alternately, machine learning algorithms will be used for covariate selection within the intention-to-treat analysis with high-dimensional propensity scores, as described above. Additionally, we will consider the flexibility buprenorphine allows for take-home use (which was not permitted in the majority of RCTs included in the Cochrane review).

2.4.4 Subgroup and Sensitivity analysis

We will conduct a range of subgroup and sensitivity analyses to assess the robustness of our results and heterogeneity in treatment effects across key client subgroups. We specify a priori targets focusing on cohort restriction, timeline restriction, variable classification and model specification in **Table 2**. Applicable results will be presented in tornado diagrams centered on the baseline relative risk from each analytical strategy. Any post hoc additions to this protocol will be identified as such in final reports.

3. Ethics and dissemination

This linked database was made available to the research team by BC Ministries of Health and Mental Health and Addiction as part of the response to the provincial opioid overdose public health emergency, and classified as a quality improvement initiative. Providence Health Care Research Institute and the Simon Fraser University Office of Research Ethics determined the analysis met

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2
3 criteria for exemption per Article 2.5 of the Tri-Council Policy Statement: Ethical Conduct for
4 Research Involving Humans.⁷¹
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6
7 This study will follow international guidelines for study conduct and reporting, including
8 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,⁷²
9 and the administration of the 'Risk of Bias in Non-Randomized Studies – of Interventions'
10 (ROBINS-I) tool to a multidisciplinary scientific advisory committee for ex-post evaluation. Results
11 will be published in peer-reviewed journals electronically and in print.
12

13
14 This study will generate robust evidence on how competing forms of opioid agonist treatment
15 compare in real-world practice over the long term, in the interest of improving retention in these
16 essential⁷³ and life-saving⁷⁴ medications.
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19 20 21 *4. Patient and Public Involvement* 22

23 No patients were involved in the design of this study. Findings will be shared in consultation with
24 local advocacy organisations of people who use drugs and people who have accessed opioid
25 agonist treatment following completion of the analysis.
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Data sharing

Study datasets: Not available. Statistical code: Available from Dr. Bohdan Nosyk (bnosyk@sfu.ca).

Contributions

MP conducted literature reviews and wrote the first draft of the article. TT, EK, NH and BN wrote key methodological components of the article and provided critical revisions. JB, SG, PG, MEK, LCM, MM, RWP, US, MES, JIT, EW, and BN aided in the methodological development and provided critical revisions to the manuscript. BN conceptualized and secured funding for the study. All authors approved the final draft.

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References

1. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *The Lancet*. 2019;393(10182):1760-72.
2. National Academies of Sciences, Engineering, Medicine. Medications for Opioid Use Disorder Save Lives, 2019.
3. Ahmadi J. Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients. *Journal of Substance Abuse Treatment*. 2003;24(3):217-20.
4. Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews* 2014(2):CD002207.
5. Johnson RE, Eissenberg T, Stitzer ML, et al. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend*. 1995;40(1):17-25.
6. Dole VP, Nyswander M. A Medical Treatment for Diacetylmorphine (Heroin) Addiction: A Clinical Trial With Methadone Hydrochloride. *JAMA* .1965;193(8):646-50.
7. Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs*. 2012;72(2):217-28.
8. British Columbia Centre on Substance Use (BCCSU). A guideline for the clinical management of opioid use disorder, 2017.
9. Johnson RE, Jaffe JH, Fudala PJ. A Controlled Trial of Buprenorphine Treatment for Opioid Dependence. *JAMA*. 1992;267(20):2750-55.
10. Sproule B, Brands B, Li S, et al. Changing patterns in opioid addiction: characterizing users of oxycodone and other opioids. *Can Fam Physician*. 2009;55(1):68-69.e695.
11. Socías ME, Wood E, Kerr T, et al. Trends in engagement in the cascade of care for opioid use disorder, Vancouver, Canada, 2006–2016. *Drug and Alcohol Dependence*. 2018;189:90-95.
12. Nielsen S, Lintzeris N, Bruno R, et al. Benzodiazepine Use among Chronic Pain Patients Prescribed Opioids: Associations with Pain, Physical and Mental Health, and Health Service Utilization. *Pain Medicine*. 2015;16(2):356-66.
13. Piske M, Zhou C, Min JE, et al. The cascade of care for opioid use disorder: a retrospective study in British Columbia, Canada. *Addiction*. 2020.
14. Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev*. 2013(12):Cd006318.
15. Farmani F, Farhadi H, Mohammadi Y. Associated Factors of Maintenance in Patients under Treatment with Methadone: A Comprehensive Systematic Review and Meta-Analysis. *Addict Health*. 2018;10(1):41-51.
16. Nath RP, Upton RA, Everhart ET, et al. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *Journal of clinical pharmacology*. 1999;39(6):619-23.
17. Fischer G, Gombas W, Eder H, et al. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction*. 1999;94(9):1337-47.
18. Mattick RP, Ali R, White JM, et al. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction*. 2003;98(4):441-52.
19. Petitjean S, Stohler R, Déglon J-J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug and Alcohol Dependence*. 2001;62(1):97-104.
20. Johnson RE, Chutuape MA, Strain EC, et al. A Comparison of Levomethadyl Acetate, Buprenorphine, and Methadone for Opioid Dependence. *New England Journal of Medicine*. 2000;343(18):1290-97.
21. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: Interactions and clinical management. *The American Journal on Addictions*. 2010;19(1):59-72.

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 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
22. Magura S, Lee JD, Hershberger J, et al. Buprenorphine and methadone maintenance in jail and post-release: A randomized clinical trial. *Drug and Alcohol Dependence*. 2009;99(1):222-30.
23. Neri S, Bruno CM, Pulvirenti D, et al. Randomized clinical trial to compare the effects of methadone and buprenorphine on the immune system in drug abusers. *Psychopharmacology*. 2005;179(3):700-04.
24. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *International Journal of Neuropsychopharmacology*. 2008;11(5):641-53.
25. Kristensen Ø, Espegren O, Asland R, et al. [Buprenorphine and methadone to opiate addicts-- a randomized trial]. *Tidsskr Nor Laegeforen*. 2005;125(2):148-51.
26. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction*. 2005;100(8):1090-100.
27. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-46.
28. Moore BA, Fiellin DA, Cutter CJ, et al. Cognitive Behavioral Therapy Improves Treatment Outcomes for Prescription Opioid Users in Primary Care Buprenorphine Treatment. *J Subst Abuse Treat*. 2016;71:54-57.
29. Voelker R. App Aids Treatment Retention for Opioid Use DisorderApp Aids Treatment Retention for Opioid Use DisorderNews From the Food and Drug Administration. *JAMA*. 2019;321(5):444-44.
30. Chen W, Hong Y, Zou X, et al. Effectiveness of prize-based contingency management in a methadone maintenance program in China. *Drug Alcohol Depend*. 2013;133(1):270-4.
31. Hser YI, Li J, Jiang H, et al. Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction*. 2011;106(10):1801-9.
32. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiology and Drug Safety*. 2017;26(9):1033-39.
33. Centers for Disease Control and Prevention (CDC). Medication-Assisted Treatment for Opioid Use Disorder Study (MAT Study) [Available from: <https://www.cdc.gov/opioids/Medication-Assisted-Treatment-Opioid-Use-Disorder-Study.html>].
34. Bell J, Trinh L, Butler B, et al. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. *Addiction*. 2009;104(7):1193-200.
35. Burns L, Gisev N, Larney S, et al. A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia. *Addiction*. 2015;110(4):646-55.
36. Saxon AJ. Commentary on Burns et al. (2015): retention in buprenorphine treatment. *Addiction*. 2015;110(4):656-7.
37. American Society of Addiction Medicine. National practice guideline for the use of medications in the treatment of addiction involving opioid use. *Journal of Addiction Medicine*. 2015;9(5):358-67.
38. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2005. (Treatment Improvement Protocol (TIP) Series, No. 43.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK64164/>

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 - 60
39. Kakko J, Gronbladh L, Svanborg KD. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry*. 2007;164(5):797-274.
40. College of Pharmacists of BC. Opioid Agonist Treatment 2019 [Available from: <https://www.bcpharmacists.org/opioid-agonist-treatment>].
41. British Columbia Ministry of Health [creator] (2018): Medical Services Plan (MSP) Payment Information File. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
42. British Columbia Ministry of Health [creator] (2018): Discharge Abstract Database (Hospital Separations). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
43. British Columbia Ministry of Health [creator] (2018): PharmaNet. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
44. BC Vital Statistics Agency [creator] (2018): Vital Statistics Deaths. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
45. Ministry of Public Safety and Solicitor General (PSSG) [creator] (2018): BC Corrections Dataset. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
46. British Columbia Ministry of Health [creator] (2018): National Ambulatory Care Reporting System (NACRS). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
47. Perinatal Services BC [creator] (2018): British Columbia Perinatal Data Registry. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
48. The American Society of Addiction Medicine (ASAM). The ASAM National Practice Guideline For The Use of Medications in the Treatment of Addiction Involving Opioid Use, 2015.
49. Pearce LA, Min JE, Piske M, et al. Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study. *BMJ*. 2020;368:m772. Published 2020 Mar 31. doi:10.1136/bmj.m772
50. Herenan M, Hernandez-Dias S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials*. 2012;9:48-55.
51. Murray EJ, Hernan MA. Adherence adjustment in the Coronary Drug Project: A call for better per-protocol effect estimates in randomized trials. *Clin Trials*. 2016;13(4):372-8.
52. Shah BR, Laupacis A, Hux JE, et al. Propensity score methods gave similar results to traditional regression modeling in observational studies: a systematic review. *Journal of Clinical Epidemiology*. 2005;58(6):550-59.
53. Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512-22.
54. Austin P, Fangyun Wu C, Lee D, et al. Comparing the high-dimensional propensity score for use with administrative data with propensity scores derived from high-quality clinical data. *Statistical Methods in Medical Research*. 2019:096228021984236.
55. Swanson SA, Hernán MA. Commentary: How to Report Instrumental Variable Analyses (Suggestions Welcome). *Epidemiology*. 2013;24(3):370-74.
56. Davies NM, Smith GD, Windmeijer F, et al. Issues in the Reporting and Conduct of Instrumental Variable Studies: A Systematic Review. *Epidemiology*. 2013;24(3):363-69.
57. Homayra F, Hongdilokkul N, Piske M, et al. Determinants of selection into buprenorphine/naloxone among people initiating opioid agonist treatment in British Columbia. *Second review at Drug and Alcohol Dependence*. 2019
58. Davies NM, Smith GD, Windmeijer F, et al. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology*. 2013;24(3):363-9.

- 1
- 2
- 3
- 4 59. Glymour MM, Tchetgen Tchetgen EJ, Robins JM. Credible Mendelian randomization studies:
5 approaches for evaluating the instrumental variable assumptions. *Am J Epidemiol.*
6 2012;175(4):332-9.
- 7 60. Ding P, VanderWeele TJ, Robins JM. Instrumental variables as bias amplifiers with general
8 outcome and confounding. *Biometrika.* 2017;104(2):291-302.
- 9 61. Hernán MA, Robins JM. Instruments for Causal Inference: An Epidemiologist's Dream?
10 *Epidemiology.* 2006;17(4):360-72.
- 11 62. Hernan MA, Robins JM. Causal Inference. 2020 ed: Boca Raton: Chapman & Hall/CRC.
- 12 63. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. *New England Journal of*
13 *Medicine.* 2017;377(14):1391-98.
- 14 64. Murray EJ, Hernan MA. Improved adherence adjustment in the Coronary Drug Project. *Trials.*
15 2018;19(1):158.
- 16 65. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice
17 Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use.
18 *Journal of addiction medicine.* 2015;9(5):358-67.
- 19 66. Naimi AI, Cole SR, Kennedy EH. An introduction to g methods. *Int J Epidemiol.*
20 2017;46(2):756-62.
- 21 67. Picciotto S, Neophytou AM. G-estimation of structural nested models: Recent applications in
22 two subfields of epidemiology. *Current Epidemiology Reports.* 2016; 3(3): 242-251.
- 23 68. Hernan MA, Cole SR, Margolick J, et al. Structural accelerated failure time models for survival
24 analysis in studies with time-varying treatments. *Pharmacoepidemiol Drug Saf.*
25 2005;14(7):477-91.
- 26 69. Vansteelandt, S. and Sjolander, S. Revisiting g-estimation of the Effect of a Time-varying
27 Exposure Subject to Time-varying Confounding. *Epidemiol Methods.* 2016; 5(1): 37–56.
- 28 70. VanderWeele T. Principles of confounder selection. *European Journal of Epidemiology.*
29 2019;34
- 30 71. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council
31 of Canada, Social Sciences and Humanities Research Council of Canada. Tri-council
32 policy statement: Ethical conduct for research involving humans. . 2010
- 33 72. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational
34 Studies in Epidemiology (STROBE) statement: guidelines for reporting observational
35 studies. *J Clin Epidemiol.* 2008;61(4):344-9.
- 36 73. World Health Organization. WHO Model Lists of Essential Medicines, 2019.
- 37 74. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment:
38 systematic review and meta-analysis of cohort studies. *BMJ.* 2017;357:j1550.
- 39 75. Weinstein ZM, Kim HW, Cheng DM, et al. Long-term retention in Office Based Opioid
40 Treatment with buprenorphine. *Journal of substance abuse treatment.* 2017;74:65-70.
- 41 76. Yang F, Lin P, Li Y, et al. Predictors of retention in community-based methadone maintenance
42 treatment program in Pearl River Delta, China. *Harm Reduct J.* 2013;10:3.
- 43 77. Pickens RW, Preston KL, Miles DR, et al. Family history influence on drug abuse severity and
44 treatment outcome. *Drug Alcohol Depend.* 2001;61(3):261-70.
- 45 78. Gerra G, Leonardi C, D'Amore A, et al. Buprenorphine treatment outcome in dually diagnosed
46 heroin dependent patients: A retrospective study. *Progress in Neuro-*
47 *Psychopharmacology and Biological Psychiatry.* 2006;30(2):265-72.
- 48 79. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and
49 buprenorphine maintenance therapy and predictors of outcome: results from a
50 randomized study. *The international journal of neuropsychopharmacology.*
51 2008;11(5):641-53.
- 52 80. Manhapra A, Rosenheck R, Fiellin D. Opioid substitution treatment is linked to reduced risk
53 of death in opioid use disorder. *BMJ.* 2017(357):j1947.
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
- 2
- 3
- 4 81. Apelt S, Scherbaum N, Soyka M. Induction and Switch to Buprenorphine-Naloxone in opioid
- 5 dependence treatment: Predictive Value of the First Four Weeks. *Heroin Addiction and*
- 6 *Related Clinical Problems*. 2014;16:87-98.
- 7 82. Dayal P, Balhara YPS. A naturalistic study of predictors of retention in treatment among
- 8 emerging adults entering first buprenorphine maintenance treatment for opioid use
- 9 disorders. *J Subst Abuse Treat*. 2017;80:1-5.
- 10 83. Cox J, Allard R, Maurais E, et al. Predictors of methadone program non-retention for opioid
- 11 analgesic dependent patients. *J Subst Abuse Treat*. 2013;44(1):52-60.
- 12 84. Nosyk B, MacNab YC, Sun H, Fischer B, Marsh DC, Schechter MT, Anis AH. Proportional
- 13 hazards frailty models for recurrent methadone maintenance treatment. *American journal*
- 14 *of epidemiology*. 2009 Sep 15;170(6):783-92.
- 15 85. Lee CS, Liebschutz JM, Anderson BJ, et al. Hospitalized opioid-dependent patients: Exploring
- 16 predictors of buprenorphine treatment entry and retention after discharge. *Am J Addict*.
- 17 2017;26(7):667-72.
- 18 86. Haddad MS, Zelenev A, Altice FL. Integrating buprenorphine maintenance therapy into
- 19 federally qualified health centers: real-world substance abuse treatment outcomes. *Drug*
- 20 *Alcohol Depend*. 2013;131(1-2):127-35.
- 21 87. Ruger JP, Chawarski M, Mazlan M, et al. Cost-effectiveness of buprenorphine and naltrexone
- 22 treatments for heroin dependence in Malaysia. *PloS one*. 2012;7(12):e50673.
- 23 88. Lions C, Carrieri MP, Michel L, et al. Predictors of non-prescribed opioid use after one year of
- 24 methadone treatment: an attributable-risk approach (ANRS-Methaville trial). *Drug Alcohol*
- 25 *Depend*. 2014;135:1-8.
- 26 89. Degenhardt L, Conroy E, Day C, et al. The impact of a reduction in drug supply on demand
- 27 for and compliance with treatment for drug dependence. *Drug and Alcohol Dependence*.
- 28 2005;79(2):129-35.
- 29 90. Gryczynski J, Mitchell SG, Jaffe JH, et al. Leaving buprenorphine treatment: patients' reasons
- 30 for cessation of care. *Journal of substance abuse treatment*. 2014;46(3):356-61.
- 31 91. Bao YP, Liu ZM, Epstein DH, et al. A meta-analysis of retention in methadone maintenance
- 32 by dose and dosing strategy. *Am J Drug Alcohol Abuse*. 2009;35(1):28-33.
- 33 92. Janjua NZ, Islam N, Kuo M, et al. Identifying injection drug use and estimating population size
- 34 of people who inject drugs using healthcare administrative datasets. *Int J Drug Policy*.
- 35 2018;55:31–39.
- 36 93. Bell J, Trinh L, Butler B, et al. Comparing retention in treatment and mortality in people after
- 37 initial entry to methadone and buprenorphine treatment. *Addiction*. 2009;104(7):1193-200.
- 38 94. Morgan JR, Schackman BR, Leff JA, et al. Injectable naltrexone, oral naltrexone, and
- 39 buprenorphine utilization and discontinuation among individuals treated for opioid use
- 40 disorder in a United States commercially insured population. *Journal of substance abuse*
- 41 *treatment*. 2018;85:90-96.
- 42 95. Australian Government Department of Health. Clinical Guidelines and Procedures for the Use
- 43 of Methadone in the Maintenance Treatment of Opioid Dependence. 2003. [Available
- 44 from: [https://www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-](https://www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-meth-toc~drugtreat-pubs-meth-s3~drugtreat-pubs-meth-s3-3.5)
- 45 [pubs-meth-toc~drugtreat-pubs-meth-s3~drugtreat-pubs-meth-s3-3.5](https://www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-meth-toc~drugtreat-pubs-meth-s3~drugtreat-pubs-meth-s3-3.5)]
- 46 96. VanderWeele T, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-
- 47 Value. *Ann Intern Med*. 2017;167:268-74.
- 48 97. Government of British Columbia. Alternative Payments Program. [Available from:
- 49 [https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-](https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-compensation/alternative-payments-program)
- 50 [compensation/alternative-payments-program](https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-compensation/alternative-payments-program).
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Table 1. Potential confounding variables affecting opioid agonist treatment retention

Covariate	Association†	Quality of evidence ^a (source)	Available?
Individual-related characteristics			
<i>Demographics</i>			
Age	+ MET retention	Level I ¹⁵	Yes
Marital status (married)	+ MET retention	Level I ¹⁵	No
Employment status (employed)	+ MET retention	Level I ¹⁵	Yes [^] *
Gender (female)	+ MET retention	Level I ¹⁵	Yes
Duration of treatment	+ MET retention	Level I ¹⁵	Yes
Ethnicity (Hispanic or African American)	- BUP retention	Level II ⁷⁵	No
Living in rural area	- MET retention	Level II ⁷⁶	Yes
Family history of addiction	- MET retention	Level II ⁷⁷	No
Homelessness	- MET/BNX retention	Level II ¹¹	Yes [^] *
Incarceration	- MET/BNX retention	Level II ¹¹	Yes
History of overdose	Risk factor for overdose	Level III ¹	Yes [*]
<i>Concurrent conditions</i>			
Psychiatric comorbidity: major depression	+ BUP retention	Level II ⁷⁸	Yes ^{***}
Schizophrenia	- BUP retention	Level II ⁷⁸	Yes ^{***}
Personality disorders	- BUP retention	Level II ⁷⁸	Yes ^{***}
Severe withdrawal at beginning of treatment	- BUP retention	Level I ⁷⁹	No
Hepatitis C virus	+ BUP retention	Level II ¹¹	Yes ^{***}
Other substance use disorders	- BUP retention	Level II ⁸⁰	Yes ^{***}
Severe chronic pain	Risk factor for overdose	Level III ¹	Yes ^{***}
Respiratory disease	Risk factor for overdose	Level III ¹	Yes ^{***}
Cocaine use upon admission to OAT	- BNX retention	Level II ⁸¹	No
Past-month injection drug use	- BNX retention	Level II ⁸²	Yes [§]
<i>Medication history</i>			
Use of sedatives within past 30 days of OAT	- BUP retention	Level II ⁸³	Yes
Number of previous MET/BNX episodes	+ MET retention	Level II ⁸⁴	Yes
Previous receipt of MET/BNX	+ BUP/MET retention	Level II ⁸⁵	Yes
Receipt of psychiatric medication ^b	+ BUP retention	Level II ⁸⁶	Yes
Receiving high opioid prescription doses ^c	Risk factor for overdose	Level III ¹	Yes
<i>Health care utilization</i>			
Emergency department visits	- BUP retention	Level II ⁸⁰	Yes
Psychiatric hospitalizations	- BUP retention	Level II ⁸⁰	Yes
Treatment-related & contextual factors			
<i>Service provision</i>			
OAT in integrated care	+ BUP retention	Level I ⁸⁷	Yes
Behavioral therapy	+ BUP/MET retention	Level I ^{29,31}	Yes [*]
Positive relationships with service staff	+ MET retention	Level II ⁸⁸	No
<i>Contextual factors</i>			
Poor availability and quality of heroin in drug supply	+ MET/BUP retention	Level II ⁸⁹	No
<i>OAT dosing</i>			
Insufficient BUP maintenance dose ^d	- BUP retention	Level II ⁹⁰	Yes
Sufficient BUP maintenance dose ^e	+ BUP retention	Level I ⁴	Yes
High MET maintenance dose ^f	+ MET retention	Level I ⁹¹	Yes
Flexible-dose strategies (compared to fixed dosing)	+ MET retention	Level I ⁹¹	Yes

Abbreviations: OAT: opioid agonist treatment; iOAT: injectable opioid agonist treatment; BUP: buprenorphine; MET: methadone; BNX: buprenorphine/naloxone. † Significant factors identified in studies. + positive association; - negative association. ^ Plan I / C/ G / Coverage (low-income Pharmacare coverage program); * proxy variable. ** factor not captured in datasets to be included in bias analysis. *** concurrent condition identified via ICD-9/10 diagnostic codes. § Identified via case finding algorithm⁹²; a. Quality of evidence ratings: Level I: systematic reviews, meta-analyses, and randomized controlled trials; Level II: cohort studies, case control studies, case studies; Level III: case reports, ideas, editorials, opinions (source: Cochrane review library <https://consumers.cochrane.org/levels-evidence>); b. anti-depressant, anti-anxiety, anti-psychotic and mood stabilizing medications; c. >90 morphine equivalents; d. Maximum of 8mg/day; e. Fixed dosing at medium (7-15 mg/day) or high doses (≥16mg/day); f. ≥60mg/day.

Table 2. Proposed subgroup and sensitivity analyses

Proposed sensitivity analysis	Rationale	Application
1. Sample restriction		
Pregnant women	To assess heterogeneity in the key populations identified in The American Society of Addiction Medicine national practice guidelines. ⁴⁸	All
PWOU with pain		All
Adolescents		All
PWOU with mental health disorders ^a		All
Individuals in the criminal justice system	May provide indirect evidence of treatment effect for those who primarily misuse PO.	All
PWOU with history of PO prescription prior to diagnosis		All
PWOU in regions with highest fentanyl concentrations ^b	May provide indirect evidence of treatment effect for those who primarily misuse fentanyl.	All
PWOU receiving care in Community Health Centres ^c	Assesses heterogeneity of treatment effect across clinical settings.	All
PWOU receiving care in stand-alone physician practices ^d		All
2. Timeline restriction		
Buprenorphine/naloxone as first-line OAT in BC ^e	To account for potential influence of this BC policy change on OAT selection. ⁸	All
3. Variable classification		
Episode discontinuation: 3 days (MET)	Alternative discontinuation thresholds have been defined at 3 or 7 days (MET) and 4 or 14 days (BUP) in other studies and guidelines ^{93, 94, 95} as opposed to discontinuation thresholds of 5 days (MET) and 6 days (BUP). ⁸	All
Episode discontinuation: 7 days (MET)		All
Episode discontinuation: 4 days (BUP)		All
Episode discontinuation: 14 days (BUP)		All
Episode discontinuation: Dose tapering ^f	To account for individuals discontinuing treatment after completing dose tapering, defined as $\leq 5\text{mg/day}$ for MET and $\leq 2\text{mg/day}$ BNX on the last day of OAT receipt.	All
Secondary outcome: Drug-related hospitalizations	Treating hospitalizations by other causes as competing risks may provide a more direct effect of exposure on outcome.	All
Secondary outcome: Drug-related deaths	Treating deaths by other causes as competing risks may provide a more direct effect of exposure on outcome.	All
Application of alternate clinical guidelines	Pertaining to both minimum effective daily doses and policies surrounding dose carries. To be executed to tailor PP analyses to other settings.	PP
Allowing for medication switching ^g	To account for individuals receiving BUP who switch to MET if withdrawal symptoms are not alleviated, ³⁹ and to account for individuals switching from MET to BUP.	All
4. Model specification		
Bias analysis	To measure the association necessary to explain the observed treatment-outcome association attributable to unmeasured factors identified in Table 1. ⁹⁶	All
Determining the association between instrumental variables and covariates	To empirically verify that our instrumental variables do not share common observed causes with the outcomes.	ITT-IV
Leveraging prior causal assumptions	To determine whether the data are compatible with prior valid assumptions of residual confounding of positive residual confounding.	ITT-IV
Over-identification tests	To assess performance of multiple IVs.	ITT-IV

Abbreviations: PWOU: people with opioid use disorder; ITT-IV: intention-to-treat instrumental variable; PP: per-protocol; BC: British Columbia; OAT: opioid agonist treatment; PO: prescription opioid; MET: methadone; BUP: buprenorphine.

a. Conditions outlined in Supplementary Appendix Tables A2 & A3. b. Restricted to the lower mainland Vancouver area after April 1st, 2016 (declaration of public health emergency); c. Physicians practicing in community health centers are remunerated on the province's 'Alternative payment plan'⁹⁷ as opposed to as indicated by the absence of physician billing record supporting OAT pharmacy dispensations; d. as indicated by prescription renewals from single physicians with low (<20 clients) OAT treatment loads; e. From June 5th, 2017 onwards; f. OAT episodes with completed tapers (with no record of reversion for at least 4 weeks) will be censored at the start of the tapering; g. Allowing continuous OAT episodes to account for switching from buprenorphine/naloxone to methadone, or from methadone to buprenorphine/naloxone as indicated by BC guidelines. If prescribed doses (during switching) do not follow BC

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3 guidelines, the observation will be censored in per-protocol analysis. We note that medication switches are intended to be captured
4 within baseline ITT analyses.
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3 **Figure 1. Study-specific dates, databases, and their data extraction period**
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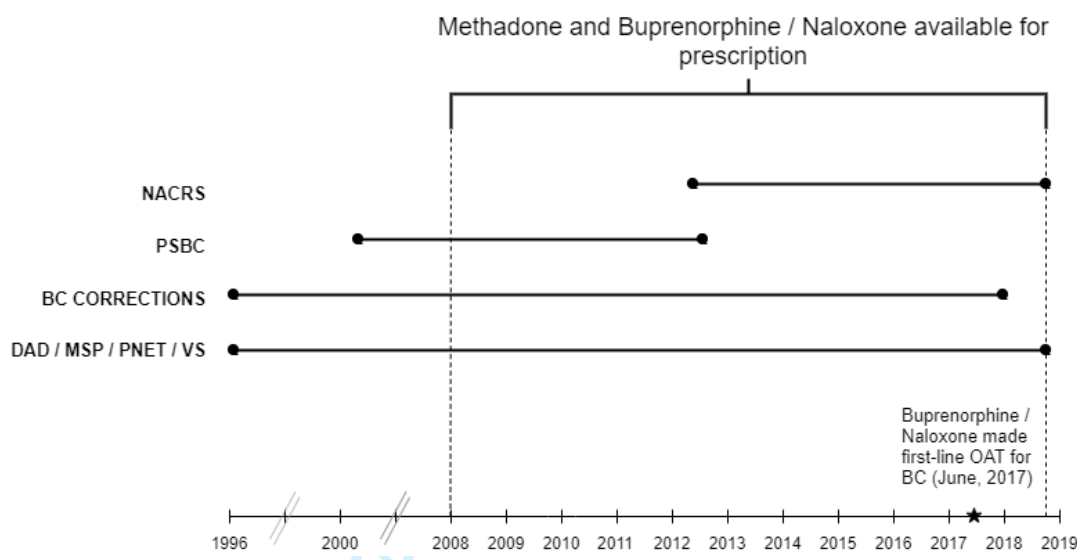
7 Abbreviations (data extraction time window): OAT: opioid agonist treatment; BC: British Columbia, Canada;
8 BC Corrections (Jan. 1, 1996 – Dec. 31, 2017); DAD: Discharge Abstract Database (Jan. 1, 1996 – Sep.
9 30, 2018); MSP: Medical Services Plan (Jan. 1, 1996 – Sep. 30, 2018); NACRS: National Ambulatory Care
10 Reporting System (Apr. 1, 2012 – Sep. 30, 2018); PNET: PharmaNet (Jan. 1, 1996 – Sep. 30, 2018); PSBC:
11 Perinatal Services British Columbia (Mar. 10, 2000 – Aug. 14, 2012); VS: Vital Statistics (Jan. 1, 1996 –
12 Sep. 30, 2018).
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Figure 1. Study-specific dates, databases, and their data extraction period



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Supplementary Appendix

Table A1. Databases used for cohort construction

Database	Description	Generating process	Key content	Limitations
PharmaNet	All prescriptions for drugs and medical supplies dispensed from pharmacies including hospital outpatient dispensations.	Electronically submitted by pharmacists dispensing medications in real time. Required for reimbursement.	Drugs dispensed (using DIN/PIN* number), date of dispensation, quantity and duration of prescription, billing information, prescriber code and drug costs.	Records of drugs dispensed within physician private practice incomplete. Third party paid amounts not explicit. Practitioner IDs in PharmaCare are not linkable to practitioner IDs in PharmaNet. No provincial health information standards authority to ensure data quality (disbanded in 2003). PharmaNet does not capture: <ul style="list-style-type: none"> • Medications administered to hospital in-patients • Antiretroviral medications dispensed from the Centre of Excellence in HIV / AIDS at St. Paul's Hospital • Chemotherapy agents dispensed by the BC Cancer Agency • Medications purchased without a prescription may not be on PharmaNet (e.g., over the counter medications, herbal products, vitamins) • Medication samples dispensed at a physician's office (some are entered by physicians with PharmaNet access) https://www2.gov.bc.ca/assets/gov/health/forms/5431save.pdf
Discharge Abstract Database (DAD)	All hospital discharges, day surgery, transfers, and deaths of inpatients. Data of BC residents treated at hospital out of province, and out-of-province residents treated within BC hospitals included.	Data files grouped into fiscal years by separation date (not admission date). Each hospital submits electronic records of patient visits to the provincial government which cleans and then submits the records to the Canadian Institute for Health Information (CIHI). CIHI regularly conducts re-abstraction to ensure data quality.	Hospitalization dates, most responsible diagnosis (ICD 9/10-CA code) and up to 24 additional diagnostic codes, 25 procedure codes using CCI/CCP procedure/ intervention codes [†] , transport method, transfers, primary physician responsible for stay, condition specific resource intensity weights, inpatient grouping. Hospital number, level of care, admission date/time, admission category, readmission, and transfer codes, discharge date/time, discharge,	Visits to emergency department, abortion procedures, outpatient care (e.g. x-rays and blood work) excluded.

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			disposition, length of stay, stay by level of care.	
Medical Services Plan (MSP) Database	All medically necessary services provided by fee-for-service practitioners covered by the province's universal insurance program: Medical Services Plan (MSP).	Majority of billing records submitted electronically by practitioners' offices for reimbursement purposes. Diagnosis codes accurate only to 3 rd digit.	Medically necessary services including laboratory and diagnostic procedures (x-rays, ultrasounds), and dental and oral surgery performed in hospital. Up to 5 diagnoses codes included (ICD-9-CA). Service date, fee item, diagnostic codes, practitioner code, service costs and location.	Inconsistent 'shadow billing' of services provided for no charge referrals, in Primary Health Care encounters claims, or by nurse practitioners. Insurance Corporation of British Columbia (ICBC) or WorkSafeBC claims; abortion services; and services provided through alternative payment plans (e.g. salaried, sessional, and service agreement contracts) excluded. Most current year of MSP payment data is 5-10% incomplete, with up to 6 month lag in billings filed.
Vital Statistics (VS)	All deaths registered in the province.	Data is checked against nationally uniform vital registration and statistics standards.	Date of death (year and month), location, underlying cause of death (ICD-9-CA and ICD-10-CA), and nature of injury codes.	Excludes abortions and out-of-province deaths of BC residents. Non-specific information on overdose deaths, drug type not indicated.
National Ambulatory Care Reporting System Database	All hospital-based and community-based ambulatory care including day surgery, outpatient and community-based clinics emergency departments	Data is collected directly from participating facilities or from regional health authorities or ministries of health.	ED records, day surgery, clinic submissions from several jurisdictions, patients' presenting complaint, and ED discharge diagnosis	There is no clear indicator of diseases and the level of the patient's type of separation from the ambulatory care service after registration to that service is not organized.
BC Corrections	The Provincial Health Officer compels Corrections Data from the Ministry of Public Safety and Solicitor General.	The Ministry of health receives inmate client file, inmate event file and inmate event movement files from the Public Safety and Solicitor General. The Ministry of Health Data Provisioning Team anonymizes client	Inmate events: incarceration in/out dates from BC corrections; Inmate moves: movements during incarceration from BC corrections	Ministry data for personal health numbers that are not in the cohort but that are associated with a Corrections Client ID that is also associated with a personal health number in the cohort are not provided, but all the Corrections data will be provided. All "youth" files excluded.

		ID and personal health numbers and provides an anonymized version of the Client File that contains anonymized IDs.		
Perinatal Database	Perinatal Services BC houses the provincial perinatal database, which consists of data collected from obstetrical facilities as well as births occurring at home attended by BC Registered Midwives.	Perinatal data is collected from facilities throughout the province and imported into the central BC Perinatal Data registry. Installation hospitals have the same software as the central system, and send data on a periodic basis to the provincial database. The non-installation hospitals have their databases maintained at the central office. Data from the Canadian Institute for Health Information (CIHI) and matched files from the British Columbia Vital Statistics Agency complement the data elements. Participation in the registry is not mandatory.	Mother: admission date, discharge date, first contact with physician/midwife date, number of births in current pregnancy, number of antenatal visit in the current pregnancy, gestational age at delivery (in week), mode of delivery, health authority, local health authority (LHA), health service delivery area (HSDA), transfer in/out to another facility, HIV testing flag, Hepatitis B testing flag, substance use flag, mental illness flag, prior still birth, prior low weight baby flag, prior neonatal death, postpartum infection, HSDA, HA, LHA, Institute transferred from/to, admission date, discharge date, institute where mother delivered, first ultrasono date, gestational age at first U/S, ICD code for diagnoses, gestational age at delivery. Baby: admission date, discharge date, HA, HSDA, LHA, birth weight, gestational age at birth, blood culture test, urine culture test, breast feeding	Substance use flag is available only from March 2008- August 2014.

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			initiation, institution to which baby was transferred from the current episode of care, Baby's length of stay for admission expressed in hour, where the baby was discharged to, or the status of the baby at the time of discharge, location where baby received care.	
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*DIN: Drug Identification Number; PIN: Product Identification Number; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada. † Coding structures used by the Canadian Institute of Health Information (CIHI); ‡ A standardized code picklist for presenting complaint developed by CIHI.

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Table A2. ICD-9/10-CA and drug identification numbers used to draw initial cohort

Database	Code no.*	Description
PharmaNet	999792, 999793, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 67000008, 67000007, 67000005, 67000006, 67000004, 67000003, 67000001, 67000002	DIN/PIN for methadone as OAT
PharmaNet	2242962, 2242963, 2242964, 2295695, 2295709, 66999994, 66999995, 66999996, 2408090, 2408104, 2424851, 2424878, 2453908, 2453916, 2468085, 2468093	DIN/PIN for buprenorphine/naloxone as OAT
PharmaNet	22123349, 22123346, 22123347, 22123348	DIN/PIN for slow-release oral morphine
PharmaNet	22123357, 66123367, 2146126, 22123340	DIN/PIN for injectable OAT
PharmaNet	999776	DIN/PIN for Narcotic compound
MSP/DAD	304	ICD-9-CA for drug dependence
MSP/DAD	305.2-305.9	ICD-9-CA for non-dependent abuse of drug
MSP/DAD	E850-E854, 969.4-969.7, 965	ICD-9-CA for drug poisoning
MSP/DAD	292, 305, 648.3, 751, 752, 753, 760, 779.5,	ICD-9-CA for cohort creation
MSP/DAD/VS/NACRS/PSBC	T40, T42.4, T43.6, Z50.3, Z71.5, Z72.2, P04.4, P96.1	ICD-10-CA for cohort creation
MSP/DAD/VS/NACRS/PSBC	F11-F16, F19	ICD-10-CA for abuse of drug
MSP/DAD/VS/NACRS/PSBC	X42, X62, Y12	ICD-10-CA for drug poisoning
MSP fee item	39,15039,13013,13014	Fee item for OAT

DAD: Discharge Abstract Database; MSP: Medical services Plan; VS: Vital statistics; NACRS: National Ambulatory Care Reporting System; PSBC: Perinatal services British Columbia; *PharmaNet database: Drug Identification Numbers (DIN)/Product Identification Numbers (PIN) used for identification; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada.

Table A3. Identification of concurrent chronic conditions

Diseases	Diagnosis code	References
MH	ICD-9-CA from DAD and MSP: 295-298,300,301, 308, 309, 311, 314, 317, 318, 319, 76071; ICD-10-CA from DAD/NACRS/VS/PSBC: F20-F25, F28-F34, F38-F43, F48, F60-F61, F69, F70-F73, F78, F79, F90, Q86.0; MSP additional diagnostic code 50B	(1), (2), (3), (4), (5), (6)
HIV	ICD-9-CA from DAD and MSP: 042-044, 079.53, 795.8, V08; ICD-10-CA from DAD/NACRS/VS: B20-B24, B97.35, F02.4, O98.7, Z21; MSP fee item: 13015, 13105, 33645, 36370	(7), (8)
HCV	ICD-9-CA from DAD and MSP: 70.41, 70.51, 70.44, 70.54, 70.7; ICD-10-CA from DAD/NACRS/VS: B17.1, B18.2, B19.2; DIN/PIN: 2370816, 2371448, 2371456, 2371464, 2371472, 2444755, 2451131, 2467550, 2432226, 2436027, 2447711, 2416441, 2418355, 2467542, 2456370, 2371553	(9),(10),(11), (12)
ODD	ICD-9-CA from DAD and MSP: 304.0, 304.7, 305.5, 965.0, E850.0-E850.2 ICD-10-CA from DAD/NACRS/VS/PSBC: F11, X42 & (T40.0-T40.4 or T40.6), X62 & (T40.0-T40.4 or T40.6), Y12 & (T40.0-T40.4 or T40.6) MSP fee item: 39,15039,13013,13014 DINPIN from Pharmanet: 999792, 999793, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 67000008, 67000007, 67000005, 67000006, 67000004, 67000003, 67000001, 67000002, 2242962, 2242963, 2242964, 2295695, 2295709, 66999994, 66999995, 66999996, 2408090, 2408104, 2424851, 2424878, 2453908, 2453916, 2468085, 2468093, 22123349, 22123346, 22123347, 22123348, 22123357, 66123367, 2146126, 22123340, 999776	(1), (13), (15),(16)
AUD	ICD-9-CA from DAD and MSP: 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 655.4, 760.71, V65.42; ICD-10-CA from DAD/NACRS/VS/PSBC: F10, Z50.2, Z71.4, Z72.1, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, Q86.0; DIN: 2293269, 2158655, 2213826, 2444275, 2451883,2534, 2542, 2041375, 2041391, 66124089, 66124085, 66124087	(13), (14)
SUD	ICD-9-CA from DAD and MSP: 292, 304.1-304.6, 304.8, 304.9, 305.2-305.4, 305.6-305.9, 648.3,655.5, 760.73,760.75,779.5, 967, 969.4,969.6,969.7,970, E851, E852,E853.2,E854.1,E854.2, E854.3; ICD-10-CA from DAD/NACRS/VS/PSBC: F12-F16, F19, P04.4, P96.1, T40.5,T40.7, T40.8, T40.9, T42.4, T43.6, X42, X62, Y12, Z50.3, Z71.5, Z72.2	(1), (13), (15),(16)
Chronic pain	ICD-9-CA from DAD and MSP: 338.2, 338.4, 307.80, 307.89, 338.0, 719.41, 719.45-719.47, 719.49, 720.0, 720.2, 720.9, 721.0-721.4, 721.6, 721.8, 721.9, 722, 723.0, 723.1, 723.3-723.9, 724.0-724.6, 724.70, 724.79, 724.8, 724.9, 729.0-729.2, 729.4, 729.5, 350, 352-357, 344.0, 344.1, 997.0, 733.0, 733.7, 733.9, 781; ICD-10-CA from DAD/NACRS/VS: F45.4, G89.0, G89.2, G89.4, M08.1, M25.50, M25.51, M25.55-M25.57, M43.2-M43.6, M45, M46.1, M46.3, M46.4, M46.9, M47, M48.0, M48.1, M48.8, M48.9, M50.8, M50.9, M51, M53.1-M53.3, M53.8, M53.9, M54, M60.8, M60.9, M63.3, M79.0-M79.2, M79.6, M79.7, M96.1, G50, G52 - G64, G82, G97, M89, R29	(2), (17), (18)

ODD: opioid use disorder; MH: mental health; HCV: hepatitis C; AUD: alcohol use disorder; SUD: substance use disorder other than OUD and AUD; DAD: Discharge Abstract Database for hospitalization; MSP: Medical Service Plan for physician billing; NACRS: National Ambulatory Care Reporting System; VS: Vital Statistics database in British Columbia; PSBC: Perinatal Services British Columbia; DIN: drug identification number from PharmaNet; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada..

References

1. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical care*. 2005;43(11):1130–9.
2. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE. A chronic disease score with empirically derived weights. *Med Care*. 1995;33(8):783–95.
3. British Columbia. Ministry of Health. Guide to the MENTAL HEALTH ACT. British Columbia. Ministry of Health; 2005.
4. Fraser Health. MENTAL HEALTH ACT: fraserhealth; 2018 [Available from: <http://www.fraserhealth.ca/health-info/mental-health-substance-use/mental-health-act/>].
5. British Columbia. Ministry of Health. Psychiatric Medications Plan (Plan G) 2018 [Available from: <https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/psychiatric-medications-plan-plan-g>].
6. Health Quality Ontario. Hospital admissions for a mental illness or an addiction 2017 [Available from: <http://indicatorlibrary.hqontario.ca/Indicator/Detailed/Mental-health-addiction-admissions/EN>].
7. Nosyk B, Colley G, Yip B, Chan K, Heath K, Lima VD, et al. Application and validation of case-finding algorithms for identifying individuals with human immunodeficiency virus from administrative data in British Columbia, Canada. *PloS one*. 2013;8(1):e54416.
8. IAS-USA. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2016 Recommendations of the International Antiviral Society–USA Panel 2016 [Available from: <https://www.iasusa.org/content/antiretroviral-drugs-treatment-and-prevention-hiv-infection-adults-2016-recommendations>].
9. Robert P Myers MM, Hemant Shah, MD MScCH HPTE, Kelly W Burak, MD MSc, Curtis Cooper, MD, and Jordan J Feld, MD MPH. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. *Canadian Journal of Gastroenterology & Hepatology*. 2015;29(1):19-34.
10. BC Centre for Disease Control. Communicable Disease Control Hepatitis C August 2016. 2016.
11. Hepatitis C Treatment Information Project. THE FOUR CLASSES OF HEP C TREATMENT DAAS 2018 [Available from: <http://www.hepctip.ca/daas/>].
12. Hepatitis C Education and Prevention Society. Current Treatments as of August 2017 2017 [Available from: <http://hepcbc.ca/current-treatments/>].
13. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend*. 2009;105(1-2):9–15.
14. National Collaborating Centre for Mental Health. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. 2011.
15. British Columbia. Ministry of Health. B.C.'s Mental Health and Substance Use Strategy 2017.
16. Antoine B. Douaihy TMK, and Carl Sullivan. Medications for Substance Use Disorders. *Soc Work Public Health*. 2013;28(0):264-78.
17. Doctors of BC. Improving Chronic Pain Management in BC. 2017.
18. Jason W. Busse SC, David N. Juurlink, D. Norman Buckley, Li Wang, Rachel J. Couban, Thomas Agoritsas, Elie A. Akl, Alonso Carrasco-Labra, Lynn Cooper, Chris Cull, Bruno R. da Costa, Joseph W. Frank, Gus Grant, Alfonso Iorio, Navindra Persaud, Sol Stern, Peter Tugwell, Per Olav Vandvik and Gordon H. Guyatt. Guideline for opioid therapy and chronic noncancer pain. *Canadian Medical Association Journal*. 2017;189(18): E659-E66.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Completed	Page # (manuscript)
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A	-
	2b	All items from the World Health Organization Trial Registration Data Set	N/A	-
Protocol version	3	Date and version identifier	✓	In online submission
Funding	4	Sources and types of financial, material, and other support	✓	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓	1
	5b	Name and contact information for the trial sponsor	N/A	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	✓	1

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2		5d	Composition, roles, and	N/A
3			responsibilities of the	-
4			coordinating centre, steering	
5			committee, endpoint adjudication	
6			committee, data management	
7			team, and other individuals or	
8			groups overseeing the trial, if	
9			applicable (see Item 21a for data	
10			monitoring committee)	
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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓	5-8
	6b	Explanation for choice of comparators	✓	5-6
Objectives	7	Specific objectives or hypotheses	✓	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓	9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓	10

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2	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A	-	
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7		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓	13-14	
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15		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A	-	
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23		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A	-	
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27	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓	10-11	
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44	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓	11, Figure 1	
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2	Sample size	14	Estimated number of participants	N/A	-
3			needed to achieve study		
4			objectives and how it was		
5			determined, including clinical		
6			and statistical assumptions		
7			supporting any sample size		
8			calculations		
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11	Recruitment	15	Strategies for achieving	N/A	-
12			adequate participant enrolment		
13			to reach target sample size		
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Methods: Assignment of interventions (for controlled trials)

Allocation:

21	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A	-
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36	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A	-
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46	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A	-
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51	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A	-
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2		17b	If blinded, circumstances under	N/A
3			which unblinding is permissible,	-
4			and procedure for revealing a	
5			participant's allocated	
6			intervention during the trial	
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Methods: Data collection, management, and analysis

Data collection methods

18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

N/A

-

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

N/A

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Data management

19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

N/A

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Statistical methods

20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

✓

11-14

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2		20b	Methods for any additional	✓
3			analyses (eg, subgroup and	
4			adjusted analyses)	15
5				
6		20c	Definition of analysis population	✓
7			relating to protocol non-	
8			adherence (eg, as randomised	13-14
9			analysis), and any statistical	
10			methods to handle missing data	
11			(eg, multiple imputation)	
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Methods: Monitoring

16	Data monitoring	21a	Composition of data monitoring	N/A	-
17			committee (DMC); summary of		
18			its role and reporting structure;		
19			statement of whether it is		
20			independent from the sponsor		
21			and competing interests; and		
22			reference to where further details		
23			about its charter can be found, if		
24			not in the protocol. Alternatively,		
25			an explanation of why a DMC is		
26			not needed		
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Ethics and dissemination

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2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A	-
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7	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A	-
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17	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A	-
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24		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	-
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29	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A	-
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38	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓	2
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43	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A	-
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50	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A	-
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2	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ 16
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14		31b	Authorship eligibility guidelines and any intended use of professional writers	✓ 16
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18		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ 16
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Appendices

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26	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A -	
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32	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A -	
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Comparative effectiveness of Buprenorphine-Naloxone versus Methadone for treatment of opioid use disorder: a population-based observational study protocol in British Columbia, Canada

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-036102.R2
Article Type:	Protocol
Date Submitted by the Author:	26-May-2020
Complete List of Authors:	<p>Piske, Micah; BC Centre for Excellence in HIV/AIDS Thomson, Trevor; BC Centre for Excellence in HIV/AIDS Krebs, Emanuel; BC Centre for Excellence in HIV/AIDS Hongdilokkul, Natt; BC Centre for Excellence in HIV/AIDS Bruneau, Julie; CRCHUM; Universite de Montreal Greenland, Sander; UCLA, Department of Epidemiology and Department of Statistics Gustafson, Paul; UBC, Department of Statistics Karim, Ehsan; UBC, School of Population and Public Health; Centre for Health Evaluation and Outcome Sciences, Providence Health Care McCandless, Lawrence; Simon Fraser University, Department of Statistics and Actuarial Sciences; SFU, Faculty of Health Sciences Maclure, Malcolm; UBC, Department of Anesthesiology, Pharmacology and Therapeutics Platt, Robert; McGill University, Department of Epidemiology, Biostatistics and Occupational Health; Lady Davis Institute for Medical Research Siebert, U; Harvard University T H Chan School of Public Health, Socías, M.; BC Centre on Substance Use; UBC, Department of Medicine, Faculty of Medicine Tsui, Judith; University of Washington, Department of Medicine, Section of General Internal Medicine Wood, Evan; BC Centre on Substance Use; UBC, Department of Medicine Nosyk, Bohdan; British Columbia Centre for Excellence in HIV/AIDS; SFU, Faculty of Health Sciences</p>
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Epidemiology, Public health, Research methods
Keywords:	Substance misuse < PSYCHIATRY, EPIDEMIOLOGY, PRIMARY CARE, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS

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Comparative effectiveness of Buprenorphine-Naloxone versus Methadone for treatment of opioid use disorder: a population-based observational study protocol in British Columbia, Canada

Piske M [1], Thomson T [1], Krebs E [1], Hongdilokkul N [1], Bruneau J [2,3], Greenland S [4], Gustafson P [5], Karim ME [6,7], McCandless LC [8,9], MacLure M [10], Platt RW [11,12], Siebert U [13,14,15], Socias ME [16,17], Tsui JI [18], Wood E [17], Nosyk B [1,9].

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Word Count: [4027/4000]

Tables: 2

Figures: 1

Supplemental Appendix Tables: 3

1
2
3 **Funding statement:** This work was supported by a Health Canada Substance Use and
4 Addictions Program Grant No. 1819-HQ-000036. The funding source was independent of the
5 design of this study and did not have any role during its execution, analyses, interpretation of the
6 data, writing, or decision to submit results. All authors had full access to the results in the study
7 and take responsibility for the integrity of the data and accuracy of the analysis.
8

9 **Competing Interests:** None declared.
10

11 **Disclosure:** "All inferences, opinions, and conclusions drawn in this study are those of the
12 authors, and do not reflect the opinions or policies of the Data Steward(s)."
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For peer review only

Abstract

Introduction: Despite a recent meta-analysis including 31 randomized controlled trials comparing methadone and buprenorphine for the treatment of opioid use disorder, important knowledge gaps remain regarding the long-term effectiveness of different treatment modalities across individuals, including rigorously-collected data on retention rates and other treatment outcomes. Evidence from real-world data represents a valuable opportunity to improve personalized treatment and patient-centered guidelines for vulnerable populations and inform strategies to reduce opioid-related mortality. Our objective is to determine the comparative effectiveness of methadone versus buprenorphine/naloxone, both overall and within key populations, in a setting where both medications are simultaneously available in office-based practices and specialized clinics.

Methods and analysis: We propose a retrospective cohort study of all adults living in British Columbia (BC) receiving opioid agonist treatment (OAT) with methadone or buprenorphine/naloxone between January 1st, 2008 and September 30th, 2018. The study will draw upon seven linked population-level administrative databases. The primary outcomes include retention in OAT and all-cause mortality. We will determine the effectiveness of buprenorphine/naloxone versus methadone using intention-to-treat and per-protocol analyses – the former emulating flexible-dose trials and the latter focusing on the comparison of the two medication regimens offered at the optimal dose. Sensitivity analyses will be used to assess the robustness of results to heterogeneity in the patient population and threats to internal validity.

Ethics and dissemination: The protocol, cohort creation, and analysis plan have been approved and classified as a quality improvement initiative exempt from ethical review (Providence Health Care Research Institute and the Simon Fraser University Office of Research Ethics). Dissemination is planned via conferences and publications, and through direct engagement and collaboration with entities that issue clinical guidelines, such as professional medical societies and public health organizations

Article Summary

Strengths and limitations of this study

- British Columbia's single-payer system represents an ideal setting for direct comparisons at the population-level and within key subgroups
- An intent-to-treat analysis with both instrumental variable and high-dimensional propensity score matching techniques will emulate trials featuring flexible dosing regimens
- A per-protocol analysis, implemented with G-estimation methods, will provide a direct comparison of the treatment regimens administered at clinical guideline-recommended doses and other guideline-recommended clinical practices
- Potential uncontrolled confounding and other threats to validity will be assessed via a range of sensitivity analyses and bias analysis

1.0 Introduction

Evidence supporting the use of opioid agonist treatment (OAT) for long-term treatment of opioid use disorder (OUD) is well established.¹ Nonetheless, a consensus study report of the National Academies of Sciences, Engineering, and Medicine, with support from the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration, recently highlighted the need for further studies to determine the most appropriate medication for key population subgroups and the comparative effectiveness of different medications over the long term.² The report further noted the refining of treatment protocols for effective use of existing medications as a priority topic. This is due in part to the fact that much of the existing evidence from randomized controlled trials (RCTs) has been generated utilizing protocols not representative of current clinical practice guidelines (which themselves are based on limited evidence) and within restrictive study cohorts over short durations (e.g., ranging from 6 to 52 weeks) that do not account for the chronic nature of OUD. The lack of consistent, high-quality evidence, therefore, continues to challenge informed decision-making when determining the best treatment option for individuals with OUD.

Numerous RCTs have indicated that buprenorphine and methadone are effective treatments for OUD.³⁻⁵ The effectiveness of methadone as a therapeutic treatment for OUD is the most established among the various forms of OAT.⁶ Methadone is a synthetic opioid agonist with high μ -opioid receptor binding affinity,⁷ but has a narrow therapeutic index, long elimination half-life and potential for interactions with alcohol and other drugs; properties which increase its risk of toxicity and other adverse effects.⁸ Buprenorphine is a safe and effective alternative to methadone treatment,⁹ working as a partial agonist with high affinity at the μ -opioid receptor and an antagonist at the κ -opioid receptor. Compared to methadone, buprenorphine features an improved safety profile with shorter induction; a milder side effect profile; milder withdrawal symptoms and fewer drug interactions; decreased risk of overdose due to a partial agonist 'ceiling effect'; and reduced risks of respiratory depression.⁸ Buprenorphine additionally may offer a decreased risk of injection, and therefore harms related to diversion when taken in the buprenorphine/naloxone formulation. As a result, most settings have allowed more flexible and take-home dosing schedules earlier in the course of treatment.⁸

Regarding the comparative effectiveness of OAT regimens, evidence from randomized studies is mixed and dependent on whether a fixed or flexible dosing schedule was assigned.⁴ Retention in buprenorphine was less effective than methadone when dosing was flexible (RR:0.83 [0.73,0.95]); however, these differences were not observed when buprenorphine dosages were fixed at

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3 medium (7-16 mg/day) (RR:0.87 [0.69,1.10]) and high (≥ 16 mg/day) doses (RR:0.79 [0.20,3.16]).⁴
4 'Flexible-dose' studies were also conducted where doses were adjusted to individual need;
5 however, several RCTs utilizing such protocols reported maximum dose limits below the
6 recommended effective maintenance or induction dosage for buprenorphine.⁴ Many of the
7 flexible-dose studies yielded equivalent results for buprenorphine compared to methadone;
8 although this finding was not supported in a systematic review integrating earlier studies with
9 more recent trials.⁴ The implications of these findings are unclear as fixed dosing regimens are
10 not recommended in clinical practice. Further, substantial heterogeneity across studies included
11 in this meta-analysis with respect to participant selection and exclusion criteria, disease severity,
12 study design, dosing protocols, observation times and how retention is measured limits
13 generalizability, particularly to key populations excluded from the RCTs. Consequently, there are
14 several factors which limit conclusions drawn from previous studies in the comparative
15 effectiveness between buprenorphine and methadone, and challenge their applicability to clinical
16 practice.
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- 27 1. Restricted participant inclusion criteria in previous RCTs meta-analyzed by Mattick et al.⁴ have
28 resulted in an unrepresentative sample of the population living with OUD included in these
29 studies. People with opioid use disorder (PWOUD) have been observed to have a high
30 prevalence of co-morbid conditions, such as mental health disorders, other substance use
31 disorders, respiratory illness, chronic pain, HCV, and HIV/AIDS.¹⁰⁻¹² We previously reported a
32 high prevalence of mental health disorders (66%), chronic pain (53%), substance use
33 disorders (43%) and alcohol use disorders (20%) in a recent population-based study of
34 PWOUD in British Columbia (BC).¹³ A majority of the RCTs included in the Cochrane review
35 excluded individuals with major psychiatric medical conditions, other serious conditions,
36 previous receipt of OAT, and those with co-dependence on other substances, such as
37 stimulants, alcohol, cannabis and sedatives. Additionally, a vast majority of these studies
38 investigated treatment among heroin users before the era of fentanyl and the dramatic rise in
39 synthetic opioid use. Furthermore, most of the RCTs did not investigate OAT effectiveness
40 among special populations outlined in the American Society of Addiction Medicine (ASAM)
41 guidelines, particularly through the exclusion of pregnant women and youth. A prior Cochrane
42 review conducted by Minozzi et al.¹⁴ investigating OAT efficacy in pregnant women with OUD,
43 reported insufficient evidence to draw firm conclusions about the equivalence of the
44 treatments for all outcomes including retention.
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2. Limited observation periods afforded by the RCTs included in the Mattick et al. study provided an insufficient timeframe to determine retention and long-term treatment response.¹⁵ The evaluation periods for RCTs in the review ranged from 6 to 48 weeks in the flexible-dose trials, 18 to 24 weeks in the low dose RCTs, 13 to 52 weeks in the medium-dose trials and 17 weeks in the one high dose RCT included. The heterogeneity of study periods across these trials limits conclusions on retention. Further challenging conclusions is the variation in the statistical methods that were employed to investigate this outcome.
3. Inconsistencies among RCTs regarding the formulation of OAT administered among participants may influence treatment outcomes due to differences in their bioavailability and effectiveness. Mattick et al. indicate nearly half of the RCTs included in their analysis utilized aqueous ethanol-based buprenorphine solutions, which have been reported to have a higher bioavailability resulting in nearly 50% higher peak plasma levels than marketed tablet forms.^{4,16} In other settings such as BC, buprenorphine/naloxone is predominantly available and prescribed in the sublingual tablet formulation. Only three studies included the buprenorphine/naloxone tablet formulation, (as opposed to buprenorphine alone), further limiting available data for this specific OAT option.
4. Buprenorphine's relative inferiority in retention compared to methadone reported in Mattick et al. was suggested to have been influenced by inadequate buprenorphine dosage during induction and maintenance in several of the referenced studies.¹⁷⁻¹⁹ One study noted their buprenorphine doses may have been too low during the induction phase (2-6 mg during the first week) and not increased quickly enough to retain patients, while rapid induction of doses up to 12-16 mg of buprenorphine may be required to maximize retention.¹⁸ Another RCT included in the flexible dosing analysis noted that their buprenorphine upper dose limit of 8 mg might have resulted in their high buprenorphine dropout rate.¹⁷ Mattick et al. report equivalent outcomes in retention between buprenorphine and methadone during fixed-doses of buprenorphine above 7mg. Seven of the eleven flexible-dose studies found no difference in retention between methadone and buprenorphine, with mean buprenorphine doses ranging from 9mg to 16mg/day.²⁰⁻²⁴ The other four flexible-dose studies, which reported methadone's superior retention to buprenorphine, indicated mean buprenorphine doses ranging from 2 mg to 16 mg/day.^{17-19,25} These findings may suggest retention is more likely observed at higher buprenorphine dosage even in flexible dosing practice. Whether the same results are observed with the buprenorphine/naloxone formulation will be important to clarify.

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3 5. Over half of the studies investigating retention included in the Cochrane meta-analysis
4 involved a form of individual or group counselling or cognitive behavioral therapy; however,
5 the contribution of this treatment to study outcomes is unclear. Numerous studies have
6 indicated that counselling or psychotherapy does not improve buprenorphine retention;²⁶⁻²⁸
7 however, several studies report contrasting results.²⁹⁻³¹ Given the inconsistency across the
8 studies with respect to adjunct psycho-social intervention, it is unclear how these additions
9 may have affected retention and influenced conclusions from the meta-analysis.
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15 In light of these challenges, observational studies may provide additional clarity on the
16 comparative effectiveness of methadone versus buprenorphine, as well as the impacts of flexible
17 dosing and adjunctive psychosocial interventions. Real-world data can provide a powerful basis
18 to improve health care decision making and offer valuable insights beyond the restricted scope of
19 RCTs.³² However, findings from observational studies on this topic are limited by confounders,
20 particularly those which are time-variant, requiring advanced statistical methods to account for
21 their effects. Nonetheless, decision-makers are increasingly relying on real-world data for
22 evidence on treatment effectiveness and its relevance to specific populations.^{32,33} To this end,
23 methadone has demonstrated better retention relative to buprenorphine/naloxone in
24 observational settings in Australia and the US,³⁴⁻³⁶ though selection bias and uncontrolled
25 (residual) confounding may bias these comparisons.⁸ This comparison is challenged by
26 uncontrolled confounding, structural differences in the setting of care (opioid treatment programs
27 for methadone and office-based treatment for buprenorphine in the US) and the mechanism by
28 which PWOUD are selected, or select themselves into one form of treatment over another.
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38 Buprenorphine/naloxone was made the recommended first-line treatment for OUD in 2017 in BC.
39 However, BC's guidelines differ from ASAM and the Substance Abuse and Mental Health
40 Services Administration's^{37,38}, in part due to the conflicting results of the fixed- and flexible-dosing
41 studies as well as differences in medication availability. Specifically, in Canada, methadone is
42 available through primary care physicians and community pharmacies, whereas US regulations
43 limit methadone availability to specialized methadone clinics. Additionally, individuals receiving
44 buprenorphine may safely switch to methadone if buprenorphine's clinical effect is insufficient,
45 with one study demonstrating their equal efficacy with a stepped care strategy.³⁹ Furthermore, the
46 improved safety profile of buprenorphine/naloxone and resulting reductions in the potential harms
47 from diversion have prompted reduced restrictions on take-home dosing for this treatment
48 modality.⁸ While this practice may positively influence treatment retention, it was not permitted in
49 the majority of RCTs included in the Cochrane review.
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3 BC is a single-payer system featuring limited co-payment for medications, with both forms of OAT
4 available in office-based settings. The availability of all forms of OAT in office-based settings in
5 BC allows for a direct comparison that is not possible in naturalistic settings in the US, given that
6 methadone can be prescribed only in stand-alone opioid treatment programs. BC is also free of
7 waiver policies, patient limits and other policies that are not supported by evidence or employed
8 for other medical disorders.⁴⁰ With a population-based linked administrative dataset featuring daily
9 dispensation data for over 78,000 person-years on methadone and buprenorphine/naloxone, we
10 are uniquely positioned to contribute high-quality, real-world evidence to resolve these issues.
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16 During a period of heightened OUD-related mortality, identifying effective treatment options is
17 critical in bridging the gap between research evidence and evidence-based care for the clinical
18 management of OUD. We propose a retrospective cohort study with both intention-to-treat and
19 per-protocol (or in this case per clinical guideline) analytic strategies to determine the
20 effectiveness of buprenorphine/naloxone versus methadone in achieving sustained retention and
21 delaying hospitalization and mortality. These analytic strategies allow for adequate comparisons
22 to the previous clinical trials, while respecting the underlying data generating process. We aim to
23 determine the comparative effectiveness both overall and within key populations through
24 conducting analyses that reflect real-world practice and adherence to clinical guidelines.
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2.0 Methods

2.1 Study design

The study is a retrospective observational study based on a provincial cohort of all BC OAT recipients from January 1st, 2008 to September 30th, 2018. The study period (**Figure 1**), corresponds to the period in which buprenorphine/naloxone was available for prescription in BC, although we have methadone prescription records since January 1st 1996. The cohort will be defined using a validated list of Drug Identification Numbers specific to OAT medications. OAT episodes will be determined from dispensed prescription database records throughout the study period. The current iteration of the cohort features seven linked population-level administrative databases, including the Medical Services Plan (capturing physician billing records),⁴¹ the Discharge Abstract Database (hospitalizations),⁴² PharmaNet (drug dispensations),⁴³ Vital Statistics (death and their underlying causes),⁴⁴ BC Corrections (capturing incarceration in provincial prisons),⁴⁵ the National Ambulatory Care Reporting System database (capturing all emergency department visits),⁴⁶ and the Perinatal database (maternal and child health for all provincial births).⁴⁷ Additional information on datasets is provided in **Supplementary Appendix Table A1**. Eligibility for inclusion in the study cohort will be individuals with receipt of OAT (either methadone or buprenorphine/naloxone) during the study period. As of the most recent data update, September 30th, 2018, our study cohort (individuals initiating OAT after January 1st, 2008) consisted of 47,563 individuals with an average duration of follow-up of 60 months (from first OAT dispensation to death, administrative censorship, or the end of study follow-up period).

We will apply specific exclusion criteria in sensitivity analyses for comparison with recent RCTs, and to generate evidence accounting for heterogeneity in key populations identified in the ASAM National Practice Guidelines, including pregnant women, individuals with pain, adolescents, individuals with co-occurring mental disorders and individuals in the criminal justice system.⁴⁸ Case-finding algorithms, applied to address possible misclassification in outpatient and hospital ICD-9/10 codes, will be used to attribute other, OUD-related chronic conditions, including mental health conditions, other substance use disorders, HIV, HCV and chronic pain (**Supplementary Appendix Tables A2 & A3**).

2.2 Outcomes

The primary exposure is a binary indicator for receipt of at least one dispensation of OAT (either methadone or buprenorphine/naloxone). Retention can then be measured at daily, weekly or monthly time intervals. The primary outcomes of interest are (i) length of continuous retention in

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3 OAT; (ii) hospitalization and (iii) all-cause mortality. If a prescription was supplied for more than
4 one day of OAT medication, we assumed that the individual received OAT for the duration of days
5 that the medication was prescribed. We defined continuous OAT retention (OAT episode) as the
6 time interval during which an individual received OAT with no breaks in days dispensed lasting
7 longer than 5 days for methadone and no longer than 6 days for buprenorphine/naloxone. These
8 objective discontinuation criteria were based on BC guidelines recommending resetting starting
9 doses after these durations of non-compliance to ensure safety.¹¹ Our data do not capture OAT
10 receipt in inpatient settings, and therefore we assumed that those who started OAT prior to their
11 hospitalization were retained in treatment throughout the duration of their hospitalization. Initiation
12 and subsequent re-initiation of OAT receipt will be determined from medication dispensation
13 records in PharmaNet and all-cause mortality from vital statistics data.
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21 *2.3 Follow-up*

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23 Each individual will be followed from OAT initiation until either administrative loss to follow-up or
24 death. To account for out-of-province migration, administrative loss to follow-up will be defined as
25 no health service utilization record in any of the linked databases for at least 66 months prior to
26 the end of study follow-up. The 66-month cut-off was empirically determined based on the
27 distribution of gaps between hospitalization records, physician billing records, and drug
28 dispensations over the entire data extraction timeframe.^{13,49}
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33 *2.4 Analysis plan*

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35 Our aim is to assess the effectiveness of buprenorphine/naloxone versus methadone in achieving
36 sustained retention and delaying mortality, and we propose to conduct intention-to-treat and per-
37 protocol (per-clinical guideline) analyses. We will report the comparative effectiveness as a
38 relative risk in order for our results to be comparable with clinical evidence from RCTs. An
39 intention-to-treat analysis allowing for flexible dosing schedules as set by prescribing physicians
40 will focus on an individual's outcome at the end of follow-up, adjusting for selection bias. High-
41 dimensional propensity score matching and instrumental variables estimation will control for
42 measured and unmeasured factors that may systematically influence the selection of either
43 buprenorphine/naloxone or methadone. However, in the presence of sub-optimal dosing, the
44 intention-to-treat effect is less meaningful for clinical decision making.⁵⁰ A longitudinal per-protocol
45 analysis, which censors patients once they deviate from the study protocol, will be used to
46 estimate the comparative effectiveness of each medication regimen when offered at the
47 recommended dose per clinical guidelines.⁵¹
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2.4.1 *Intention-to-treat approach*

Accounting for factors that may influence which individuals receive buprenorphine/naloxone versus methadone is one of the key challenges for estimating the causal relationship between treatment and outcome in the comparative effectiveness of methadone versus buprenorphine/naloxone. An intention-to-treat approach, allowing for dosing schedules as set by prescribing physicians, therefore emulating a flexible-dose trial, will focus explicitly on adjusting for uncontrolled confounders that influence treatment selection. We propose two complementary estimation strategies – high-dimensional propensity score matching and instrumental variables – based on different assumptions to account for unmeasured confounders that may influence the selection of either buprenorphine/naloxone or methadone. As these assumptions are not explicitly testable, concordance in findings will strengthen our inferences.

2.4.1.1 *High-dimensional propensity score estimation*

Like covariate adjustment in standard multiple regression, propensity score matching is a means of controlling for potential bias due to measured confounders. The probability of treatment selection is modeled as a function of measured covariates among individuals. Controls are matched to treated individuals based on their estimated propensity score, which is the individual probability of receiving the medication.

Applications with investigator-selected covariates have found this approach controls confounding comparably to traditional multiple regression.⁵² Residual confounding due to unmeasured variables is an obvious limitation of both approaches, however. High-dimensional propensity score (hdPS) is a semi-automated data-driven approach to identify potentially important proxy variables from administrative data for inclusion in propensity score models.⁵³ It identifies covariates collected for billing and routine administrative purposes as proxies for uncontrolled confounders, eliminating those with very low prevalence and minimal potential for controlling bias. In the final hdPS step, propensity score techniques are used to adjust for the selected investigator-specified covariates and proxy variables identified as important by the hdPS algorithm. Comparisons of the performance of the hdPS against investigator-specified propensity scores constructed with health administrative and clinical registry-based data have generally found improved performance, approaching that of clinical registry-based analyses.⁵⁴

2.4.1.2 *Instrumental variable estimation*

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3 IV methods are a common approach to handling unmeasured confounders, where selection into
4 a treatment group (i.e., those accessing buprenorphine/naloxone compared to methadone) is
5 influenced by factors that may not be observed.⁵⁵ The goal of IV methods is to reduce confounding
6 bias without measuring all factors driving treatment decisions. Typical IV methods require a
7 variable – the ‘instrument’ – that meets three conditions: (1) the instrument is monotonically
8 associated with the treatment; (2) the instrument does not affect the outcome except through
9 treatment (also known as the exclusion restriction assumption); and (3) the instrument does not
10 share any uncontrolled causes with the outcome (is not itself confounded).
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16 Physician preference has been used as an IV in prior comparative effectiveness applications.⁵⁶
17 In a recent analysis on the determinants of treatment selection, we found unexplained (residual)
18 between-physician variance accounted for 28.4% of the explained variation in the odds of
19 selecting buprenorphine/naloxone whereas the unexplained between-individual variance
20 accounted for 18.5%.⁵⁷ Physician preference will be measured in our application by the
21 prescriber’s selection of medication regimen (methadone or buprenorphine/naloxone) for their
22 most recent OAT-naïve clients. This IV will serve as a starting point for our analysis, although we
23 will compare the relative performance of this measure (and similar variations, i.e., preference in
24 the past twenty naïve patients, etc.), with other instruments noted in a recent review.⁵⁶
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31 We will follow current methodological standards for selection, validation and reporting of IVs.⁵⁵
32 Validation entails an empirical assessment of condition 1 above, and we will conduct F-tests from
33 the first-stage regression to support this condition. However, there is less consensus on assessing
34 conditions 2 and 3. In following Swanson and Hernan,⁵⁵ we propose to assess condition 2 using
35 clinical knowledge of a scientific advisory committee to build a case that the instrument does not
36 affect the outcome except through treatment (i.e., that one individual’s potential outcomes are not
37 affected by the choice of medication for other individuals). For condition 3, we propose to show
38 empirically that the proposed instrumental variables are not associated with the available
39 covariates listed in **Table 1**.^{55,56,58,59-76} We will also consider alternative empirical approaches for
40 assessing conditions 2 and 3, consistent with recommendations of Glymour et al.⁷⁷
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48 The use of IVs is controversial, in part because conditions (2) and (3) listed above are not explicitly
49 testable for unmeasured confounders.⁵⁵ Others have warned of bias amplification if instruments
50 are controlled in a conventional manner,⁷⁸ and counterarguments have been made regarding the
51 use of physician preference as an instrument.⁷⁹ The choice between propensity score and IV
52 approaches depends on whether the selection mechanism for treatment is identifiable or not,
53 respectively. While both approaches have faced criticism, concordance in their results will
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3 strengthen the inference, while discordance (overall or within a given subgroup) may indicate a
4 need for additional, possibly experimental, studies to validly estimate effects.
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2.4.2 Per-protocol approach

G-methods including marginal structural modelling, use of the parametric G-formula (or G-computation) and G-estimation of structural nested models offer the advantage of controlling for time-varying confounders that may be acting as both a confounder and intermediate variable, simultaneously.⁸⁰ In this application, a daily dose at or above the minimum effective dosing threshold may be the result of spending sufficient time in treatment to titrate up to this dose, among other considerations (including individual-, prescriber- and facility-level factors). In turn, higher daily dosing is associated with longer retention – the key aspect of the estimation problem requiring G-methods.

Of the three G-methods listed above, G-estimation of structural nested models is most appropriate in this application,^{81,82} as we are explicitly concerned with the comparative effect of methadone versus buprenorphine/naloxone at the optimal dose ($\geq 80\text{mg/day}$ for methadone; $\geq 16\text{mg/day}$ for buprenorphine/naloxone).^{8,83,84} The interaction between dosage and time-varying factors can obscure the causal effect of treatment on the outcome, which necessitated the use of G-estimation. Specifically, we propose a structural nested accelerated failure time model.⁸⁵ This model postulates that the length of time to the outcome (see Section 2.2) under continuous exposure (treatment type at optimal dose) to be accelerated/decelerated by a factor to the length of time to the outcome if continuously unexposed⁸⁶ (i.e., on MET as opposed to BNX).

Taking as given the assumption of conditional exchangeability, the estimation procedure is a two-step iterative process that exploits the conditional independence between the exposure and potential outcomes. The first step estimates the counterfactual time-to-event outcome under no exposure as a function of observed variables, and the second step finds the G-estimate, the effect-parameter value that results in the treatment being unrelated to the potential outcome.^{85,86} The procedure is repeated at each time step, beginning at the final observation, moving backward until treatment initiation.

We will apply G-estimation on continuous OAT episodes to obtain the treatment effects of methadone and buprenorphine/naloxone, at the optimal dose, on the study outcomes. For each OAT episode, we will specify a model for the levels of OAT dosage to perform G-estimation, and then estimate the potential outcomes with a structural accelerated failure time model. To address for effect modification between time-varying factors, we will follow the setup presented by Vansteelandt & Sjolander.⁸⁷

2.4.3 Covariate selection

While the assumption of no uncontrolled confounding cannot be verified in observational settings, we adjust for all potential confounders available within our linked database.⁸⁸ We identified these covariates by conducting a systematic literature review for articles published up to September 2, 2019 to identify factors associated with OAT retention. The following search string was included in PubMed: (“opiate substitution treatment”[MeSH] OR “opioid agonist treatment”[MeSH] OR “buprenorphine”[MeSH] OR “methadone”[MeSH]) AND (“retention”[MeSH] OR “determinants”[MeSH] OR “factors”[MeSH] OR “predictor”[MeSH]). The search was restricted to studies on humans reported in English and published after December 31, 2000 to ensure findings were relevant to current treatment options. A total of 55 articles resulted from this search, which were screened for inclusion. **Table 1** highlights fixed and time-varying individual, contextual and treatment-related factors associated with OAT retention, whether these factors were positively or negatively associated with OAT retention and the quality of the underlying evidence. We specify factors captured (directly or with reasonable proxies) and not captured within our database, with the latter serving as candidates for probabilistic bias analysis. Alternately, machine learning algorithms will be used for covariate selection within the intention-to-treat analysis with high-dimensional propensity scores, as described above. Additionally, we will consider the flexibility buprenorphine allows for take-home use (which was not permitted in the majority of RCTs included in the Cochrane review).

2.4.4 Subgroup and Sensitivity analysis

We will conduct a range of subgroup and sensitivity analyses to assess the robustness of our results and heterogeneity in treatment effects across key client subgroups. We specify a priori targets focusing on cohort restriction, timeline restriction, variable classification and model specification in **Table 2**.⁸⁹⁻⁹³ Applicable results will be presented in tornado diagrams centered on the baseline relative risk from each analytical strategy. Secondary outcomes such as psychiatric hospitalizations, emergency department visits, and incarceration may also be considered in additional sensitivity analysis. Any post hoc additions to this protocol will be identified as such in final reports.

3. Ethics and dissemination

This linked database was made available to the research team by BC Ministries of Health and Mental Health and Addiction as part of the response to the provincial opioid overdose public health emergency, and classified as a quality improvement initiative. Providence Health Care Research

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3 Institute and the Simon Fraser University Office of Research Ethics determined the analysis met
4 criteria for exemption per Article 2.5 of the Tri-Council Policy Statement: Ethical Conduct for
5 Research Involving Humans.⁹⁴
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8 This study will follow international guidelines for study conduct and reporting, including
9 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,⁹⁵
10 and the administration of the 'Risk of Bias in Non-Randomized Studies – of Interventions'
11 (ROBINS-I) tool to a multidisciplinary scientific advisory committee for ex-post evaluation. Results
12 will be published in peer-reviewed journals electronically and in print.
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15 This study will generate robust evidence on how competing forms of opioid agonist treatment
16 compare in real-world practice over the long term, in the interest of improving retention in these
17 essential⁹⁶ and life-saving⁹⁷ medications.
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21 22 23 *4. Patient and Public Involvement* 24

25 No patients were involved in the design of this study. Findings will be shared in consultation with
26 local advocacy organisations of people who use drugs and people who have accessed opioid
27 agonist treatment following completion of the analysis.
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Data sharing

Study datasets: Not available. Statistical code: Available from Dr. Bohdan Nosyk (bnosyk@sfu.ca).

Contributions

MP conducted literature reviews and wrote the first draft of the article. TT, EK, NH and BN wrote key methodological components of the article and provided critical revisions. JB, SG, PG, MEK, LCM, MM, RWP, US, MES, JIT, EW, and BN aided in the methodological development and provided critical revisions to the manuscript. BN conceptualized and secured funding for the study. All authors approved the final draft.

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References

1. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *The Lancet*. 2019;393(10182):1760-72.
2. National Academies of Sciences, Engineering, Medicine. Medications for Opioid Use Disorder Save Lives, 2019.
3. Ahmadi J. Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients. *Journal of Substance Abuse Treatment*. 2003;24(3):217-20.
4. Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews* 2014(2):CD002207.
5. Johnson RE, Eissenberg T, Stitzer ML, et al. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend*. 1995;40(1):17-25.
6. Dole VP, Nyswander M. A Medical Treatment for Diacetylmorphine (Heroin) Addiction: A Clinical Trial With Methadone Hydrochloride. *JAMA* .1965;193(8):646-50.
7. Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs*. 2012;72(2):217-28.
8. British Columbia Centre on Substance Use (BCCSU). A guideline for the clinical management of opioid use disorder, 2017.
9. Johnson RE, Jaffe JH, Fudala PJ. A Controlled Trial of Buprenorphine Treatment for Opioid Dependence. *JAMA*. 1992;267(20):2750-55.
10. Sproule B, Brands B, Li S, et al. Changing patterns in opioid addiction: characterizing users of oxycodone and other opioids. *Can Fam Physician*. 2009;55(1):68-69.e695.
11. Socías ME, Wood E, Kerr T, et al. Trends in engagement in the cascade of care for opioid use disorder, Vancouver, Canada, 2006–2016. *Drug and Alcohol Dependence*. 2018;189:90-95.
12. Nielsen S, Lintzeris N, Bruno R, et al. Benzodiazepine Use among Chronic Pain Patients Prescribed Opioids: Associations with Pain, Physical and Mental Health, and Health Service Utilization. *Pain Medicine*. 2015;16(2):356-66.
13. Piske M, Zhou C, Min JE, et al. The cascade of care for opioid use disorder: a retrospective study in British Columbia, Canada. *Addiction*. 2020.
14. Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev*. 2013(12):Cd006318.
15. Farmani F, Farhadi H, Mohammadi Y. Associated Factors of Maintenance in Patients under Treatment with Methadone: A Comprehensive Systematic Review and Meta-Analysis. *Addict Health*. 2018;10(1):41-51.
16. Nath RP, Upton RA, Everhart ET, et al. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *Journal of clinical pharmacology*. 1999;39(6):619-23.
17. Fischer G, Gombas W, Eder H, et al. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction*. 1999;94(9):1337-47.
18. Mattick RP, Ali R, White JM, et al. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction*. 2003;98(4):441-52.
19. Petitjean S, Stohler R, Déglon J-J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug and Alcohol Dependence*. 2001;62(1):97-104.
20. Johnson RE, Chutuape MA, Strain EC, et al. A Comparison of Levomethadyl Acetate, Buprenorphine, and Methadone for Opioid Dependence. *New England Journal of Medicine*. 2000;343(18):1290-97.
21. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: Interactions and clinical management. *The American Journal on Addictions*. 2010;19(1):59-72.

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22. Magura S, Lee JD, Hershberger J, et al. Buprenorphine and methadone maintenance in jail and post-release: A randomized clinical trial. *Drug and Alcohol Dependence*. 2009;99(1):222-30.
23. Neri S, Bruno CM, Pulvirenti D, et al. Randomized clinical trial to compare the effects of methadone and buprenorphine on the immune system in drug abusers. *Psychopharmacology*. 2005;179(3):700-04.
24. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *International Journal of Neuropsychopharmacology*. 2008;11(5):641-53.
25. Kristensen Ø, Espegren O, Asland R, et al. [Buprenorphine and methadone to opiate addicts-- a randomized trial]. *Tidsskr Nor Laegeforen*. 2005;125(2):148-51.
26. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction*. 2005;100(8):1090-100.
27. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-46.
28. Moore BA, Fiellin DA, Cutter CJ, et al. Cognitive Behavioral Therapy Improves Treatment Outcomes for Prescription Opioid Users in Primary Care Buprenorphine Treatment. *J Subst Abuse Treat*. 2016;71:54-57.
29. Voelker R. App Aids Treatment Retention for Opioid Use Disorder App Aids Treatment Retention for Opioid Use Disorder News From the Food and Drug Administration. *JAMA*. 2019;321(5):444-44.
30. Chen W, Hong Y, Zou X, et al. Effectiveness of prize-based contingency management in a methadone maintenance program in China. *Drug Alcohol Depend*. 2013;133(1):270-4.
31. Hser YI, Li J, Jiang H, et al. Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction*. 2011;106(10):1801-9.
32. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiology and Drug Safety*. 2017;26(9):1033-39.
33. Centers for Disease Control and Prevention (CDC). Medication-Assisted Treatment for Opioid Use Disorder Study (MAT Study) [Available from: <https://www.cdc.gov/opioids/Medication-Assisted-Treatment-Opioid-Use-Disorder-Study.html>].
34. Bell J, Trinh L, Butler B, et al. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. *Addiction*. 2009;104(7):1193-200.
35. Burns L, Gisev N, Larney S, et al. A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia. *Addiction*. 2015;110(4):646-55.
36. Saxon AJ. Commentary on Burns et al. (2015): retention in buprenorphine treatment. *Addiction*. 2015;110(4):656-7.
37. American Society of Addiction Medicine. National practice guideline for the use of medications in the treatment of addiction involving opioid use. *Journal of Addiction Medicine*. 2015;9(5):358-67.
38. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2005. (Treatment Improvement Protocol (TIP) Series, No. 43.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK64164/>

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39. Kakko J, Gronbladh L, Svanborg KD. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry*. 2007;164(5):797-274.
40. College of Pharmacists of BC. Opioid Agonist Treatment 2019 [Available from: <https://www.bcpharmacists.org/opioid-agonist-treatment>].
41. British Columbia Ministry of Health [creator] (2018): Medical Services Plan (MSP) Payment Information File. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
42. British Columbia Ministry of Health [creator] (2018): Discharge Abstract Database (Hospital Separations). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
43. British Columbia Ministry of Health [creator] (2018): PharmaNet. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
44. BC Vital Statistics Agency [creator] (2018): Vital Statistics Deaths. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
45. Ministry of Public Safety and Solicitor General (PSSG) [creator] (2018): BC Corrections Dataset. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
46. British Columbia Ministry of Health [creator] (2018): National Ambulatory Care Reporting System (NACRS). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
47. Perinatal Services BC [creator] (2018): British Columbia Perinatal Data Registry. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2018). <http://www.health.gov.bc.ca/data/>.
48. The American Society of Addiction Medicine (ASAM). The ASAM National Practice Guideline For The Use of Medications in the Treatment of Addiction Involving Opioid Use, 2015.
49. Pearce LA, Min JE, Piske M, et al. Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study. *BMJ*. 2020;368:m772. Published 2020 Mar 31. doi:10.1136/bmj.m772
50. Herenan M, Hernandez-Dias S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials*. 2012;9:48-55.
51. Murray EJ, Hernan MA. Adherence adjustment in the Coronary Drug Project: A call for better per-protocol effect estimates in randomized trials. *Clin Trials*. 2016;13(4):372-8.
52. Shah BR, Laupacis A, Hux JE, et al. Propensity score methods gave similar results to traditional regression modeling in observational studies: a systematic review. *Journal of Clinical Epidemiology*. 2005;58(6):550-59.
53. Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512-22.
54. Austin P, Fangyun Wu C, Lee D, et al. Comparing the high-dimensional propensity score for use with administrative data with propensity scores derived from high-quality clinical data. *Statistical Methods in Medical Research*. 2019:096228021984236.
55. Swanson SA, Hernán MA. Commentary: How to Report Instrumental Variable Analyses (Suggestions Welcome). *Epidemiology*. 2013;24(3):370-74.
56. Davies NM, Smith GD, Windmeijer F, et al. Issues in the Reporting and Conduct of Instrumental Variable Studies: A Systematic Review. *Epidemiology*. 2013;24(3):363-69.
57. Homayra F, Hongdilokkul N, Piske M, et al. Determinants of selection into buprenorphine/naloxone among people initiating opioid agonist treatment in British Columbia. *Second review at Drug and Alcohol Dependence*. 2019
58. Davies NM, Smith GD, Windmeijer F, et al. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology*. 2013;24(3):363-9.

- 1
- 2
- 3
- 4 59. Weinstein ZM, Kim HW, Cheng DM, et al. Long-term retention in Office Based Opioid Treatment with buprenorphine. *Journal of substance abuse treatment*. 2017;74:65-70.
- 5 60. Yang F, Lin P, Li Y, et al. Predictors of retention in community-based methadone maintenance treatment program in Pearl River Delta, China. *Harm Reduct J*. 2013;10:3.
- 6 61. Pickens RW, Preston KL, Miles DR, et al. Family history influence on drug abuse severity and treatment outcome. *Drug Alcohol Depend*. 2001;61(3):261-70.
- 7 62. Gerra G, Leonardi C, D'Amore A, et al. Buprenorphine treatment outcome in dually diagnosed heroin dependent patients: A retrospective study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2006;30(2):265-72.
- 8 63. Soyka M, Zingg C, Koller G, et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *The international journal of neuropsychopharmacology*. 2008;11(5):641-53.
- 9 64. Manhara A, Rosenheck R, Fiellin D. Opioid substitution treatment is linked to reduced risk of death in opioid use disorder. *BMJ*. 2017(357):j1947.
- 10 65. Apelt S, Scherbaum N, Soyka M. Induction and Switch to Buprenorphine-Naloxone in opioid dependence treatment: Predictive Value of the First Four Weeks. *Heroin Addiction and Related Clinical Problems*. 2014;16:87-98.
- 11 66. Dayal P, Balhara YPS. A naturalistic study of predictors of retention in treatment among emerging adults entering first buprenorphine maintenance treatment for opioid use disorders. *J Subst Abuse Treat*. 2017;80:1-5.
- 12 67. Cox J, Allard R, Maurais E, et al. Predictors of methadone program non-retention for opioid analgesic dependent patients. *J Subst Abuse Treat*. 2013;44(1):52-60.
- 13 68. Nosyk B, MacNab YC, Sun H, Fischer B, Marsh DC, Schechter MT, Anis AH. Proportional hazards frailty models for recurrent methadone maintenance treatment. *American journal of epidemiology*. 2009 Sep 15;170(6):783-92.
- 14 69. Lee CS, Liebschutz JM, Anderson BJ, et al. Hospitalized opioid-dependent patients: Exploring predictors of buprenorphine treatment entry and retention after discharge. *Am J Addict*. 2017;26(7):667-72.
- 15 70. Haddad MS, Zelenev A, Altice FL. Integrating buprenorphine maintenance therapy into federally qualified health centers: real-world substance abuse treatment outcomes. *Drug Alcohol Depend*. 2013;131(1-2):127-35.
- 16 71. Ruger JP, Chawarski M, Mazlan M, et al. Cost-effectiveness of buprenorphine and naltrexone treatments for heroin dependence in Malaysia. *PloS one*. 2012;7(12):e50673.
- 17 72. Lions C, Carrieri MP, Michel L, et al. Predictors of non-prescribed opioid use after one year of methadone treatment: an attributable-risk approach (ANRS-Methaville trial). *Drug Alcohol Depend*. 2014;135:1-8.
- 18 73. Degenhardt L, Conroy E, Day C, et al. The impact of a reduction in drug supply on demand for and compliance with treatment for drug dependence. *Drug and Alcohol Dependence*. 2005;79(2):129-35.
- 19 74. Gryczynski J, Mitchell SG, Jaffe JH, et al. Leaving buprenorphine treatment: patients' reasons for cessation of care. *Journal of substance abuse treatment*. 2014;46(3):356-61.
- 20 75. Bao YP, Liu ZM, Epstein DH, et al. A meta-analysis of retention in methadone maintenance by dose and dosing strategy. *Am J Drug Alcohol Abuse*. 2009;35(1):28-33.
- 21 76. Janjua NZ, Islam N, Kuo M, et al. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. *Int J Drug Policy*. 2018;55:31-39.
- 22 77. Glymour MM, Tchetgen Tchetgen EJ, Robins JM. Credible Mendelian randomization studies: approaches for evaluating the instrumental variable assumptions. *Am J Epidemiol*. 2012;175(4):332-9.
- 23
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- 4 78. Ding P, VanderWeele TJ, Robins JM. Instrumental variables as bias amplifiers with general
- 5 outcome and confounding. *Biometrika*. 2017;104(2):291-302.
- 6 79. Hernán MA, Robins JM. Instruments for Causal Inference: An Epidemiologist's Dream?
- 7 *Epidemiology*. 2006;17(4):360-72.
- 8 80. Hernan MA, Robins JM. Causal Inference. 2020 ed: Boca Raton: Chapman & Hall/CRC.
- 9 81. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. *New England Journal of*
- 10 *Medicine*. 2017;377(14):1391-98.
- 11 82. Murray EJ, Hernan MA. Improved adherence adjustment in the Coronary Drug Project. *Trials*.
- 12 2018;19(1):158.
- 13 83. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice
- 14 Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use.
- 15 *Journal of addiction medicine*. 2015;9(5):358-67.
- 16 84. Naimi AI, Cole SR, Kennedy EH. An introduction to g methods. *Int J Epidemiol*.
- 17 2017;46(2):756-62.
- 18 85. Picciotto S, Neophytou AM. G-estimation of structural nested models: Recent applications in
- 19 two subfields of epidemiology. *Current Epidemiology Reports*. 2016; 3(3): 242-251.
- 20 86. Hernan MA, Cole SR, Margolick J, et al. Structural accelerated failure time models for survival
- 21 analysis in studies with time-varying treatments. *Pharmacoepidemiol Drug Saf*.
- 22 2005;14(7):477-91.
- 23 87. Vansteelandt, S. and Sjolander, S. Revisiting g-estimation of the Effect of a Time-varying
- 24 Exposure Subject to Time-varying Confounding. *Epidemiol Methods*. 2016; 5(1): 37–56.
- 25 88. VanderWeele T. Principles of confounder selection. *European Journal of Epidemiology*.
- 26 2019;34
- 27 89. Bell J, Trinh L, Butler B, et al. Comparing retention in treatment and mortality in people after
- 28 initial entry to methadone and buprenorphine treatment. *Addiction*. 2009;104(7):1193-200.
- 29 90. Morgan JR, Schackman BR, Leff JA, et al. Injectable naltrexone, oral naltrexone, and
- 30 buprenorphine utilization and discontinuation among individuals treated for opioid use
- 31 disorder in a United States commercially insured population. *Journal of substance abuse*
- 32 *treatment*. 2018;85:90-96.
- 33 91. Australian Government Department of Health. Clinical Guidelines and Procedures for the Use
- 34 of Methadone in the Maintenance Treatment of Opioid Dependence. 2003. [Available
- 35 from: [https://www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-](https://www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-meth-toc~drugtreat-pubs-meth-s3~drugtreat-pubs-meth-s3-3.5)
- 36 [pubs-meth-toc~drugtreat-pubs-meth-s3~drugtreat-pubs-meth-s3-3.5](https://www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-meth-toc~drugtreat-pubs-meth-s3~drugtreat-pubs-meth-s3-3.5)]
- 37 92. VanderWeele T, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-
- 38 Value. *Ann Intern Med*. 2017;167:268-74.
- 39 93. Government of British Columbia. Alternative Payments Program. [Available from:
- 40 [https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-](https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-compensation/alternative-payments-program)
- 41 [compensation/alternative-payments-program](https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/physician-compensation/alternative-payments-program).
- 42 94. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council
- 43 of Canada, Social Sciences and Humanities Research Council of Canada. Tri-council
- 44 policy statement: Ethical conduct for research involving humans. 2010
- 45 95. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational
- 46 Studies in Epidemiology (STROBE) statement: guidelines for reporting observational
- 47 studies. *J Clin Epidemiol*. 2008;61(4):344-9.
- 48 96. World Health Organization. WHO Model Lists of Essential Medicines, 2019.
- 49 97. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment:
- 50 systematic review and meta-analysis of cohort studies. *BMJ*. 2017;357:j1550.
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Table 1. Potential confounding variables affecting opioid agonist treatment retention

Covariate	Association†	Quality of evidence ^a (source)	Available?
Individual-related characteristics			
<i>Demographics</i>			
Age	+ MET retention	Level I ¹⁵	Yes
Marital status (married)	+ MET retention	Level I ¹⁵	No
Employment status (employed)	+ MET retention	Level I ¹⁵	Yes [^] *
Gender (female)	+ MET retention	Level I ¹⁵	Yes
Duration of treatment	+ MET retention	Level I ¹⁵	Yes
Ethnicity (Hispanic or African American)	- BUP retention	Level II ⁵⁹	No
Living in rural area	- MET retention	Level II ⁶⁰	Yes
Family history of addiction	- MET retention	Level II ⁶¹	No
Homelessness	- MET/BNX retention	Level II ¹¹	Yes [^] *
Incarceration	- MET/BNX retention	Level II ¹¹	Yes
History of overdose	Risk factor for overdose	Level III ¹	Yes [*]
<i>Concurrent conditions</i>			
Psychiatric comorbidity: major depression	+ BUP retention	Level II ⁶²	Yes ^{***}
Schizophrenia	- BUP retention	Level II ⁶²	Yes ^{***}
Personality disorders	- BUP retention	Level II ⁶²	Yes ^{***}
Severe withdrawal at beginning of treatment	- BUP retention	Level I ⁶³	No
Hepatitis C virus	+ BUP retention	Level II ¹¹	Yes ^{***}
Other substance use disorders	- BUP retention	Level II ⁶⁴	Yes ^{***}
Severe chronic pain	Risk factor for overdose	Level III ¹	Yes ^{***}
Respiratory disease	Risk factor for overdose	Level III ¹	Yes ^{***}
Cocaine use upon admission to OAT	- BNX retention	Level II ⁶⁵	No
Past-month injection drug use	- BNX retention	Level II ⁶⁶	Yes [§]
<i>Medication history</i>			
Use of sedatives within past 30 days of OAT	- BUP retention	Level II ⁶⁷	Yes
Number of previous MET/BNX episodes	+ MET retention	Level II ⁶⁸	Yes
Previous receipt of MET/BNX	+ BUP/MET retention	Level II ⁶⁹	Yes
Receipt of psychiatric medication ^b	+ BUP retention	Level II ⁷⁰	Yes
Receiving high opioid prescription doses ^c	Risk factor for overdose	Level III ¹	Yes
<i>Health care utilization</i>			
Emergency department visits	- BUP retention	Level II ⁶⁴	Yes
Psychiatric hospitalizations	- BUP retention	Level II ⁶⁴	Yes
Treatment-related & contextual factors			
<i>Service provision</i>			
OAT in integrated care	+ BUP retention	Level I ⁷¹	Yes
Behavioral therapy	+ BUP/MET retention	Level I ^{29,31}	Yes [*]
Positive relationships with service staff	+ MET retention	Level II ⁷²	No
<i>Contextual factors</i>			
Poor availability and quality of heroin in drug supply	+ MET/BUP retention	Level II ⁷³	No
<i>OAT dosing</i>			
Insufficient BUP maintenance dose ^d	- BUP retention	Level II ⁷⁴	Yes
Sufficient BUP maintenance dose ^e	+ BUP retention	Level I ⁴	Yes
High MET maintenance dose ^f	+ MET retention	Level I ⁷⁵	Yes
Flexible-dose strategies (compared to fixed dosing)	+ MET retention	Level I ⁷⁵	Yes

Abbreviations: OAT: opioid agonist treatment; iOAT: injectable opioid agonist treatment; BUP: buprenorphine; MET: methadone; BNX: buprenorphine/naloxone. † Significant factors identified in studies. + positive association; - negative association. ^ Plan I / C/ G / Coverage (low-income Pharmacare coverage program); * proxy variable. ** factor not captured in datasets to be included in bias analysis. *** concurrent condition identified via ICD-9/10 diagnostic codes. § Identified via case finding algorithm⁷⁶; a. Quality of evidence ratings: Level I: systematic reviews, meta-analyses, and randomized controlled trials; Level II: cohort studies, case control studies, case studies; Level III: case reports, ideas, editorials, opinions (source: Cochrane review library <https://consumers.cochrane.org/levels-evidence>); b. anti-depressant, anti-anxiety, anti-psychotic and mood stabilizing medications; c. >90 morphine equivalents; d. Maximum of 8mg/day; e. Fixed dosing at medium (7-15 mg/day) or high doses (≥16mg/day); f. ≥60mg/day.

Table 2. Proposed subgroup and sensitivity analyses

Proposed sensitivity analysis	Rationale	Application	
1. Sample restriction			
Pregnant women	To assess heterogeneity in the key populations identified in The American Society of Addiction Medicine national practice guidelines. ⁴⁸	All	
PWOD with pain		All	
Adolescents		All	
PWOD with mental health disorders ^a		All	
Individuals in the criminal justice system		All	
PWOD with history of PO prescription prior to diagnosis		May provide indirect evidence of treatment effect for those who primarily misuse PO.	All
PWOD in regions with highest fentanyl concentrations ^b		May provide indirect evidence of treatment effect for those who primarily misuse fentanyl.	All
PWOD receiving care in Community Health Centres ^c	Assesses heterogeneity of treatment effect across clinical settings.	All	
PWOD receiving care in stand-alone physician practices ^d		All	
2. Timeline restriction			
Buprenorphine/naloxone as first-line OAT in BC ^e	To account for potential influence of this BC policy change on OAT selection. ⁸	All	
3. Variable classification			
Episode discontinuation: 3 days (MET)	Alternative discontinuation thresholds have been defined at 3 or 7 days (MET) and 4 or 14 days (BUP) in other studies and guidelines ^{89,90,91} as opposed to discontinuation thresholds of 5 days (MET) and 6 days (BUP). ⁸	All	
Episode discontinuation: 7 days (MET)		All	
Episode discontinuation: 4 days (BUP)		All	
Episode discontinuation: 14 days (BUP)		All	
Episode discontinuation: Dose tapering ^f	To account for individuals discontinuing treatment after completing dose tapering, defined as $\leq 5\text{mg/day}$ for MET and $\leq 2\text{mg/day}$ BNX on the last day of OAT receipt.	All	
Secondary outcome: Drug-related hospitalizations	Treating hospitalizations by other causes as competing risks may provide a more direct effect of exposure on outcome.	All	
Secondary outcome: Drug-related deaths	Treating deaths by other causes as competing risks may provide a more direct effect of exposure on outcome.	All	
Application of alternate clinical guidelines	Pertaining to both minimum effective daily doses and policies surrounding dose carries. To be executed to tailor PP analyses to other settings.	PP	
Allowing for medication switching ^g	To account for individuals receiving BUP who switch to MET if withdrawal symptoms are not alleviated, ³⁹ and to account for individuals switching from MET to BUP.	All	
4. Model specification			
Bias analysis	To measure the association necessary to explain the observed treatment-outcome association attributable to unmeasured factors identified in Table 1. ⁹²	All	
Determining the association between instrumental variables and covariates	To empirically verify that our instrumental variables do not share common observed causes with the outcomes.	ITT-IV	
Leveraging prior causal assumptions	To determine whether the data are compatible with prior valid assumptions of residual confounding of positive residual confounding.	ITT-IV	
Over-identification tests	To assess performance of multiple IVs.	ITT-IV	

Abbreviations: PWOD: people with opioid use disorder; ITT-IV: intention-to-treat instrumental variable; PP: per-protocol; BC: British Columbia; OAT: opioid agonist treatment; PO: prescription opioid; MET: methadone; BUP: buprenorphine.

a. Conditions outlined in Supplementary Appendix Tables A2 & A3. b. Restricted to the lower mainland Vancouver area after April 1st, 2016 (declaration of public health emergency); c. Physicians practicing in community health centers are remunerated on the province's 'Alternative payment plan'⁹³ as opposed to as indicated by the absence of physician billing record supporting OAT pharmacy dispensations; d. as indicated by prescription renewals from single physicians with low (<20 clients) OAT treatment loads; e. From June 5th, 2017 onwards; f. OAT episodes with completed tapers (with no record of reversion for at least 4 weeks) will be censored at the start of the tapering; g. Allowing continuous OAT episodes to account for switching from buprenorphine/naloxone to methadone, or from methadone to buprenorphine/naloxone as indicated by BC guidelines. If prescribed doses (during switching) do not follow BC

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3 guidelines, the observation will be censored in per-protocol analysis. We note that medication switches are intended to be captured
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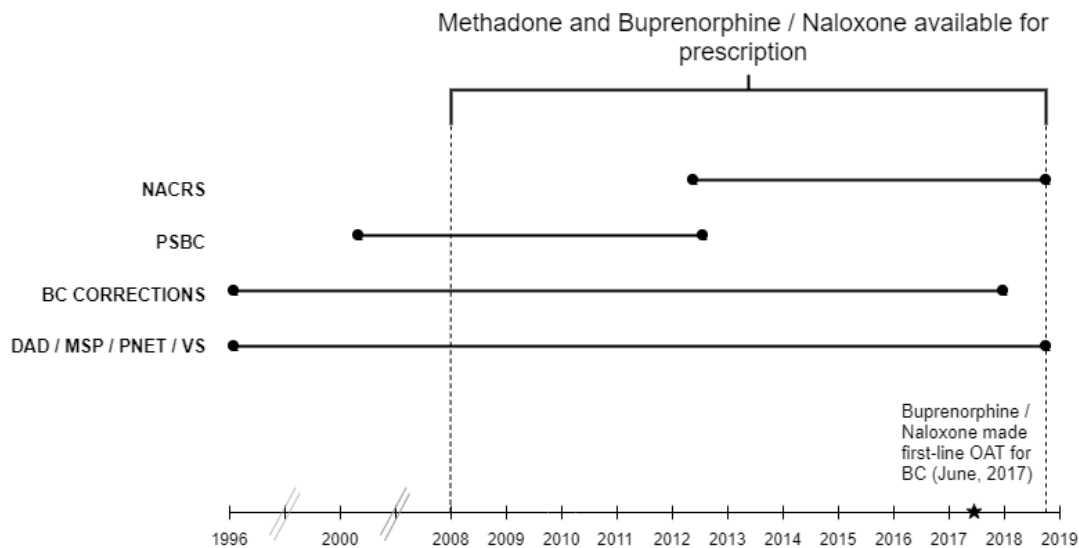
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3 **Figure 1. Study-specific dates, databases, and their data extraction period**
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7 Abbreviations (data extraction time window): OAT: opioid agonist treatment; BC: British Columbia, Canada;
8 BC Corrections (Jan. 1, 1996 – Dec. 31, 2017); DAD: Discharge Abstract Database (Jan. 1, 1996 – Sep.
9 30, 2018); MSP: Medical Services Plan (Jan. 1, 1996 – Sep. 30, 2018); NACRS: National Ambulatory Care
10 Reporting System (Apr. 1, 2012 – Sep. 30, 2018); PNET: PharmaNet (Jan. 1, 1996 – Sep. 30, 2018); PSBC:
11 Perinatal Services British Columbia (Mar. 10, 2000 – Aug. 14, 2012); VS: Vital Statistics (Jan. 1, 1996 –
12 Sep. 30, 2018).
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Figure 1. Study-specific dates, databases, and their data extraction period



Supplementary Appendix

Table A1. Databases used for cohort construction

Database	Description	Generating process	Key content	Limitations
PharmaNet	All prescriptions for drugs and medical supplies dispensed from pharmacies including hospital outpatient dispensations.	Electronically submitted by pharmacists dispensing medications in real time. Required for reimbursement.	Drugs dispensed (using DIN/PIN* number), date of dispensation, quantity and duration of prescription, billing information, prescriber code and drug costs.	Records of drugs dispensed within physician private practice incomplete. Third party paid amounts not explicit. Practitioner IDs in PharmaCare are not linkable to practitioner IDs in PharmaNet. No provincial health information standards authority to ensure data quality (disbanded in 2003). PharmaNet does not capture: <ul style="list-style-type: none"> • Medications administered to hospital in-patients • Antiretroviral medications dispensed from the Centre of Excellence in HIV / AIDS at St. Paul's Hospital • Chemotherapy agents dispensed by the BC Cancer Agency • Medications purchased without a prescription may not be on PharmaNet (e.g., over the counter medications, herbal products, vitamins) • Medication samples dispensed at a physician's office (some are entered by physicians with PharmaNet access) https://www2.gov.bc.ca/assets/gov/health/forms/5431save.pdf
Discharge Abstract Database (DAD)	All hospital discharges, day surgery, transfers, and deaths of inpatients. Data of BC residents treated at hospital out of province, and out-of-province residents treated within BC hospitals included.	Data files grouped into fiscal years by separation date (not admission date). Each hospital submits electronic records of patient visits to the provincial government which cleans and then submits the records to the Canadian Institute for Health Information (CIHI). CIHI regularly conducts re-abstraction to ensure data quality.	Hospitalization dates, most responsible diagnosis (ICD 9/10-CA code) and up to 24 additional diagnostic codes, 25 procedure codes using CCI/CCP procedure/ intervention codes [†] , transport method, transfers, primary physician responsible for stay, condition specific resource intensity weights, inpatient grouping. Hospital number, level of care, admission date/time, admission category, readmission, and transfer codes, discharge date/time, discharge,	Visits to emergency department, abortion procedures, outpatient care (e.g. x-rays and blood work) excluded.

			disposition, length of stay, stay by level of care.	
Medical Services Plan (MSP) Database	All medically necessary services provided by fee-for-service practitioners covered by the province's universal insurance program: Medical Services Plan (MSP).	Majority of billing records submitted electronically by practitioners' offices for reimbursement purposes. Diagnosis codes accurate only to 3 rd digit.	Medically necessary services including laboratory and diagnostic procedures (x-rays, ultrasounds), and dental and oral surgery performed in hospital. Up to 5 diagnoses codes included (ICD-9-CA). Service date, fee item, diagnostic codes, practitioner code, service costs and location.	Inconsistent 'shadow billing' of services provided for no charge referrals, in Primary Health Care encounters claims, or by nurse practitioners. Insurance Corporation of British Columbia (ICBC) or WorkSafeBC claims; abortion services; and services provided through alternative payment plans (e.g. salaried, sessional, and service agreement contracts) excluded. Most current year of MSP payment data is 5-10% incomplete, with up to 6 month lag in billings filed.
Vital Statistics (VS)	All deaths registered in the province.	Data is checked against nationally uniform vital registration and statistics standards.	Date of death (year and month), location, underlying cause of death (ICD-9-CA and ICD-10-CA), and nature of injury codes.	Excludes abortions and out-of-province deaths of BC residents. Non-specific information on overdose deaths, drug type not indicated.
National Ambulatory Care Reporting System Database	All hospital-based and community-based ambulatory care including day surgery, outpatient and community-based clinics emergency departments	Data is collected directly from participating facilities or from regional health authorities or ministries of health.	ED records, day surgery, clinic submissions from several jurisdictions, patients' presenting complaint, and ED discharge diagnosis	There is no clear indicator of diseases and the level of the patient's type of separation from the ambulatory care service after registration to that service is not organized.
BC Corrections	The Provincial Health Officer compels Corrections Data from the Ministry of Public Safety and Solicitor General.	The Ministry of health receives inmate client file, inmate event file and inmate event movement files from the Public Safety and Solicitor General. The Ministry of Health Data Provisioning Team anonymizes client	Inmate events: incarceration in/out dates from BC corrections; Inmate moves: movements during incarceration from BC corrections	Ministry data for personal health numbers that are not in the cohort but that are associated with a Corrections Client ID that is also associated with a personal health number in the cohort are not provided, but all the Corrections data will be provided. All "youth" files excluded.

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		ID and personal health numbers and provides an anonymized version of the Client File that contains anonymized IDs.		
Perinatal Database	Perinatal Services BC houses the provincial perinatal database, which consists of data collected from obstetrical facilities as well as births occurring at home attended by BC Registered Midwives.	Perinatal data is collected from facilities throughout the province and imported into the central BC Perinatal Data registry. Installation hospitals have the same software as the central system, and send data on a periodic basis to the provincial database. The non-installation hospitals have their databases maintained at the central office. Data from the Canadian Institute for Health Information (CIHI) and matched files from the British Columbia Vital Statistics Agency complement the data elements. Participation in the registry is not mandatory.	Mother: admission date, discharge date, first contact with physician/midwife date, number of births in current pregnancy, number of antenatal visit in the current pregnancy, gestational age at delivery (in week), mode of delivery, health authority, local health authority (LHA), health service delivery area (HSDA), transfer in/out to another facility, HIV testing flag, Hepatitis B testing flag, substance use flag, mental illness flag, prior still birth, prior low weight baby flag, prior neonatal death, postpartum infection, HSDA, HA, LHA, Institute transferred from/to, admission date, discharge date, institute where mother delivered, first ultrasono date, gestational age at first U/S, ICD code for diagnoses, gestational age at delivery. Baby: admission date, discharge date, HA, HSDA, LHA, birth weight, gestational age at birth, blood culture test, urine culture test, breast feeding	Substance use flag is available only from March 2008- August 2014.

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			initiation, institution to which baby was transferred from the current episode of care, Baby's length of stay for admission expressed in hour, where the baby was discharged to, or the status of the baby at the time of discharge, location where baby received care.	
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*DIN: Drug Identification Number; PIN: Product Identification Number; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada. † Coding structures used by the Canadian Institute of Health Information (CIHI); ‡ A standardized code picklist for presenting complaint developed by CIHI.

Table A2. ICD-9/10-CA and drug identification numbers used to draw initial cohort

Database	Code no.*	Description
PharmaNet	999792, 999793, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 67000008, 67000007, 67000005, 67000006, 67000004, 67000003, 67000001, 67000002	DIN/PIN for methadone as OAT
PharmaNet	2242962, 2242963, 2242964, 2295695, 2295709, 66999994, 66999995, 66999996, 2408090, 2408104, 2424851, 2424878, 2453908, 2453916, 2468085, 2468093	DIN/PIN for buprenorphine/naloxone as OAT
PharmaNet	22123349, 22123346, 22123347, 22123348	DIN/PIN for slow-release oral morphine
PharmaNet	22123357, 66123367, 2146126, 22123340	DIN/PIN for injectable OAT
PharmaNet	999776	DIN/PIN for Narcotic compound
MSP/DAD	304	ICD-9-CA for drug dependence
MSP/DAD	305.2-305.9	ICD-9-CA for non-dependent abuse of drug
MSP/DAD	E850-E854, 969.4-969.7, 965	ICD-9-CA for drug poisoning
MSP/DAD	292, 305, 648.3, 751, 752, 753, 760, 779.5,	ICD-9-CA for cohort creation
MSP/DAD/VS/NACRS/PSBC	T40, T42.4, T43.6, Z50.3, Z71.5, Z72.2, P04.4, P96.1	ICD-10-CA for cohort creation
MSP/DAD/VS/NACRS/PSBC	F11-F16, F19	ICD-10-CA for abuse of drug
MSP/DAD/VS/NACRS/PSBC	X42, X62, Y12	ICD-10-CA for drug poisoning
MSP fee item	39,15039,13013,13014	Fee item for OAT

DAD: Discharge Abstract Database; MSP: Medical services Plan; VS: Vital statistics; NACRS: National Ambulatory Care Reporting System; PSBC: Perinatal services British Columbia; *PharmaNet database: Drug Identification Numbers (DIN)/Product Identification Numbers (PIN) used for identification; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada.

Table A3. Identification of concurrent chronic conditions

Diseases	Diagnosis code	References
MH	ICD-9-CA from DAD and MSP: 295-298,300,301, 308, 309, 311, 314, 317, 318, 319, 76071; ICD-10-CA from DAD/NACRS/VS/PSBC: F20-F25, F28-F34, F38-F43, F48, F60-F61, F69, F70-F73, F78, F79, F90, Q86.0; MSP additional diagnostic code 50B	(1), (2), (3), (4), (5), (6)
HIV	ICD-9-CA from DAD and MSP: 042-044, 079.53, 795.8, V08; ICD-10-CA from DAD/NACRS/VS: B20-B24, B97.35, F02.4, O98.7, Z21; MSP fee item: 13015, 13105, 33645, 36370	(7), (8)
HCV	ICD-9-CA from DAD and MSP: 70.41, 70.51, 70.44, 70.54, 70.7; ICD-10-CA from DAD/NACRS/VS: B17.1, B18.2, B19.2; DIN/PIN: 2370816, 2371448, 2371456, 2371464, 2371472, 2444755, 2451131, 2467550, 2432226, 2436027, 2447711, 2416441, 2418355, 2467542, 2456370, 2371553	(9),(10),(11), (12)
ODD	ICD-9-CA from DAD and MSP: 304.0, 304.7, 305.5, 965.0, E850.0-E850.2 ICD-10-CA from DAD/NACRS/VS/PSBC: F11, X42 & (T40.0-T40.4 or T40.6), X62 & (T40.0-T40.4 or T40.6), Y12 & (T40.0-T40.4 or T40.6) MSP fee item: 39,15039,13013,13014 DINPIN from Pharmanet: 999792, 999793, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 67000008, 67000007, 67000005, 67000006, 67000004, 67000003, 67000001, 67000002, 2242962, 2242963, 2242964, 2295695, 2295709, 66999994, 66999995, 66999996, 2408090, 2408104, 2424851, 2424878, 2453908, 2453916, 2468085, 2468093, 22123349, 22123346, 22123347, 22123348, 22123357, 66123367, 2146126, 22123340, 999776	(1), (13), (15),(16)
AUD	ICD-9-CA from DAD and MSP: 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 655.4, 760.71, V65.42; ICD-10-CA from DAD/NACRS/VS/PSBC: F10, Z50.2, Z71.4, Z72.1, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, Q86.0; DIN: 2293269, 2158655, 2213826, 2444275, 2451883,2534, 2542, 2041375, 2041391, 66124089, 66124085, 66124087	(13), (14)
SUD	ICD-9-CA from DAD and MSP: 292, 304.1-304.6, 304.8, 304.9, 305.2-305.4, 305.6-305.9, 648.3,655.5, 760.73,760.75,779.5, 967, 969.4,969.6,969.7,970, E851, E852,E853.2,E854.1,E854.2, E854.3; ICD-10-CA from DAD/NACRS/VS/PSBC: F12-F16, F19, P04.4, P96.1, T40.5,T40.7, T40.8, T40.9, T42.4, T43.6, X42, X62, Y12, Z50.3, Z71.5, Z72.2	(1), (13), (15),(16)
Chronic pain	ICD-9-CA from DAD and MSP: 338.2, 338.4, 307.80, 307.89, 338.0, 719.41, 719.45-719.47, 719.49, 720.0, 720.2, 720.9, 721.0-721.4, 721.6, 721.8, 721.9, 722, 723.0, 723.1, 723.3-723.9, 724.0-724.6, 724.70, 724.79, 724.8, 724.9, 729.0-729.2, 729.4, 729.5, 350, 352-357, 344.0, 344.1, 997.0, 733.0, 733.7, 733.9, 781; ICD-10-CA from DAD/NACRS/VS: F45.4, G89.0, G89.2, G89.4, M08.1, M25.50, M25.51, M25.55-M25.57, M43.2-M43.6, M45, M46.1, M46.3, M46.4, M46.9, M47, M48.0, M48.1, M48.8, M48.9, M50.8, M50.9, M51, M53.1-M53.3, M53.8, M53.9, M54, M60.8, M60.9, M63.3, M79.0-M79.2, M79.6, M79.7, M96.1, G50, G52 - G64, G82, G97, M89, R29	(2), (17), (18)

ODD: opioid use disorder; MH: mental health; HCV: hepatitis C; AUD: alcohol use disorder; SUD: substance use disorder other than OUD and AUD; DAD: Discharge Abstract Database for hospitalization; MSP: Medical Service Plan for physician billing; NACRS: National Ambulatory Care Reporting System; VS: Vital Statistics database in British Columbia; PSBC: Perinatal Services British Columbia; DIN: drug identification number from PharmaNet; ICD-9/10-CA: International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions, Canada..

References

1. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical care*. 2005;43(11):1130–9.
2. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE. A chronic disease score with empirically derived weights. *Med Care*. 1995;33(8):783–95.
3. British Columbia. Ministry of Health. Guide to the MENTAL HEALTH ACT. British Columbia. Ministry of Health; 2005.
4. Fraser Health. MENTAL HEALTH ACT: fraserhealth; 2018 [Available from: <http://www.fraserhealth.ca/health-info/mental-health-substance-use/mental-health-act/>].
5. British Columbia. Ministry of Health. Psychiatric Medications Plan (Plan G) 2018 [Available from: <https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/psychiatric-medications-plan-plan-g>].
6. Health Quality Ontario. Hospital admissions for a mental illness or an addiction 2017 [Available from: <http://indicatorlibrary.hqontario.ca/Indicator/Detailed/Mental-health-addiction-admissions/EN>].
7. Nosyk B, Colley G, Yip B, Chan K, Heath K, Lima VD, et al. Application and validation of case-finding algorithms for identifying individuals with human immunodeficiency virus from administrative data in British Columbia, Canada. *PloS one*. 2013;8(1):e54416.
8. IAS-USA. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2016 Recommendations of the International Antiviral Society–USA Panel 2016 [Available from: <https://www.iasusa.org/content/antiretroviral-drugs-treatment-and-prevention-hiv-infection-adults-2016-recommendations>].
9. Robert P Myers MM, Hemant Shah, MD MScCH HPTE, Kelly W Burak, MD MSc, Curtis Cooper, MD, and Jordan J Feld, MD MPH. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. *Canadian Journal of Gastroenterology & Hepatology*. 2015;29(1):19-34.
10. BC Centre for Disease Control. Communicable Disease Control Hepatitis C August 2016. 2016.
11. Hepatitis C Treatment Information Project. THE FOUR CLASSES OF HEP C TREATMENT DAAS 2018 [Available from: <http://www.hepctip.ca/daas/>].
12. Hepatitis C Education and Prevention Society. Current Treatments as of August 2017 2017 [Available from: <http://hepcbc.ca/current-treatments/>].
13. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend*. 2009;105(1-2):9–15.
14. National Collaborating Centre for Mental Health. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. 2011.
15. British Columbia. Ministry of Health. B.C.'s Mental Health and Substance Use Strategy 2017.
16. Antoine B. Douaihy TMK, and Carl Sullivan. Medications for Substance Use Disorders. *Soc Work Public Health*. 2013;28(0):264-78.
17. Doctors of BC. Improving Chronic Pain Management in BC. 2017.
18. Jason W. Busse SC, David N. Juurlink, D. Norman Buckley, Li Wang, Rachel J. Couban, Thomas Agoritsas, Elie A. Akl, Alonso Carrasco-Labra, Lynn Cooper, Chris Cull, Bruno R. da Costa, Joseph W. Frank, Gus Grant, Alfonso Iorio, Navindra Persaud, Sol Stern, Peter Tugwell, Per Olav Vandvik and Gordon H. Guyatt. Guideline for opioid therapy and chronic noncancer pain. *Canadian Medical Association Journal*. 2017;189(18): E659-E66.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Completed	Page # (manuscript)
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A	-
	2b	All items from the World Health Organization Trial Registration Data Set	N/A	-
Protocol version	3	Date and version identifier	✓	In online submission
Funding	4	Sources and types of financial, material, and other support	✓	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓	1
	5b	Name and contact information for the trial sponsor	N/A	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	✓	1

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2		5d	Composition, roles, and	N/A
3			responsibilities of the	-
4			coordinating centre, steering	
5			committee, endpoint adjudication	
6			committee, data management	
7			team, and other individuals or	
8			groups overseeing the trial, if	
9			applicable (see Item 21a for data	
10			monitoring committee)	
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Introduction

Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

6b Explanation for choice of comparators

Objectives 7 Specific objectives or hypotheses

Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

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2	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A -	
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7		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓ 13-14	
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15		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A -	
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23		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A -	
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27	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ 10-11	
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44	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ 11, Figure 1	
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2	Sample size	14	Estimated number of participants	N/A	-
3			needed to achieve study		
4			objectives and how it was		
5			determined, including clinical		
6			and statistical assumptions		
7			supporting any sample size		
8			calculations		
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11	Recruitment	15	Strategies for achieving	N/A	-
12			adequate participant enrolment		
13			to reach target sample size		
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Methods: Assignment of interventions (for controlled trials)

Allocation:

21	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A	-
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36	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A	-
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46	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A	-
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51	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A	-
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2		17b	If blinded, circumstances under	N/A
3			which unblinding is permissible,	-
4			and procedure for revealing a	
5			participant's allocated	
6			intervention during the trial	
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	N/A	-
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A	-
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A	-
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓	11-14

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2		20b	Methods for any additional	✓
3			analyses (eg, subgroup and	
4			adjusted analyses)	15
5				
6		20c	Definition of analysis population	✓
7			relating to protocol non-	
8			adherence (eg, as randomised	13-14
9			analysis), and any statistical	
10			methods to handle missing data	
11			(eg, multiple imputation)	
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Methods: Monitoring

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16	Data monitoring	21a	Composition of data monitoring	N/A
17			committee (DMC); summary of	-
18			its role and reporting structure;	
19			statement of whether it is	
20			independent from the sponsor	
21			and competing interests; and	
22			reference to where further details	
23			about its charter can be found, if	
24			not in the protocol. Alternatively,	
25			an explanation of why a DMC is	
26			not needed	
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31		21b	Description of any interim	N/A
32			analyses and stopping	-
33			guidelines, including who will	
34			have access to these interim	
35			results and make the final	
36			decision to terminate the trial	
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39	Harms	22	Plans for collecting, assessing,	N/A
40			reporting, and managing	-
41			solicited and spontaneously	
42			reported adverse events and	
43			other unintended effects of trial	
44			interventions or trial conduct	
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47	Auditing	23	Frequency and procedures for	N/A
48			auditing trial conduct, if any, and	-
49			whether the process will be	
50			independent from investigators	
51			and the sponsor	
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Ethics and dissemination

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2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A	-
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7	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A	-
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17	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A	-
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24		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	-
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29	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A	-
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38	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓	2
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43	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A	-
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50	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A	-
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2	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓	16	
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14		31b	Authorship eligibility guidelines and any intended use of professional writers	✓	16	
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18		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓	16	
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25	Appendices					
26	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A	-	
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32	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	-	
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