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Comparative effectiveness of urine drug screening strategies alongside opioid agonist treatment in British Columbia, Canada: a population-based observational study protocol

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ABSTRACT

Introduction Urine drug tests (UDTs) are commonly used for monitoring opioid agonist treatment (OAT) responses, supporting the clinical decision for take-home doses and monitoring potential diversion. However, there is limited evidence supporting the utility of mandatory UDTs—particularly the impact of UDT frequency on OAT retention. Real-world evidence can inform patient-centred approaches to OAT and improve current strategies to address the ongoing opioid public health emergency. Our objective is to determine the safety and comparative effectiveness of alternative UDT monitoring strategies as observed in clinical practice among OAT clients in British Columbia, Canada from 2010 to 2020.

Methods and analysis We propose a population-level retrospective cohort study of all individuals 18 years of age or older who initiated OAT from 1 January 2010 to 17 March 2020. The study will draw on eight linked health administrative databases from British Columbia. Our primary outcomes include OAT discontinuation and retention. Real-world evidence can inform patient-centred approaches to OAT and improve current strategies to address the ongoing opioid public health emergency. Our objective is to determine the safety and comparative effectiveness of alternative UDT monitoring strategies as observed in clinical practice among OAT clients in British Columbia, Canada from 2010 to 2020.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ British Columbia’s single-payer healthcare system constitutes an ideal setting for direct comparisons of medical care and monitoring strategies at the population level and within key subgroups.

⇒ A per-protocol analysis, implemented with inverse probability censorship weights and clone-censor-weight approaches, will provide a direct comparison of static and dynamic monitoring strategies administered as observed in clinical practice throughout the province of British Columbia, Canada.

⇒ Potential uncontrolled confounding and other threats to validity will be assessed via a range of sensitivity analyses.

INTRODUCTION

Urine drug testing (UDT) is commonly used alongside opioid agonist treatment (OAT) to assess medication adherence and ongoing illegal drug use as a proxy for monitoring treatment response. UDTS can assess progress by confirming intake of prescribed OAT, validating self-reported substance use and supporting clinical decisions for take-home doses.1 2 UDTS, thus, provide one element of the ongoing clinical assessment of treatment response, which also includes ongoing evaluation of psychosocial well-being, quality of life, progress towards substance use goals, and improvement in health and social functioning.3 An additional rationale for UDT is to provide a means of monitoring the possibility of diversion, and potentially serve as a deterrent against diversion.4–6 British Columbia’s (BC) approach to OAT management embeds patient-centred care where a positive UDT result for opioids and other substances should not discontinue treatment.1 Although provincial,11 national13 and
international guidelines recommend a non-punitive approach to positive UDT results, several qualitative and observational studies have documented that take-home doses are postponed during initiation or curtailed as a result of illicit drug use as clinical stability has not been attained. Other responses from consistently positive UDT results during OAT include counselling, referral to a specialist and/or OAT discontinuation if risks to the client or public outweigh benefits.

In BC, UDTs can be administered in a laboratory setting, in a primary care office or within treatment facilities via point of care immunoassay testing kits. The sensitivity of laboratory-based tests in detecting illicit opioid use ranges from 98% to 100%, with a specificity of 50%–91%. While point of care tests feature a sensitivity of 80%–98%, and a reported positive predictive value of 86% for opiates. Another study reported a 79.4% sensitivity for opiates, 65.4% for benzodiazepines, 33.3% for buprenorphine, 37.5% for cocaine, 78.3% for amphetamines and 92.5% for oxycodone/oxymorphone. Test sensitivity can decrease with longer detection times of substances and can otherwise vary according to personal patterns of use. Point of care test kits carry obvious advantages for clients, they feature cross-reactivity that could affect test results. Further, these tests typically cannot discern substances within a particular drug class. The increasing toxicity and adulteration of the illegal drug supply in BC, Canada and elsewhere thus further challenges interpretation of UDT results.

Additional guidance on the use of UDTs for OAT clients in BC was issued in 2021, updating guidelines published in 2017. The updated guidance recommends testing frequency should be determined by the client’s treatment response and specifies a maximum of 26 UDTs per year, or biweekly screening. During induction, UDTs for both buprenorphine/naloxone and methadone clients are recommended monthly or when clinically indicated. After completing induction, UDTs are recommended based on prescriber judgement. Given methadone’s pharmacological properties and longer half-life, previous UDT guidelines recommended more frequent testing as a means of monitoring diversion and patient response. While induction for buprenorphine/naloxone lasts 1–2 weeks, methadone induction can last weeks to months. Clients receiving take-home doses are recommended less frequent UDTs: 6–8 random tests per year for methadone clients and 2–4 for buprenorphine/naloxone clients. Although not described as contingency management, previous and current BC guidelines use UDTs to assess substance use abstinence and reward clients with take-home doses. However, recent evidence has shown that contingency management does not demonstrate added value for OAT retention, abstinence or adherence.

BC’s guidelines are more stringent than others internationally in recommending testing with a periodic frequency as opposed to occasional testing. While international guidelines on UDT frequency vary widely, guidelines typically provide distinct recommendations for the induction phase, postinduction (ie, reaching a dose that allows clients to be adequately supported in their daily lives without withdrawal symptoms or cravings) and for clients receiving take-home doses. Most of these guidelines acknowledge that buprenorphine/naloxone stabilisation is achieved earlier (as little as 3–5 days) in comparison to methadone, where more than 5 weeks are often needed to attain stabilisation. We summarise the recommendations from a convenience sample of three Canadian provincial and ten national guidelines on UDT protocols in North America, Australia and Europe (table 1). National guidelines from the USA, Canada and France recommend at least weekly UDT during OAT induction. Guidelines in the UK, Australia and New Zealand call for frequent UDTs during induction regardless of a specific frequency. From the thirteen clinical guidelines we assessed, eight recommended prescribers’ judgement to determine UDT frequency during induction.

Following successful induction and stabilisation, guidelines follow a frequency from monthly to random, with most guidelines recommending a minimum number of tests per year, ranging from 211–13 to 12.3 5 7 13 Other, 10 of 13 guidelines we assessed recommended prescriber judgement postinduction. For clients receiving take-home doses, Canadian guidelines specify testing frequency based on the type of OAT a client receives ranging from monthly testing to twice a year. Nine guidelines specify that clinical decision regarding take-home doses is necessary to dictate UDT frequency. Six of 13 clinical guidelines recommended more frequent UDTs for clients on methadone compared with buprenorphine/naloxone, including national and provincial guidelines in Canada. This was true both postinduction and for those receiving take-home doses.

The lack of concordance in clinical guidelines on the frequency of UDT alongside OAT is a reflection of the paucity of evidence supporting this practice. Evidence referenced in UDT guidelines was derived from randomised controlled trial study protocols and systematic reviews reporting inconclusive results or no significant differences for the effects of UDT on OAT retention. While one recent study from a single clinical practice in Massachusetts demonstrated the utility of UDT in validating self-reported illicit drug use, the systematic review by Dupouy et al concludes that UDTs had no or inconclusive evidence of effectiveness in improving substance use disorder treatment outcomes or retention. The systematic review included eight studies concluding that evidence related to UDTs was insufficient to inform clinical judgement and of poor quality. The testing frequency, study setting and type of assay were inconsistent among the studies included in the systematic review, ultimately leading to inconclusive results for the implementation of UDTs in the treatment of substance use disorder. A separate systematic review by McEachern et al, concluded that, compared with scheduled frequency,
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Minimum/maximum tests</th>
<th>Recommended UDT frequency for OAT</th>
<th>Take-home doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BC, CAN, (2021)</strong></td>
<td>Max. 26 at POC per patient/year</td>
<td>BNX: Monthly or frequently when clinically indicated. MET: Monthly. Frequently as required and when clinically indicated. If UDT is &lt;monthly, patient safety can be increased with DWI.</td>
<td>BNX: Scheduled when clinically indicated; ≥ 2–4 random tests yearly, frequency increased if there’s safety concerns. MET: Scheduled when clinically indicated with ≥6–8 random tests yearly, frequency increased if there’s safety concerns.</td>
</tr>
<tr>
<td><strong>CRISM, CAN, (2018)</strong></td>
<td>N/A</td>
<td>Varies per province. BNX: At least 1 UDT before initiation; After each patient appointment; Random. MET: At least 1 UDT before initiation; 1–2 per week to every 1–4 months.</td>
<td>Varies per province. BNX: Until clinical stability is achieved. MET: Combination of time since treatment initiation and repeated negative UDTs.</td>
</tr>
<tr>
<td><strong>CAMH, CAN, (2021)</strong></td>
<td>N/A</td>
<td>Weekly while stabilising. Every 1–3 months; Random.</td>
<td>BNX: ≥1 month (induction and dose escalation). MET: Same as BNX; More frequent to confirm abstinence or take-home doses; scheduled and random.</td>
</tr>
<tr>
<td><strong>SAMHSA, USA, (2021)</strong></td>
<td>N/A</td>
<td>≥1 before initiation; at providers discretion: frequency consistent with office visits, reduced as UDTs are frequently negative, and random as visits become less frequent.</td>
<td>Tailored to each patient.</td>
</tr>
<tr>
<td><strong>ASAM, USA, (2017)</strong></td>
<td>Min. 8 per patient/year</td>
<td>Weekly and on a random schedule; more frequent.</td>
<td>Tailored to each patient.</td>
</tr>
<tr>
<td><strong>CSAM, California, USA, (2019)</strong></td>
<td>Follows ASAM ≥1 monthly</td>
<td>Follows ASAM. POC tests are optional. Before treatment initiation; Random and at least once a month.</td>
<td>Lab testing required for state specified ‘regular’ take-home criteria changes.</td>
</tr>
<tr>
<td><strong>UK, 2017</strong></td>
<td>Min. 2 per patient/year</td>
<td>Random but frequent in initial phases; Tailored to each patient.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>NICE CKS, UK, revised 2022</strong></td>
<td>2–4 per year (stability)</td>
<td>Random but frequent; based on clinical judgement; tailored to each patient.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Australia, 2014</strong></td>
<td>Max. 36 per patient/year</td>
<td>Frequent during dose initiation and stabilisation; random; based on clinical judgement.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>New South Wales, AUS, 2018</strong></td>
<td>Max. 36 per patient/year</td>
<td>Based on treatment needs (high, medium, low). Minimum clinical and medical review (1–6 months). UDTs mimic medical and clinical review frequency.</td>
<td>Regular UDTs (risk assessment for take-home doses)</td>
</tr>
<tr>
<td><strong>Western Australia, AUS, 2014</strong></td>
<td>Max. 36 per patient/year</td>
<td>BUP: N/A MET: Random. Based on clinical judgement; Only if results are likely to be important.</td>
<td>Regular UDTs (risk assessment for take-home doses)</td>
</tr>
<tr>
<td><strong>New Zealand, 2014</strong></td>
<td>N/A</td>
<td>Each service is responsible for the frequency of UDTs. Random testing is recommended.</td>
<td>UDTs must be positive for prescribed OAT.</td>
</tr>
<tr>
<td><strong>France, 2004</strong></td>
<td>N/A</td>
<td>Compulsory before starting MET; As clinically required; UDTs related to medication allowance: 28 days for BUP; 14 days for MET</td>
<td>Tailored to each patient.</td>
</tr>
</tbody>
</table>

*BC guidelines in CRISM are excluded from the information contained in the table.

ASAM, American Society of Addiction Medicine; BC, British Columbia; BNX, buprenorphine/naloxone; BUP, buprenorphine (without naloxone); CAMH, Centre for Addiction and Mental Health; CKS, Clinical Knowledge Summaries; CRISM, Canadian Research Initiative on Substance Misuse; CSAM, California Society of Addiction Medicine; DWI, daily witnessed ingestion; MET, methadone; N/A, not available; NICE, National Institute for Health and Care Excellence; POC, point of care; SAMHSA, Substance Abuse and Mental Health Services Administration.
random UDTs can provide more information on the use of other substances in addition to OAT, though the review noted challenges in rural regions with limited laboratory testing resources. These reviews highlight the inadequacy of the underlying evidence base in supporting informed guidance on UDT frequency among people on OAT. Current evidence and guidelines thus rely heavily on clinical judgement, which can be prone to bias35 and may reflect clinical convention rather than evidence-based practice.39

These clinical conventions are influenced by the risk of diversion, though evidence to support this concern are also sparse. The limited evidence on the association between UDT frequency and opioid diversion is focused on chronic pain settings rather than OUD.40–42 BC Coroner’s reports indicate that opioid-related deaths with diverted OAT are relatively rare; of 333 unintended opioid-related deaths recorded between 2009 and 2013, methadone had been prescribed within 60 days in over 30% of fatalities related to prescription opioids, however, just 14 people (17%) did not have an active prescription.43 Out of 1854 overdose deaths in 2016–2017, 615 had drug toxicology testing completed where only 31 tested positive for methadone (5%) and none for buprenorphine/naloxone.44 Though relaxations in UDT monitoring frequency and take-home dosing occurred during the COVID-19 pandemic in the USA, deaths involving methadone declined before and after March 2020 while monthly overdose deaths not involving methadone increased by 78 deaths per month before March 2020, by 1078 deaths in March 2020 and by 69 deaths per month after March 2020.45

Otherwise, while full-agonist treatments such as methadone and slow release oral morphine are pharmaceuticals that have a higher risk of overdose among the opioid-naïve,1 OAT medications produce muted feelings of euphoria,46 and thus may be less desirable than other illicit options. Studies from harm reduction sites, inpatient and community-based clinics in BC, Massachusetts and Michigan, respectively, have supported this notion,47–49 and the introduction of fentanyl and illegal benzodiazepines50 to the drug supply in North America have further shifted the pattern of consumption as well as increased the tolerance level for opioids.51–54 Recent studies from two ongoing community-recruited cohorts of people who use drugs in Vancouver, BC, have shown that, due to the unpredictability of the illegal drug supply, some clients diverted OAT as a means to reduce fentanyl-related risks given its lower street cost than fentanyl.55 56 Qualitative studies of users of diverted OAT have indicated use as a signal of interest in receiving treatment for opioid use.57

Qualitative studies assessing clients’ perspectives on UDT have suggested that random drug testing, or pill counts, may be systemic barriers to daily life.58 59 UDTs and callbacks for clinic pill counts, along with limited access to take-home doses and daily witnessed ingestion requirements, have all been cited as challenges to stable retention in treatment.58 60 Patient dissatisfaction has been expressed in settings with inflexible clinic protocols, including shorter follow-up intervals following positive UDTs.60 Travel times and accessibility of laboratory services are noted barriers to treatment in BC in particular.61 Changing medication dosing based on UDT results can be perceived as paternalistic among individuals on

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**Figure 1** Databases, data extraction time frame and study period. Health administrative databases from British Columbia (BC), Canada. Medical Services Plan (MSP), Discharge Abstract Database (DAD), BC Vital Statistics (BCVS) and PharmaNet (PNET) available from 1 January 1996 to 31 August 2021. BC Corrections and Social Development and Poverty Reduction (SDPR) available from 1 January 2010 to 31 December 2020. National Ambulatory Care Reporting System (NACRS) available from 1 April 2012 to 31 August 2021. Perinatal Services BC (PSBC) available from 1 August 2000 to 31 March 2021. Study period begins on January 2010, ending on 17 March 2020. UDT; urine drug test.
aspects of clinical management of individuals on OAT.64

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mended in determining frequency of testing, it is unclear
Furthermore, as provider discretion is often recom-


<table>
<thead>
<tr>
<th>Component</th>
<th>Theoretical target trial</th>
<th>Emulating using observational data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>Individuals initiating OAT with no prior OAT dispensations.</td>
<td>Incident new-user design: People initiating OAT in BC between 1 January 2001 and 17 March 2020 with no history of OAT, dating back to 1 January 1996. Prevalent new-user design: people initiating OAT with no history of OAT in the past 30 days.</td>
</tr>
<tr>
<td>criteria</td>
<td></td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Treatment</td>
<td>Individuals are randomly assigned to a UDT strategy of none, weekly, monthly, quarterly or biannual screening.</td>
<td>Treatment strategies are assigned according to the frequency of UDT requisition records.</td>
</tr>
<tr>
<td>strategies</td>
<td></td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Primary</td>
<td>1. Treatment discontinuation 2. All-cause mortality.</td>
<td>Treatment discontinuation: interruptions in prescribed doses lasting at least 5 days for methadone and at least 6 days for buprenorphine/naloxone. All-cause mortality: the date of death was identified within the provincial Vital Statistics database.</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Follow-up</td>
<td>From treatment initiation until the earliest of treatment discontinuation, death, lost to follow-up or end of study follow-up</td>
<td>From treatment initiation until the earliest of treatment discontinuation, death, pregnancy, taper initiation or end of study period (17 March 2020).</td>
</tr>
<tr>
<td>Causal</td>
<td>Intention-to-treat and per-protocol effect</td>
<td>Per-protocol effect only.</td>
</tr>
<tr>
<td>contrasts</td>
<td></td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Analysis plan</td>
<td>Intention-to-treat analysis: Cox model estimating the relative risk of discontinuation across strategies. Per-protocol analysis: individuals are censored when they deviate from the initial treatment strategies. Per-protocol effect estimation requires adjustments for prebaseline and postbaseline prognostic factors associated with adherence to the strategies of interest.</td>
<td>As treatment strategies are not observed at baseline we follow a clone-censor-weight approach.</td>
</tr>
</tbody>
</table>

BC, British Columbia; OAT, opioid agonist treatment; UDT, urine drug test.

OAT.62 As such, despite guidelines emphasising patient-oriented care and advising that UDTs should not be used punitively, qualitative evidence demonstrates UDTs may foster distrust, damage the rapport between client and provider, and compromise treatment outcomes.63 Furthermore, as provider discretion is often recommended in determining frequency of testing, it is unclear whether client characteristics such as housing, employment, ethnicity or other factors are considered in decisions on the frequency of UDT monitoring and other aspects of clinical management of individuals on OAT.64

In summary, despite widespread recommendations for and use of UDT alongside OAT, there is sparse evidence that it represents an effective tool in helping to stabilise and prolong retention among individuals in treatment. Furthermore, qualitative evidence suggests it may serve as a barrier to treatment and compromise client-physician rapport. As such, we aimed to determine the safety and comparative effectiveness of alternative UDT monitoring strategies as observed in clinical practice among buprenorphine/naloxone and methadone clients in BC, Canada: 2010–2021. We note that while monitoring the risk of diversion is one of the uses of UDTs, this phenomenon is not directly observable in health administrative data. The question of diversion represents a distinct and testable hypothesis which lies outside the scope of this study. We will focus on the individual-level effects of UDT on OAT, which should be the primary consideration in clinical decision-making in this context.

METHODS
Study design
We propose a population-level retrospective study based on a linkage of eight provincial health administrative databases from BC, Canada to satisfy study objectives. The BC PharmaNet database,65 (capturing medication dispensations) will be used to identify all OAT dispensations for directly observed and take-home doses. As BC residents are required to enrol in the provincial single-payer health insurance plan, these records are comprehensive, excluding only dispensations to individuals in federal corrections facilities and during hospitalisation. These data are linked with records from the Discharge Abstract Database,66 (records of hospitalisations), Medical Services Plan,67 (MSP; physician billing records), BC Vital Statistics,68 (capturing deaths and their underlying cause), BC Provincial Corrections,69 (records of entry into incarcerations and releases to community), Perinatal Care Database,70 (capturing maternal/infant care and outcomes), National Ambulatory Care Reporting System Database,71 (capturing ED visits) and BC Social Development and Poverty Reduction database,72 (capturing social assistance receipt). The databases are deterministically linked using a unique, individual-level deidentified personal health number.73 A summary of the data extraction timeline from the various linked databases can be found in figure 1.

All individuals 18 years of age or older who initiate an OAT regimen between 1 January 2010 to 17 March 2020 will be included, providing as much complete follow-up as
allowed by the linked datasets prior to the disruptions in care prompted by the COVID-19 pandemic. Women with known pregnancy at OAT initiation will be excluded from the analysis, as care plans including urine drug screening frequency may differ during pregnancy from general care for OUD. Otherwise, UDTs are typically billed through MSP on a fee-for-service basis, however, some clients receive care in community health centres and other settings in which physicians bill the alternative payment plan.\textsuperscript{71} As a result, individuals with no MSP records will be censored within fourteen days of initial OAT dispensation. We will further censor individuals with a gap larger than 4 weeks between MSP records for OAT assessments and refills to account for switching care to a prescriber working under the alternative payment plan. The key elements of our proposed study design are summarised in table 2. Our planned study start is April 2023 and will be completed within a 6-month period.

Time zero will be defined as the date of first OAT dispensation in community. We will execute both incident user and prevalent new user study designs to ensure the clinical experience of both initial entrants and those accessing treatment in successive attempts are captured. The former design will exclude clients with any prior OAT dispensations (to be confirmed with data reaching back to 1 January 1996), while for the latter we will apply a 30-day washout period (ie, no OAT dispensations received in the prior 30 days) and otherwise adjust for past OAT exposure. All analyses will be stratified according to the form of medication received at OAT initiation. OAT episodes initiated using slow-release oral morphine or injectable forms of OAT—first introduced in BC as treatment options in 2017\textsuperscript{4} and 2016,\textsuperscript{75} respectively, will be excluded given the relatively limited experience and observational data available for these treatments. Some episodes may be initiated with multiple forms of OAT prescribed concurrently; these episodes will also be excluded.

Study follow-up will begin at treatment initiation and extends to the earliest of treatment discontinuation, death, pregnancy, taper initiation (date of second consecutive weekly dosage decrease), medication switch or end of study follow-up (17 March 2020). Observations will be updated on a weekly basis from the date of initiation of each episode until treatment discontinuation or censorship.

**Key measures**

The primary exposure proposed is the UDT monitoring strategy used during OAT. Specifically, we aim to compare UDT monitoring strategies which differ with respect to the frequency UDT billing records are observed. We will consider both static and dynamic strategies to account for differences in guideline recommendations during and after induction, as well as during receipt of take-home doses. We will initially consider five static monitoring strategies: no UDTs, and weekly, monthly, quarterly and biannual UDTs. The dynamic strategy allows for changes to UDT strategy after completing the induction phase of treatment. We will consider no UDTs, weekly and monthly prior to induction completion, and no UDTs, weekly, monthly, quarterly after induction, amounting to 12 possible strategies. We will have a 1-week allowance for UDT billing for the weekly strategy, 2-week allowance for the monthly strategy and a 6-week allowance for both the quarterly and biannual strategies. We chose these intervals to capture the range of recommendations on testing frequency, both in BC and internationally. These intervals are predetermined; however, the analysis will allow us to evaluate these strategies based on their observed frequency in real-world clinical settings.

Our primary outcomes proposed include OAT discontinuation, drug-related hospitalisation and all-cause mortality. Discontinuation will be defined as a break in prescribed doses lasting at least 5 days for methadone and at least 6 days for buprenorphine/naloxone, consistent with clinical guidelines on dose reversion following discontinuation.\textsuperscript{4} All-cause mortality is observed via linkage to vital statistics records.

**Statistical analysis**

Our proposed analysis is informed by analogous studies executed by the HIV-CAUSAL collaboration, comparing both static and dynamic CD4-monitoring strategies in people living with HIV.\textsuperscript{76–78} To emulate a ‘per-protocol’ target trial where each eligible individual is randomly assigned to 1 of the 5 static monitoring strategies (or 1 of the 12 dynamic monitoring strategies), we will create an expanded dataset by making five exact replicates of each individual (one per strategy). When an individual’s data are no longer consistent with a given strategy, we will artificially censor the corresponding replicate at that time. Replicates will be censored at the point of deviation from protocol; that is, when they are monitored sooner than indicated by a given strategy or when they are not monitored soon enough. The primary exposure will thus be fixed over time and capture the true observed frequency of UDTs.

**Inverse probability of censorship weight estimation**

Inverse probability of censorship weights (IPCW) will be constructed to account for the potential that the censoring strategy employed may introduce time-dependent selection bias. As treatment strategies are not observed at baseline, we propose to employ the ‘clone-censor-weight’ approach,\textsuperscript{79 80} which entails weighting each replicate by the inverse of the probability of having one’s own observed monitoring history at each time step.\textsuperscript{81 82} The weights will be defined as:

\[
SW(t) = \prod_{k=0}^{t} \frac{Pr[N(k) = 0 | C(k) = 0, N(k-1) = 0, A, Z, G, t = 1]}{Pr[N(k) = 0 | C(k) = 0, L(t) = 0, C(k) = 0, N(k-1) = 0, A, Z, G, t = 1]},
\]

where \(N(t)\) is the indicator of artificial censoring by changing the strategy at time \(t\), \(C(t)\) an indicator of censoring by loss to follow-up at time \(t\), and \(L(t)\) is any time varying factors at time \(t\). A is the strategy assigned at baseline, \(Z\) is the vector of baseline covariates and \(G\) is
an indicator for whether the baseline eligibility criteria are met.

Assumptions for IPCW to correct for informative censoring include: (1) no unmeasured confounders; (2) correct model specification (model to derive the weights); (3) positivity, entailing that the probability of deviating from protocol is non-zero at all follow-up times and for each client; (4) consistency, which entails the observed outcome under a treatment strategy is identical to what would have been observed had we assigned patients to the treatment strategy and (5) the censorship weights can remove imbalance between treatment strategies through standardised differences defined for each main factor as the weighted difference between groups divided by the weighted pooled SD. A variable with a standardised difference below 10% is considered balanced.

For the primary and secondary outcomes, we will present HRs obtained from a marginal structural Cox model with censorship weights and robust variance to control for repeated weekly observations and, in the prevalent new user design, repeated episodes within individuals.

\[
PL_{w} (\beta) = \prod_{i=1}^{N} \prod_{t=0}^{T_i} \left( \frac{Y_{it} \exp(\beta_1 L_{it} + \beta_2 A_{it})}{\sum_{k=1}^{K} Y_{kt} \exp(\beta_1 L_{kt} + \beta_2 A_{kt})} \right) dN_{it} w_{it}
\]

Comparing fixed monitoring strategies

We will first impose a fixed monitoring strategy featuring set UDT monitoring intervals that do not change throughout the OAT episode, from initiation to completion.

**Figure 2** Proposed dynamic strategy compared with delayed 1-month static strategy. (A) represents six hypothetical individuals’ contributions and trajectories in the dynamic strategy scenario, where a change in strategy is allowed after completing induction. (B) displays the same six hypothetical individuals for the static strategies under the 1-month start scenario. Person A in (A) switches from weekly to monthly monitoring after reaching the postinduction phase, and therefore, is not censored; however, under the 1-month static scenario this individual is censored after week 7 as the UDT requisition on week 5 implied the individual was still following the weekly strategy. Note that person D, F are excluded in (B) as they have no UDTs within the first month and are thus not eligible for the 1-month and 3-month start analyses. In (A), person E and B are both censored prior to the postinduction phase, as (B) shows they had switched to the monthly UDT strategy. However, in (B) they are not as the 1-month start allows for the strategies to reset, and therefore, they are included in the 1-month strategy until they discontinue OAT. Person C remained uncensored in both (A,B) as they were consistently on the 1-month UDT strategy under both scenarios. OAT, opioid agonist treatment; UDT, urine drug test.

**Figure 3** Covariates derived from the administrative databases for previous studies. ED, emergency department; OAT, opioid agonist treatment.
discontinuation or censorship. For example, considering a weekly strategy, UDT is required every 1–14 days due to the allowance period; otherwise individuals are censored for deviation from the monitoring strategy. This form of censoring is informative, similarly to the informative censoring introduced with the replicates, and IPCW will be implemented to correct for the informative censoring.

Comparing dynamic monitoring strategies
We also propose to construct dynamic strategies that allow change over time during the treatment episode, pending sufficient sample sizes to achieve model convergence. This approach will allow for a change in UDT frequency once induction is completed, defined as the first 2-week period of with no change in the average daily dosage.84 This strategy is proposed based on several guidelines recommending a change in UDT frequency after completing induction. An illustration of the counting process and censoring rules for this and other study designs is provided in figure 2. This will result in 12 different levels of the primary exposure, which is expressed as a bivariate pair of strategies preinduction and postinduction. If the strategy change is not as defined, such as a strategy change before completing induction or another change after induction, it will be censored. Similar to the fixed strategy approach, the informative censoring introduced in this scenario requires correction through IPCW.

Covariate selection
While the assumption of no uncontrolled confounding cannot be verified in observational settings, we will adjust for all potential confounders available within our linked database,85 such as recent drug-related hospitalisation or ED (figure 3). We previously identified these covariates by conducting a systematic literature review of articles published up to 2 September 2019 regarding factors associated with OAT retention among.86 We propose to augment this listing with additional variables available in our linked administrative data which we hypothesise to influence both UDT monitoring frequency and OAT retention. These additional measures will include variables to capture the physician–client relationship that we hypothesise will impact adherence to the assigned strategy and other time varying covariates (figure 4). We will construct variables on the proportion of other non-OAT billing records or prescriptions from the same physician (polychotomous), and the clients’ relationship with general practitioners (polychotomous)87 based on the amount and proportion of physician billing records. We hypothesise that UDTs prior to episode initiation may influence censoring of the ‘no UDT’ strategy in particular. We, therefore, propose to include a covariate to capture whether an initial UDT was provided within 7 days of treatment initiation (dichotomous). All time-varying covariates will be updated weekly, pending achievement of model convergence. Results from UDTs will not be available in the administrative data, therefore, we will be unable to observe whether changes in strategies are due to positive or negative test results. As BC clinical guidelines recommend that UDTs not be used punitively, results should not impact changes in testing schedules and our methodology will still provide recommendations based on the assumption the results of UDTs will not be used punitively.
**Table 3** Proposed subgroup and sensitivity analyses

<table>
<thead>
<tr>
<th>Proposed sensitivity analysis</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sample restriction</td>
<td>To account for individuals that may have more strict or lenient UDT strategies due to OAT experience.</td>
</tr>
<tr>
<td>Additional stratification by OAT history</td>
<td></td>
</tr>
<tr>
<td>Allowing for medication switching*</td>
<td>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 or other medication.</td>
</tr>
<tr>
<td>Extend wash-out period to 90 days</td>
<td>To assess the sensitivity of gap times between episodes and account for any changes that may be impacted by more recent OAT experience.</td>
</tr>
<tr>
<td>Inclusion criteria requiring past mental health condition</td>
<td>Individuals with mental health conditions may have different care requirements and results may be impacted based on differing care.</td>
</tr>
<tr>
<td>Inclusion criteria requiring past non-opioid substance use disorder diagnosis</td>
<td>Individuals with prior indications of non-opioid substance use disorder may require different monitoring strategies based on care requirements.</td>
</tr>
<tr>
<td>2. Timeline restriction</td>
<td></td>
</tr>
<tr>
<td>Introduction of fentanyl in the illegal drug supply (2014)</td>
<td>The change in the illegal drug supply may have altered both treatment retention (outcome), and the extent to which prescribers ordered UDT screens (exposure).</td>
</tr>
<tr>
<td>3. Exposure classification</td>
<td></td>
</tr>
<tr>
<td>Stratified analyses on UDT modality—point-of-care and lab-based</td>
<td>Point-of-care UDTs, introduced in 2009 with lab-based requiring individuals to go to a lab after the physician makes a requisition. Reclassifying the exposure can measure if there is a difference in retention for the type of UDT. This approach has nine different static strategies instead of five. Further stratification by immunoassay type is not possible as immunoassay information is not available for point-of-care testing.</td>
</tr>
<tr>
<td>Increasing the allowance time between UDTs for the strategies</td>
<td>Ensure the results are not sensitive to the defined allowance time for each strategy.</td>
</tr>
<tr>
<td>4. Model specification</td>
<td></td>
</tr>
<tr>
<td>Starting study from 3 months into treatment</td>
<td>UDT monitoring strategies may change over time in practice. Starting the study from a predefined time point may account for the differences in treatment strategies.</td>
</tr>
<tr>
<td>Starting study at first take-home dose postinduction</td>
<td>UDT monitoring strategies are different for individuals who receive take-home dosing. Guidelines suggest take-home dosing should be available only when a client is stabilised and UDT guidelines for monitoring are stricter during induction than for those receiving take-homes.</td>
</tr>
<tr>
<td>Dynamic strategies to account for adaptive clinical practice</td>
<td>Static strategies may not fit for clinical practice when treatment strategies change over time after stabilisation or when take-home doses are received.</td>
</tr>
</tbody>
</table>

*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 (switching) do not follow BC. BC, British Columbia; BUP, buprenorphine; MET, methadone; OAT, opioid agonist treatment; UDT, urine drug test.

**Subgroup and sensitivity analysis**

We will execute sensitivity analyses by restricting the cohort and study timeline, as well as altering the definitions of both the artificial censuring rules used to construct the primary exposure and the primary outcome (table 3). For similar reasons to proposing the dynamic strategies we propose to restrict the cohort to those retained for at least 4 weeks and 12 weeks as well as those who receive take-home doses postinduction and who had received at least one UDT within these time frames (implying exclusion of the ‘no UDT’ strategy in this sensitivity analysis). We will execute the same static monitoring strategy, using the time from their last recorded UDT (ie, occurring before the 12-week time point) for censorship assignment to avoid misclassification, while also adding a covariate indicating their monitoring strategy in weeks 0–12 to account for potential confounding by indication. This will provide an additional robustness check for the proposed dynamic monitoring strategies using the simpler fixed monitoring strategy analytical setup. To prevent immortal time bias, all inferences on this selected subgroup will be qualified accordingly, to ensure no comparisons are made with individuals not reaching the temporal threshold. Applicable results will be presented in tornado diagrams centred on the baseline relative risk from each analytical strategy. Any post hoc additions to or deviations from this protocol will be identified as such in final reports.

**Patient and public involvement**

While no patients were explicitly involved in the design of this study, its conception was influenced by prior engagement with local advocacy organisations of people who use drugs and people who have accessed OAT.⁶¹ Qualitative feedback on this and other related objectives outlined in the parent grant R01DA050629 were used to prioritise this analysis given the potential impact on client engagement. Findings will be shared with local advocacy groups following completion of the analysis.
ETHICS AND DISSEMINATION

Databases are 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. This study is classified as a quality improvement initiative. Providence Health Care Research Institute and the Simon Fraser University Office of Research Ethics determined the analysis met criteria for exemption per Article 2.5 of the 2018 Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. This study will follow international guidelines for study conduct and reporting, including Strengthening the Reporting of Observational Studies in Epidemiology guidelines. We will otherwise administer the ‘Risk of Bias in Non-Randomised Studies-Of Interventions’ tool to a multidisciplinary scientific advisory committee for ex post evaluation. Results will be disseminated to local advocacy groups and decision-makers, national and international clinical guideline developers, presented at international conferences and published in peer-reviewed journals electronically and in print. This study will generate robust evidence on how UDT frequency compares in real-world practice for OAT retention over the long term in the interest of improving retention in these essential medications.87

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