STUDY PROTOCOL

REVISED Impact of guidance issued during COVID-19 to expand take-home doses of opioid agonist treatment (OAT) in Ireland: protocol for a population-based analysis of prescribing practices and patient outcomes 2018 to 2023

[version 2; peer review: 2 approved, 1 approved with reservations]

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Abstract

Background

It is increasingly suggested that clinical guidelines and practices be updated to permanently expand relaxation around access to opioid agonist treatment (OAT) take-home doses after COVID-19. Despite a risk of OAT drug diversion, flexibility in take-home doses is valued by patients and associated with improved quality of life and retention. However, few studies have examined the effects of changes to take-home dose policies on prescribing practices and patient outcomes, with mixed results.

Aims

This protocol relates to three inter-related studies. The first study will examine the impact of guidance issued on March 13th 2020 to all clinicians involved in the delivery of OAT to give the maximum number of take-home doses having given due consideration to the safety of the patient, on prescribing practices for take-home doses of methadone and buprenorphine in primary care. The second study will

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examine the association between increased take-home doses of OAT following March 13th 2020 guidance and treatment discontinuation in primary care. The third study will examine methadone-related deaths in Ireland before and after the guidance issue, and whether methadone-related deaths varied by whether the deceased was on OAT treatment at the time of death.

Methods

Retrospective observational studies will be carried out. The first study will use a time series design to examine changes in prescribing practices of take-home doses. The second study will use a retrospective cohort study design with proportional hazard Cox models to evaluate the association between increased take-home doses and treatment discontinuation. The third study will use a repeated cross-sectional study design with interrupted time series analysis, stratified by OAT treatment status, to assess changes in methadone-related deaths.

Discussion

It is anticipated that the studies will generate evidence with potential to inform both clinical and policy decision making with respect to take-home dosing of OAT.

Keywords
Opioid Agonist Treatment, Take-home dosing, Opioid Use Disorder, Covid-19, retention, mortality

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REVISED **Amendments from Version 1**

The updated version of this protocol includes an improved background section with an additional paragraph introducing more explicitly the need for the proposed studies. We also highlighted additional possible contributions put forward by *Aldabergenov et al.* to explain the increase in methadone-related mortality observed by in the UK. We clarified the formulation of the objectives. In the methods section, a setting paragraph providing a detailed description of the delivery of OAT in Ireland, was included. For the second objective, we modified the index date to take place at the end of the exposure window for both exposed and unexposed groups so individuals are at risk of discontinuation from the onset of observation period and modified Figure 1 to provide greater clarity on the cohort and exposure groups. Finally, in the discussion section, we revised the manuscript to remove any doubt for the reader that the study designs cannot establish causality and any observed associations will only remain hypothesis generating.

Any further responses from the reviewers can be found at the end of the article

Introduction

Ireland has one of the highest rates of problematic opioid use in Europe, with an estimated prevalence rate of 7 per 1,000 population, corresponding to 19,875 problematic opioid users in 2019[1]. Drug overdose remains the primary cause of mortality among people with an opioid use disorder (OUD), and is increasing in the USA, the UK, Canada and across Europe, including Ireland[2]. Preventive interventions, including opioid agonist treatment (OAT), contribute to reducing overdose mortality. OAT, with methadone or buprenorphine, is first line treatment for OUD, and is available free of charge to all individuals with OUD in Ireland as it is safe and effective in suppressing illicit opioid use[3,4], improving mental and physical well-being[5], and reducing risk of all-cause, and overdose mortality[6]. However, a recent global systematic review identified that mortality rates are six times higher when a person drops out of OAT, with the greatest risk observed in the first four weeks post treatment cessation[7]. These findings suggest that enhancing treatment retention is critical for preventing mortality among people with OUD. Nevertheless, retention remains low internationally, with a median 12-month retention rate of 57% found in a systematic review of 37 studies[8].

One challenge to treatment retention is the prolonged requirement for daily observed dosing, also referred to as supervised dosing, in community pharmacies or addiction clinics[8]. The National Clinical Guidelines for OAT in Ireland, developed in 2016, recommend methadone as the drug of first choice in the treatment of OUD, with daily supervised consumption during the induction and stabilisation phase. In the maintenance phase, when a person demonstrates ongoing stability, a reduction from daily supervised consumption may be considered, with a maximum of 6 days' supply of take-home doses. Although the timing and frequency of take-home doses of OAT differ between countries, people are generally only considered eligible for progressively unsupervised (take-home) dosing after completing a minimum time in treatment with steadily negative drug screening tests[7]. These guidelines acknowledge that facilitating access to take-home doses, with the objective of retaining a person in OAT and therefore reducing their individual risk of death needs to be balanced against the risk of increased availability of illicit methadone or buprenorphine resulting from diversion, raising the risk of methadone or buprenorphine related mortality at a population level.

The public health measures introduced in 2020 to suppress COVID-19 made OAT provision under existing regulations and clinical guidelines difficult, as services such as supervised dosing are profoundly dependent on regular in-person health care delivery[9]. In response to these challenges, many countries introduced longer take-home dosing policies for dispensed OAT medications[10]. Contingency OAT guidelines, recommending increased access to buprenorphine and the relaxation of take-home dosing, were introduced in Ireland in March 2020, to facilitate quick and uninterrupted access to OAT during the pandemic. On March 13th 2020, guidance was issued to all clinicians involved in OAT delivery to give the maximum number of take-home doses having given due consideration to the safety of the patient[11].

It is increasingly suggested that clinical guidelines and practices should be updated to permanently expand relaxation around access to OAT take-home doses[10,12–14], as flexibility in take-home doses is perceived positively by people and associated with improved retention and quality of life[15–17]. However, few studies have examined the effects of changes to take-home dose policies on prescribing practices and patient outcomes, with mixed results[7,14,18–20]. A study conducted in Ontario, Canada observed that the flexibility in take-home dosing was primarily seen in people who were already receiving take-home doses prior to the pandemic. By November 2020, prescribing for take-home dosing had largely returned to pre-pandemic patterns[18]. Nevertheless, evidence from Canada indicates that providing increased take-home doses of OAT was linked to reduced treatment dropout at six-months, and with no increase in overdose mortality during the same period[7]. While encouraging, these findings should be interpreted with caution as overdose deaths were only examined among those in treatment and for a relatively short duration of follow-up[7]. Mixed evidence is emerging from the US regarding mortality[14,20], with one study supporting a permanent expansion of take-home dosing as they observed no change in methadone-related deaths following increased take-home doses[14], and another warning against permanently relaxing take-home dosing as they observed an increase in methadone-related deaths after the policy change[20]. The situation in Europe may be different to North America as the European Union Drugs Agency (EUDA) reports an increasing burden of diversion and misuse of OAT medications, with drug-related deaths and treatment demand associated with these medications increasing over the past decade. A retrospective study of post-mortem toxicology of OAT-related deaths in England, observed that methadone-related mortality grew by 64% in the first wave of COVID-19, and this increase

was greatest among cases where there was no methadone prescription at time of death. The authors acknowledge that multiple factors could account for the increase in methadone-related deaths in those not prescribed OAT, including reduced access to psychological supports, harm reduction and out reach services such as naloxone among those not in treatment. The increase in methadone-related death seen in people not prescribed it raises the possibility that an important change to the drug market that occurred during the COVID-19 pandemic in England was an increased availability of methadone. This possibility raises the question of diversion[21]. Prescribed and non-prescribed buprenorphine related mortality remained low and did not significantly change[21]. In Ireland, methadone is the most common opioid implicated in drug poisoning deaths, with numbers increasing between 2012 and 2021[22].

Although guidance regarding OAT take-home dosing changed in Ireland in 2020, there is no evidence published on the actual changes in prescribing practices of take-home dosing in Ireland, and whether any such changes were sustained over time. In addition, it is important to assess any potential impacts of changes to take-home dosing on patient outcomes, including treatment discontinuation, a known risk factor for mortality, and overdose deaths. We will address these questions through three interlinked objectives:

(1) Examine the impact of changes in guidance for the provision of OAT take-home doses on prescribing practices for take-home doses of methadone and buprenorphine in primary care

(2) Assess the association between increased take-home doses of OAT, following changes in guidance, and treatment discontinuation in primary care

(3) Examine methadone-related deaths before and after changes in guidance for the provision of OAT take-home doses and by treatment status at time of death (i.e. whether the deceased was in active OAT treatment vs. out of OAT treatment at the time of death)

Methods

Setting

Methadone and buprenorphine are available free of charge to all persons undergoing OAT for opioid use disorder in Ireland. In 1998 the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations were introduced in Ireland, which involved the establishment of a national register, the Central Treatment List (CTL). The Misuse of Drugs Regulations were updated in 2017 to authorise access to buprenorphine or buprenorphine/naloxone for OAT on the same statutory basis as methadone. All individuals in receipt of OAT are registered on the CTL, with each person linked to one specific prescriber and a single pharmacy dispensing site. A total of 10,251 people were in receipt of OAT in 2019[23]. OAT is provided in specialist outpatient addiction clinics or in primary care settings, with approximately 60% of people in treatment in specialist addiction clinics[24,25]. Previous studies of OAT in Ireland suggest that access to take-home doses is greater in primary care than in outpatient clinics[26,27].

Data sources

Pharmacy claims. All OAT (methadone and buprenorphine) primary care prescriptions dispensed in community pharmacies in Ireland are recorded on the Health Service Executive Primary Care Reimbursement Services Opioid Substitution Treatment Scheme (PCRS–OSTS). Anonymised individual level dispensing records for methadone and buprenorphine for the years 2018 to 2023 inclusive will be provided for this project. Records include patient sex, year of birth, anonymised prescribing doctor number, geographical area, drug dispensed, prescription start and end dates, daily dose, number of days at dose, total quantity dispensed, supervised dosing in pharmacy, and number of days supervised. Drug dispensed are coded using the World Health Organisation's Anatomical Therapeutic Chemical classification.

Drug poisoning deaths. The National Drug Related Death Index (NDRDI) is an epidemiological database that records all poisoning deaths by drugs and/or alcohol. It follows the EUDA standard protocol to collect data on drug-related deaths[28]. To ensure completeness, mortality data are collected from multiple sources and cross-checked to avoid duplication. Coronial files are the primary source and include post mortem toxicology reports. Other data sources include: General Mortality Register through the Central Statistics Office (CSO), acute hospitals data via the HSE Hospital In-Patient Enquiry (HIPE) system and the CTL. Drug poisoning deaths are defined as deaths directly due to the toxic effect of one or more drugs, as directed by the Coroner on the certificate of death registration and/or the record of verdict. Up to 15 drugs implicated in drug poisoning deaths by the Coroner are included in the NDRDI. Anonymised individual level data on drug poisoning deaths will be provided for the years 2018–2023, including the deceased's month and year of death, geographic area, socio-demographic information (year of birth, sex, homeless status at time of death), history of chronic pain, problem drug use at time of death (history of opioid dependency; history of opioid use; history of previous overdose), drug treatment history (on OAT at the time of death as recorded in Central Treatment List), and whether methadone and/or buprenorphine were implicated in the poisoning death.

Study 1. Impact of guidance recommending increased access to take-home doses of OAT medications on OAT take-home dose prescribing in primary care

Design. We will conduct an interrupted time series design of all people dispensed OAT (methadone or buprenorphine) in primary care in Ireland, as recorded in the PCRS-OSTS, between January 2018 and December 2023.

Outcome. The percentage of people dispensed a range of take-home dosing categories (0, 1 to 6, 7 to 13, ≥14 days) of (a) methadone and (b) buprenorphine will be calculated for each week of the study period. The numerator will be the weekly count of people dispensed each category of take-home dosing, with

the total number of people dispensed the medication during the same week as the denominator.

Statistical analysis plan. Similar to a recent Canadian study[18], we will use autoregressive integrated moving average (ARIMA) models to examine the impact of guidance issued to prescribers on the weekly percentage of people dispensed each category of take-home dose[29]. Any underlying long-term trend will be assessed through confirming stationarity using the augmented Dickey-Fuller test[18,30]. The final models will be identified using the residual autocorrelation function (ACF), partial autocorrelation function (PACF), and inverse autocorrelation function plots and the Ljung-Box test for white noise[18,29,30]. To identify the impact of the guidance, a step change function will be included in the model taking the value of 0 before guidance release on March 13th 2020 and 1 afterwards[29].

The analysis will be stratified by OAT drug (methadone or buprenorphine), sex, age class, and geographic area to identify any specific subgroup patterns. As there may be a reluctance to prescribe take-home doses to people on high dose methadone due to a higher risk of opioid-related overdose than buprenorphine[6], we will also stratify by methadone dosage (maximum methadone daily dose <100 mg vs. ≥100 mg). In addition, to account for practice variation at the prescriber level, we will stratify models by prescriber OAT practice size. For each prescriber, the OAT practice size will be defined as the total number of unique people who were prescribed methadone or buprenorphine during the 4 weeks prior to the guidance release, and categorised into quartiles.

Study 2 – Association between clinical decision to increase number of take-home doses of OAT and OAT discontinuation in primary care

Design. We will conduct a retrospective cohort study to examine the association between increased take-home dosing and treatment discontinuation among people in active treatment with OAT in Ireland on March 13th 2020 (i.e. before the introduction of guidance to increase take-home dosing). The accrual window will be defined as the four weeks preceding the guidance release (February 15th to March 13th 2020). The cohort will be defined as individuals dispensed OAT through the PCRS-OSTS on at least 14 out of 28 days during the accrual window and dispensed on March 13th 2020.

Exposure: increase in OAT take-home doses. Individual baseline take-home dosing regimen will be defined as the highest weekly number of take-home doses observed during the accrual window. The exposure window will be defined as the 4 weeks following the guidance change (March 14th, 2020, to April 10th, 2020). We will calculate the number of take-home doses on each OAT prescription during the exposure window. Using these data we will classify individuals as exposed if they experience an increase in their weekly number of take-home doses by at least ≥1 day(s) during the exposure window compared to their baseline regimen. Individuals whose take-home dose regimen did not meet this criteria will be classified as unexposed. The index date will be defined as the first day after the exposure window, i.e. April 11th 2020. All unexposed individuals will be required to be actively treated with methadone or buprenorphine until the end of the exposure period to ensure comparability between groups. People who had their OAT drug changed (from methadone to buprenorphine or vice versa) during the accrual or exposure windows will be excluded. Figure 1 displays the definition of the study cohort and exposure groups.

Outcome. OAT prescription coverage will be determined for each individual using the recorded prescription details. The primary outcome will be the time to treatment discontinuation, defined as the time between index date and first subsequent OAT discontinuation. OAT discontinuation will be defined as not receiving a new methadone or buprenorphine prescription within 14 days of the end of coverage of the previously dispensed OAT prescription. We use this definition based on previous studies[7,8], and following consultation with clinical and Patient and Public Involvement (PPI) partners.

Statistical analysis plan. We will use a Cox proportional hazards (PH) model to compare treatment discontinuation at both 6 and 12 months between exposed and unexposed individuals, adjusting for potential confounders. Based on previous literature[8] and clinical judgement, potential confounders include: age, sex, age at first OAT treatment in primary care, prescriber OAT practice size (as defined above), methadone or buprenorphine daily dose, and region. Observations will be right-censored at the 6 and 12 months endpoints. The PH assumption will be confirmed by visually inspecting the log-negative-log survival curves and the Schoenfeld residuals to examine model fit. Where the PH assumption is not verified, stratified models or time interaction models will be used if appropriate. Adjusted hazard ratios and corresponding 95% Confidence Intervals (CIs) will be presented.

A sensitivity analysis will be conducted using a continuous variable for exposure as the number of additional days receiving take-home doses of methadone or buprenorphine during the exposure window compared to the baseline level. Furthermore, the proposed analysis is based on changes to take-home dose regimen during the exposure window, and does not account for any additional changes in dispensing patterns over the study follow-up. Therefore, we will also model time to discontinuation accounting for variations in take-home doses over time by including take-home dose as a time-varying covariate using an extended Cox model[31].

Study 3. Methadone-related deaths before and after prescribing guidance to expand take-home methadone doses

Design. Using drug-related death data, we will conduct a repeated cross-sectional study examining the number of methadone-related deaths between 2018 and 2023. All methadone and buprenorphine related deaths (alone or in combination with other substances) from January 2018 to December 2023 recorded by the NDRDI will be included.

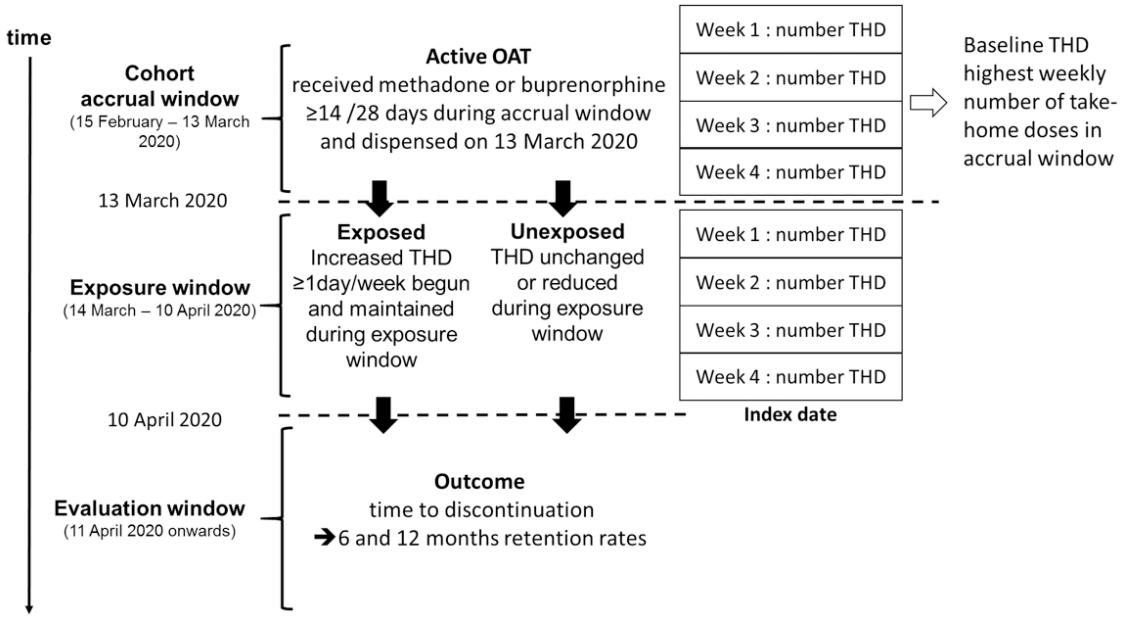

Figure 1. Definition of Study Cohort and Exposure Groups in Study 2.

Outcome. The primary outcome will be the bi-monthly number of methadone-related deaths, defined as deaths directly due to the toxic effect of methadone, alone or in combination with other substances, as directed by the Coroner on the certificate of death registration and/ or the record of verdict, between January 2018 and December 2023. We will report the number of buprenorphine-related deaths but anticipate the numbers will be too low to analyse. We chose bi-monthly, as monthly figures may be too small, based on data from the NDRDI which reports 122 to 129 annual methadone-related deaths between 2018–2021[22].

Statistical analysis plan. Interrupted time series analysis (ITSA) will be used to model trends in methadone-related deaths. We will conduct separate segmented regression models for the primary outcome, assessing change in bi-monthly level and slope, and present regression coefficients (β) and 95% CIs before and after the guidance change. Any potential lag time between the guidance change and its implementation will be informed by the first study. To assess for residual autocorrelation, ACF and PACF plots will be visually inspected and the Ljung-Box test for white noise will be used[29]. We will conduct a stratified analysis for (1) deaths among people on OAT at time or death and (2) deaths among those not in treatment at the time of death.

We will also assess whether bi-monthly non-methadone poisoning deaths (i.e. drug-related deaths where methadone was not implicated by the Coroner on the certificate of death registration and/ or the record of verdict) provide a secular trend comparison, which will help assess whether a change in the trend line of methadone-related deaths is associated with the take-home policy change or could be attributed to other factors affecting trends in drug overdose deaths more generally. As suggested by Harris and colleagues, non-methadone deaths satisfy the 2 *a priori* criteria for a secular trend variable: a theory-based association between methadone and non-methadone deaths (i.e., methadone and non-methadone related deaths may be subject to the same broader social factors, including COVID-19 related context e.g. lockdowns, social distancing, self-isolation, closure of non-essential services, increase in telemedicine, and restrictions on public gatherings etc.) and the absence of a theory-based association with the guidance change (i.e., trends in non-methadone poisoning deaths are not dependent on a change in the methadone take-home policy)[19]. A third, empirical, criterion to consider is whether methadone and non-methadone poisoning deaths are closely or moderately correlated before the policy change. If the two outcomes are not correlated, in the pre-intervention period then non-methadone poisoning deaths is not appropriate for post-intervention comparison. Two recent studies, reporting conflicting findings, used non-methadone poisoning deaths for secular trend purposes, but without providing empirical justification[14,20]. We will use Spearman ρ to measure the pre-intervention secular trend correlations between methadone and non-methadone poisoning deaths before the guidance change.

All analyses will be conducted using SAS software (Enterprise Guide v 7.1, Base v 9.4; SAS Institute, Cary, NC) and use a type-1 error rate of 0.05. We will present our findings following the guidelines outlined in the Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement[32,33].

Discussion

Strengths and limitations

The changes in guidelines implemented during the COVID-19 pandemic demonstrated the healthcare system's capacity for rapid and substantial adaptation. However, there is a need

for published evidence on prescribing practices and patient outcomes associated with these changes[10]. This study aims to address significant gaps in knowledge by investigating the impact of guidance on take-home dosing in primary care in Ireland, as well as key outcomes such as discontinuation and mortality. By including all people on a national prescribing register over a seven-year study period, the external validity will be high. We will use appropriate statistical methods such as ARIMA and PH models and conduct gender and age-sensitive analyses to provide a comprehensive perspective. To the authors' knowledge, these will be the first studies to report on the impact of COVID-19 related OAT guidance on observed prescribing practices, treatment discontinuation and OAT drug related mortality in Ireland. In a context of mixed international findings, this will provide important evidence to inform future service delivery.

However, some limitations of the studies can be anticipated. Firstly, the observations will be limited to changes in take-home doses and discontinuation in primary care settings, excluding data from specialist centres typically attended by less stable or homeless people. Approximately 40% of people receiving OAT in Ireland are treated in primary care settings[24]. For treatment discontinuation outcomes, interruption of community dispensing for 14 days or more will be classified as treatment cessation. However, people may experience interruptions due to transfer to specialist services, hospital, prison, moving abroad, or death, which will be incorrectly classified as discontinuing treatment. There will be no possibility of quantifying this misclassification bias, however the primary care OAT cohort is generally regarded as more stable, and less likely to be incarcerated, or hospitalised for overdose than people attending specialist clinics. Secondly, for the methadone-related mortality, although we can determine whether the deceased was on OAT at the time of death, we will be unable to ascertain whether methadone was prescribed or diverted, as there is no linkage between prescribing practices and mortality data. Thirdly, the simultaneous increase in individuals receiving OAT in Ireland[23], and additional OAT changes such as reduced frequency of urine drug testing[16], alongside the implementation of guidance on take-home dosing introduce residual confounding that may influence the outcomes examined. Furthermore, while the studies employ robust methods like ITSA and comparative trend analysis of non-methadone-related deaths to explore the relationship between the intervention and observed outcomes, the study designs cannot establish causality. The Bradford Hill criteria can be used to assess causal inference; nonetheless any observed associations will remain hypothesis generating only.

Public and Patient Involvement (PPI)

This protocol was developed in active partnership with PPI co-author AOH, Community Coordinator at UISCE – the National Advocacy Service for People who use Drugs (PWUD) in Ireland. UISCE is currently the advocate/representative for the community of PWUD at several treatment and harm-reduction strategic committees in Ireland. Ongoing engagement with PWUD will take place, particularly those who may access OAT, throughout the lifetime of this project. Several meetings with service users (men and women) will be organised to support the development of the project, interpretation of the results and to guide meaningful dissemination among service users, ensuring this project is truly participatory from a PPI perspective. Throughout the course of this project, we will adopt the Guidance for Reporting Involvement of Patients and the Public (GRIPP) standardised reporting guideline. Its use will ensure the contribution of the PPI project team member will be fully communicated in dissemination and provide evidence of the value of stakeholder, public and patient involvement in health services research.

Ethics and consent statement

This project has been approved by the Royal College of Surgeons in Ireland Research Ethics Committee (REC202407028) on September 10th 2024. The studies were designed to comply with the European General Data Protection Regulation (GDPR) 2018, the Data Protection Act 2018, and the relevant provisions of the Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations. Since only anonymised data will be used in this project, it falls outside the scope of the GDPR. and participant consent was waived by the ethical approval committee. The data controllers will satisfy themselves that the data is truly anonymous such that information related to an individual entity or person cannot be directly or indirectly identified. No information available to the researchers will allow for re-identification of individuals within the data. We will implement good data management practices and security measures for all information used in this study, including the establishment of transparent data sharing agreements with data controllers. Furthermore, we will ensure that data is published only in aggregated formats, with any data point representing fewer than five individuals being suppressed to maintain confidentiality. Comprehensive data protection impact assessments have been conducted in compliance with the Data Protection Act. Data security and management strategies will focus on ensuring data quality, and using encrypted, password-protected storage devices accessible only to authorised researchers.

Dissemination

Findings will be disseminated through publication in peer-reviewed journals and to relevant national and international conferences. We will also publish our research findings in *UISCE magazine*, a peer-led publication disseminated nationally to services attended by PWUD.

Conclusion

There is a need for published evidence on the impact of OAT guidance changes, particularly around take-home dosing. Across three studies, this project will use routinely collected data to provide insight on changes in prescribing practices, treatment discontinuation and OAT drug-related mortality associated with the take-home dosing guidance changes introduced during the pandemic. In a context of mixed international findings, these studies have the potential to inform future policy and service delivery, benefiting people receiving OAT.

Abbreviations

ACF	Autocorrelation Function
ARIMA	Auto Regressive Integrated Moving Average

CI	Confidence Interval
EUDA	European Union Drugs Agency
GDPR	General Data Protection Regulation
GRIPP	Guidance for Reporting Involvement of Patients and the Public
ITSA	Interrupted Time Series Analysis
NDRDI	National Drug Related Death Index
OAT	Opioid Agonist Treatment
OUD	Opioid Use Disorder
PACF	Partial Autocorrelation Function
PCRS-OSTS	Primary Care Reimbursement Services - Opioid Substitution Treatment Scheme
PH	Proportional Hazards
PPI	Patient and Public Involvement
PWUD	People Who Use Drugs

Data availability

No data are associated with this article.

Contributions (CRediT taxonomy)

GC and EK Conceptualisation

GC, EK, LD, KEB, DC, AOH Funding acquisition

GC, LD and KEB Methodology

GC and LD Writing – original draft

GC, EK, LD, KEB, DC, AOH, SL Writing – review and editing

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Open Peer Review

Current Peer Review Status: ✔ ✔ ?

Version 2

Reviewer Report 30 May 2025

https://doi.org/10.21956/hrbopenres.15533.r46663

✔ **Eugenia Oviedo-Joekes**
The University of British Columbia, Vancouver, British Columbia, Canada

The authors have done a thoughtful work in this second version. I have no other comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Person-Centered Care in Addiction and Public Health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 28 May 2025

https://doi.org/10.21956/hrbopenres.15533.r46753

? **Roman Ivasiy**
Yale School of Medicine, New Haven, USA

Thank you for the opportunity to review this important and timely study, which has the potential to significantly impact OAT delivery policy in Europe and globally.

I believe there are a few recommendations that could improve the methodology, particularly in the second study of the manuscript. From my understanding, the authors are considering only the first treatment episodes of OAT for the selected cohort, which may be appropriate if most patients had only one within the observation period, but it usually does not fully reflect the real-life experiences of people who use drugs. I suggest using frailty survival models to better account for

multiple treatment episodes. These models would allow for the inclusion of repeated treatment episodes.
Additionally, I am concerned that including time-dependent covariates only in the sensitivity analysis may not be sufficient. It would be much more convincing if time-dependent covariates, such as dose and take-home dosing, were incorporated into the main model. Both of these factors have the potential to increase over time and are inevitably associated with treatment retention, as both are proven to be associated with longer retention. As the duration of OAT episodes increases, the chances of dose adjustments and extended supply days rise, making them crucial factors to include in the main analysis to keep it unbiased systematically. Therefore, controlling for the dose changes over time is essential to assess the effect of the THD.

Additionally, I believe including some more recent studies on the topic of THD expansion during COVID in the introduction would provide readers with valuable context. Some of these studies include:

1. Ivasiy R, Madden LM, Meteliuk A, Machavariani E, et al. (2024) - (**Ref 1**)
2. Krawczyk N, et al. (2023) - (**Ref 2)**

References

1. Ivasiy R, Madden LM, Meteliuk A, Machavariani E, et al.: The impact of emergency guidance to the COVID-19 pandemic on treatment entry, retention and mortality among patients on methadone in Ukraine.*Addiction*. 2024; **119** (9): 1585-1596 PubMed Abstract | Publisher Full Text
2. Krawczyk N, Rivera BD, Levin E, Dooling BCE: Synthesising evidence of the effects of COVID-19 regulatory changes on methadone treatment for opioid use disorder: implications for policy.*Lancet Public Health*. 2023; **8** (3): e238-e246 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Opiod Use Disorder, HIV, HCV, Healthcare Service Reserch

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 16 April 2025

https://doi.org/10.21956/hrbopenres.15533.r46662

Kristen A Morin
Northern Ontario School of Medicine University, Sudbury, Ontario, Canada

Thank you to the authors for their thoughtful revisions. I have no further comments

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Opioid agonist treament (OAT), epidemiology, health services research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 12 March 2025

https://doi.org/10.21956/hrbopenres.15418.r46017

Eugenia Oviedo-Joekes
The University of British Columbia, Vancouver, British Columbia, Canada

STUDY PROTOCOL
Impact of guidance issued during COVID-19 to expand take-home doses of opioid agonist treatment (OAT) in Ireland: protocol for a population-based analysis of prescribing practices and patient outcomes 2018 to 2023

This protocol will examine the impact of Ireland's COVID-19 policy change that expanded take-home opioid agonist treatment (OAT) doses. It will assess how this change influenced prescribing practices, treatment discontinuation rates, and methadone-related deaths. The protocol employs retrospective observational designs, with three studies: Study 1 analyzes changes in prescribing practices using a time series design, Study 2 assesses the association between increased take-home doses and treatment discontinuation through a cohort study, and Study 3 examines methadone-related deaths before and after the policy change using an interrupted time series analysis.

The protocol has several strengths. The work is very timely, as take-home practices are a right that people in OAT have struggled to reclaim, and a central principle of person-centered addiction care: autonomy. The COVID-19 pandemic allows many clients to benefit from take-home dosing, however in many regions these policies are being rolled back without evidence. The present study will add substantial evidence to the current landscape of the role of policy changes regarding take-homes and clients' outcomes. Another strength, this protocol is being developed in collaboration with people with lived/ing experience, who will partner in all aspects of the study. While the data used in the study might not be person-centered, this collaboration ensures the process takes into consideration the perspectives of those most affected by the policies and their consequences. Finally, the authors have developed three complementary studies using data from a national prescribing register over a seven-year study period that will allow for a comprehensive picture given the available data.

The present submission could be improved in clarity in the methods, some definitions read ambiguous. Particular attention to the subtext when writing is encouraged, to avoid the reader to make stigmatizing assumptions. While is true that regarding 'hard outcomes' more evidence is welcomed, there is plenty of evidence, including systematic reviews, of the benefits of take-home dosing, from the clients' perspectives, providers perspectives, there are studies showing no association with treatment outcomes. The background gives the impression that overall, the results are mixed. This can be improved.

Specific comments

Background
"Nevertheless, 6-month retention rates remain low, typically falling between 30% and 50%" This refers to Ireland? Is this common across the countries and continents mentioned? Is this for methadone and buprenorphine?

Why do you consider "the prolonged requirement for daily observed dosing" a 'potential challenge' and not directly a 'challenge'? Is there not enough evidence that shows this is a barrier to access care?

Were the National Clinical Guidelines for OAT in Ireland (2016) developed with consultation with people of lived/living experience? Despite the guidelines, is there any data on how many clients

actually benefitted from take-homes?

The change in the guidelines in 2020 towards providing the maximum number of take-home doses does not seem to be in consideration to the safety of the patient, but in the safety of the community. These changes were to protect the community from COVID. The systems of control and stigma toward people with OUD became a secondary issue. I think it is very important to be reflective of these issues among structurally disadvantaged populations, and not continue perpetuating structural violence. This is extremely relevant since many of the incredible advances in addiction and public health gained during the COVID pandemic are being rolled back, despite the evidence (i.e., non-events) now that the system does not have to protect the community anymore with those measures.

The authors cite the study finding "A retrospective study of post-mortem toxicology of OAT-related deaths in England, observed that methadone-related mortality grew by 64% in the first wave of COVID-19, and this increase occurred in cases where there was no methadone prescription at time of death [...]" concluding that this increase was "possibly from diversion arising from increased access to take-home doses". This is a simplification of the study of Aldabergenov et al. First, they cite a long list of protecting factors of those with a prescription. Then, they provide evidence from other studies that take-home diversion has not been proved to drive negative outcomes, beyond specific cases. What is the evidence the authors have to indicate that a 64% increase in methadone mortality is due to take-home diversion? How are these calculations done? Given that the methadone levels detected were unchanged in both groups relative to previous years, and the prescribed group had higher levels than the non-prescribed (although not significant), how does that explain 'sharing' or 'selling' their own medication (what will they use instead?)?.

The language from the three interlinked objective, where does it come from? In objective 1, is it necessary to include all that language that seem to come from the guidance document?

In objective 2, You are looking at the association of the difference in take-home prescriptions before/after March 13th 2020 with treatment discontinuation? If so, this needs to be expressed in a clearer manner.

Objective 3, "[...] and whether methadone-related deaths varied by whether the deceased was in active OAT treatment at the time of death." This line does not read well. You mean to compare methadone-related deaths with and without an active methadone OAT prescription? (if it can be distinguished of methadone prescribed for pain)

Methods
For study 1, have the authors considered geographic area as a stratification? Yes, no? Why? Centralized areas and decentralized areas or urban/rural areas, for example, will present distinct patters of acceptance/need of the guidance.

Study 2, we are talking about prescriptions increases, correct? The wording "increase TH doses" reads like the dose itself will be increased.

The exposure variable has 2 levels: 1) maintained increase of at least one day of take-home dispensation, and 2) not meeting the prior condition. "All unexposed individuals will be required to be actively treated with methadone or buprenorphine on this assigned index date and until the

end of the exposure period to ensure comparability between groups". Isn't time to discontinuation the outcome variable of study 2? "The primary outcome will be the time to treatment discontinuation, defined as the time between index date and first subsequent OAT discontinuation"

Figure 1 is not self-explanatory, and it does not really help discern between the cohort and exposure groups.

Study 3 outcome, can you clarify the definition of cause of death? Is it a code? There is some ambiguity, when one side it says "directly due to the toxic effect of methadone", but in the other side is says "methadone-related". Also, when more than one substance is present, how is the death coded? Does the death certificate have that certainty, or the death is attributed to the 'toxic effect of methadone'?

In the statistical analysis of study 3, the authors mention again that the increase in methadone-related deaths after the expansion in take-home dispensations, implying causation, citing Aldabergenov et al., offering no evidence of such connection. This is particularly relevant when the authors indicate that there is no linkage between prescribing practices and mortality data. Therefore, it is important to exercise caution particularly when writing about structurally disadvantage populations to avoid re-stigmatizing them with between the lines' assumptions.

Discussion (cont.)
The authors, also in the discussion, imply that they can offset the challenge to establish causation with their robust methodology. This sentence needs to be corrected. The present study design does not allow proving causal relationships.

Dissemination
Regarding the dissemination in the UISCE magazine, can the authors elaborate a bit on this? Will this publication be led or co-led with people with lived/ing experience?

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Person-Centered Care in Addiction and Public Health

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Apr 2025

Louise Durand

The present submission could be improved in clarity in the methods, some definitions read ambiguous. Particular attention to the subtext when writing is encouraged, to avoid the reader to make stigmatizing assumptions. While is true that regarding 'hard outcomes' more evidence is welcomed, there is plenty of evidence, including systematic reviews, of the benefits of take-home dosing, from the clients' perspectives, providers perspectives, there are studies showing no association with treatment outcomes. The background gives the impression that overall, the results are mixed. This can be improved.

Specific comments

1. Background: "Nevertheless, 6-month retention rates remain low, typically falling between 30% and 50%" This refers to Ireland? Is this common across the countries and continents mentioned? Is this for methadone and buprenorphine?

Response:
To clarify, we have modified this statement using evidence from a systematic review.
"Nevertheless, retention remains low internationally, with a median 12-month retention rate of 57% found in a systematic review of 37 studies [8]."

1. Why do you consider "the prolonged requirement for daily observed dosing" a 'potential challenge' and not directly a 'challenge'? Is there not enough evidence that shows this is a barrier to access care?

Response:
We have removed "potential" and modified the manuscript accordingly.

"One challenge to treatment retention is the prolonged requirement for daily observed dosing, also referred to as supervised dosing, in community pharmacies or addiction clinics."

1. Were the National Clinical Guidelines for OAT in Ireland (2016) developed with consultation with people of lived/living experience? Despite the guidelines, is there any data on how many clients actually benefitted from take-homes?

Response:
Yes, the 2016 National Clinical Guidelines for OAT were developed in consultation with people with lived and living experience. A working group comprising representatives from the College of Psychiatrists of Ireland, the Irish College of General Practitioners, the Pharmaceutical Society of Ireland, and HSE Addiction Services consulted with key stakeholders including 2 service user representative groups, UISCE (Advocacy Group for People who use drugs in Ireland) and SURF (Service User Representative Forum) and staff working in the services. Expert opinion from Professor Michael Farrell, Director of the National Drug and Alcohol Research Centre at the University of New South Wales, was

obtained both during the process and on completion.

With respect to data on take-home doses, there is no published evidence regarding how many clients access/benefitted from take-home doses in Ireland over the study period.

1. The change in the guidelines in 2020 towards providing the maximum number of take-home doses does not seem to be in consideration to the safety of the patient, but in the safety of the community. These changes were to protect the community from COVID. The systems of control and stigma toward people with OUD became a secondary issue. I think it is very important to be reflective of these issues among structurally disadvantaged populations, and not continue perpetuating structural violence. This is extremely relevant since many of the incredible advances in addiction and public health gained during the COVID pandemic are being rolled back, despite the evidence (i.e., non-events) now that the system does not have to protect the community anymore with those measures.

Response:
Thank you for this considered reflection. We totally agree with Reviewer 2 that people who use drugs are subjected to structural stigma, which is harmful to their health and wellbeing. In fact, in recent years UISCE have co-produced / co-delivered an annual workshop with co-authors for students in the RCSI on reducing stigma for people who use drugs in the health services. In our discussions for this study, our agreed aim was to understand what changes took place in Ireland following changes in guidelines, and whether those changes were sustained over time. Reviewer 2 noted that “public health gained during the COVID pandemic are being rolled back”, we do not have evidence of this in the Irish context, it is for this very reason we are undertaking this study. Furthermore, given the high levels of drug poisoning deaths in Ireland, we also wanted to understand the impact of any changes on treatment discontinuation (a known risk factor for mortality) and methadone -related deaths. This goal in no way seeks to further stigmatise people who use drugs – our goal is to accumulate evidence scientifically to inform services and generate further research questions to improve care and reduce mortality among people who use drugs in Ireland. We appreciate and acknowledge that observational epidemiological studies cannot infer causation and we are explicit that our findings are hypothesis generating (see response #15).

1. The authors cite the study finding “A retrospective study of post-mortem toxicology of OAT-related deaths in England, observed that methadone-related mortality grew by 64% in the first wave of COVID-19, and this increase occurred in cases where there was no methadone prescription at time of death [...]” concluding that this increase was “possibly from diversion arising from increased access to take-home doses”. This is a simplification of the study of Aldabergenov et al. First, they cite a long list of protecting factors of those with a prescription. Then, they provide evidence from other studies that take-home diversion has not been proved to drive negative outcomes, beyond specific cases. What is the evidence the authors have to indicate that a 64% increase in methadone mortality is due to take-home diversion? How are these calculations done? Given that the methadone levels detected were unchanged in both groups relative to previous years, and the prescribed group had higher levels

than the non-prescribed (although not significant), how does that explain 'sharing' or 'selling' their own medication (what will they use instead?)?.

Response:
Thank you for your comments with respect to our citation of Aldabergenov et al. In response to "What is the evidence the authors have to indicate that a 64% increase in methadone mortality is due to take-home diversion", we do not state that this increase is due solely to diversion – we indicate that diversion is one possibility. However, Reviewer 2 is correct we did not provide alternative explanations as put forward by the authors. We have addressed this limitation, and highlighted other possible contributions as suggested:

"A retrospective study of post-mortem toxicology of OAT-related deaths in England, observed that methadone-related mortality grew by 64% in the first wave of COVID-19, and this increase was greatest among cases where there was no methadone prescription at time of death. The authors acknowledge that multiple factors could account for the increase in methadone-related deaths in those not prescribed OAT, including reduced access to psychological supports, harm reduction and out – reach services such as naloxone among those not in treatment. The increase in methadone-related death seen in people not prescribed it raises the possibility that an important change to the drug market that occurred during the COVID-19 pandemic in England was an increased availability of methadone. This possibility raises the question of diversion (Aldabergenov et al., 2022). Prescribed and non-prescribed buprenorphine related mortality remained low and did not significantly change (Aldabergenov et al., 2022)*. In Ireland, methadone is the most common opioid implicated in drug poisoning deaths, with numbers increasing between 2012 and 2021* (Kelleher et al., 2021)."

1. The language from the three interlinked objective, where does it come from? In objective 1, is it necessary to include all that language that seem to come from the guidance document?

Response:
We included detail with respect to time, person and the specific guidance issued to ensure clarity in the study objective. We felt this was a useful means of signposting, which is reflected in the methods. However, we appreciate your comment that perhaps this level of detail is not necessary in the objective and have simplified to:

1. *Examine the impact of changes in guidance for the provision of OAT take-home doses in Ireland, on prescribing practices for take-home doses of methadone and buprenorphine in primary care*

1. In objective 2, You are looking at the association of the difference in take-home prescriptions before/after March 13th 2020 with treatment discontinuation? If so, this needs to be expressed in a clearer manner.

Response:
Apologies for the lack of clarity with respect to objective 2. We have clarified here, also reflecting on your comments with respect to our language used in objective 1.

1. *Assess the association between increased take-home doses of OAT, following changes in guidance, and treatment discontinuation in primary care*

1. Objective 3, "[…] and whether methadone-related deaths varied by whether the deceased was in active OAT treatment at the time of death." This line does not read well. You mean to compare methadone-related deaths with and without an active methadone OAT prescription? (if it can be distinguished of methadone prescribed for pain)

Response:
As stated in the methods section, data on drug poisoning deaths are available from the National Drug Related Death Index (NDRDI). We have provided additional detail on this epidemiological database (see below), which clarifies the sources of data used by the NDRDI. The NDRDI determines whether a person is on OAT at the time of death through data from the national treatment register for OAT, the central treatment list. Treatment status is not in this instance determined by whether a person was in receipt of a prescription from dispensing records, so pain medications are not a confounder. To ensure further clarity, we have also provided detail on the treatment register in the 'Setting' section at the beginning of the methods section, which we hope clarifies the Irish system further.

*"**Setting***
Methadone and buprenorphine are available free of charge to all persons undergoing OAT for opioid use disorder in Ireland. In 1998 the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations were introduced in Ireland, which involved the establishment of a national register, the Central Treatment List (CTL). The Misuse of Drugs Regulations were updated in 2017 to authorise access to buprenorphine or buprenorphine/naloxone for OAT on the same statutory basis as methadone. All individuals in receipt of OAT are registered on the CTL, with each person linked to one specific prescriber and a single pharmacy dispensing site. A total of 10,251 people were in receipt of OAT in 2019 (Durand et al., 2023)*. OAT is provided in specialist outpatient addiction clinics or primary care settings, with approximately 60% of people in treatment in specialist addiction clinics* (Delargy et al., 2019; Durand et al., 2021)*. Previous studies of OAT in Ireland suggest that access to take-home doses is greater in primary care"*

***"Drug poisoning deaths.** The National Drug Related Death Index (NDRDI) is an epidemiological database that records all poisoning deaths by drugs and/or alcohol. It follows the EUDA standard protocol to collect data on drug-related deaths (EMCDDA, 2012). To ensure completeness, mortality data are collected from multiple sources and cross-checked to avoid duplication. Coronial files are the primary source and include post mortem toxicology reports. Other data sources include: General Mortality Register through the Central Statistics Office (CSO), acute hospitals data via the HSE Hospital In-Patient Enquiry (HIPE) system and the CTL. Drug poisoning deaths are defined as deaths directly due to the toxic effect of one or more drugs, as directed by the Coroner on the certificate of death registration and/ or the record of verdict. Up to 15 drugs implicated in drug poisoning deaths by the Coroner are included in the NDRDI. Anonymised individual level data on drug poisoning deaths will be provided for the years 2018-2023, including the deceased's month and year of death, geographic area, socio-demographic information (year of birth, sex, homeless status at time of death), history of chronic pain, problem drug use at time of death (history of opioid dependency; history of opioid use; history of previous*

overdose), drug treatment history (on OAT at the time of death as recorded in Central Treatment List), and whether methadone and/or buprenorphine were implicated in the poisoning death."

We have also revised objective 3 as recommended:

1. *Examine methadone-related deaths before and after changes in guidance for the provision of OAT take-home doses and by treatment status at time of death (i.e. whether the deceased was in active OAT treatment vs. out of OAT treatment at the time of death)*

1. Methods: For study 1, have the authors considered geographic area as a stratification? Yes, no? Why? Centralized areas and decentralized areas or urban/rural areas, for example, will present distinct patters of acceptance/need of the guidance.

Response:
Thank you for raising this excellent point. We have indeed considered stratifying/adjusting for geographic information. This is important as COVID-19 measures may have affected urban/rural territories differently, notably in term of travel restrictions. While estimated rates of problematic opioid use are 4 times higher in county Dublin compared to rest of the country (Hanrahan et al., 2022), access to OAT can be problematic in rural areas (Delargy et al., 2019) and the large majority of services are often located in Dublin. The data provided by the PCRS will include the dispensing pharmacy health region, which will give an indication of the area where people are dispensed OAT. Unfortunately this level of granularity will not allow to distinguish urban vs rural areas as some health regions include both major cities and rural areas. We anticipate being able to meaningfully separate the greater Dublin area vs the rest of the country which is the approach taken in other publications (Hanrahan et al., 2022). We included this level of stratification explicitly in the statistical plan for objective 1.
"The analysis will be stratified by OAT drug (methadone or buprenorphine), sex, age class, and geographic area to identify any specific subgroup patterns."

1. Study 2, we are talking about prescriptions increases, correct? The wording "increase TH doses" reads like the dose itself will be increased.

Response:
Reviewer 2 is correct, the exposure variable is increased number of take-home doses, not the drug dosage. We have clarified this in the text as highlighted below.
" Using these data we will classify individuals as exposed if they experience an increase in their weekly number of take-home doses by at least $\geq$1 day(s) during the exposure window compared to their baseline regimen."

1. The exposure variable has 2 levels: 1) maintained increase of at least one day of take-home dispensation, and 2) not meeting the prior condition. "All unexposed individuals will be required to be actively treated with methadone or buprenorphine on this assigned index date and until the end of the exposure period to ensure comparability between groups". Isn't time to discontinuation the outcome variable of study 2? "The primary outcome will be the time to treatment discontinuation, defined

as the time between index date and first subsequent OAT discontinuation"

Response:
Due to the design of the study we set an exposure window where all individuals need to be observed in order for us to define their exposure group, similar to existing literature (Gomes et al., 2022). As a consequence, to avoid "immortal bias", individuals in the unexposed group need to stay in treatment at least until the end of the exposure window. We have modified the index date to take place at the end of the exposure window for both exposed and unexposed groups so individuals are at risk of discontinuation from the onset of observation period. Time to discontinuation is therefore defined as the time between the index date and first subsequent OAT discontinuation, and can only be observed after the end of the exposure window.
*"**Exposure**: increase in OAT take-home doses. Individual baseline take-home dosing regimen will be defined as the highest weekly number of take-home doses observed during the accrual window. The exposure window will be defined as the 4 weeks following the guidance change (March 14th, 2020, to April 10th, 2020). We will calculate the number of take-home doses on each OAT prescription during the exposure window. Using these data we will classify individuals as exposed if they experience an increase in their weekly number of take-home doses by at least* ≥ 1 day(s) during the exposure window compared to their baseline regimen. Individuals whose take-home dose regimen did not meet this criteria will be classified as unexposed. The index date will be defined as the first day after the exposure window, i.e. April 11th 2020. All unexposed individuals will be required to be actively treated with methadone or buprenorphine until the end of the exposure period to ensure comparability between groups. Patients who had their OAT drug changed (from methadone to buprenorphine or vice versa) during the accrual or exposure windows will be excluded. *Figure 1 displays the definition of the study cohort and exposure groups."*

1. Figure 1 is not self-explanatory, and it does not really help discern between the cohort and exposure groups.

Response:
Thank you for this feedback, we have taken time to reflect on your comments and have modified figure 1 to provide greater clarity on the cohort and exposure groups. We hope this is helpful to the reader.

https://hrbopenresearch.s3.eu-west-1.amazonaws.com/linked/200121.14044-Louise_Durand-Response.pdf

1. Study 3 outcome, can you clarify the definition of cause of death? Is it a code? There is some ambiguity, when one side it says "directly due to the toxic effect of methadone", but in the other side is says "methadone-related". Also, when more than one substance is present, how is the death coded? Does the death certificate have that certainty, or the death is attributed to the 'toxic effect of methadone'?

Response
Thank you for this comment. We use methadone-related death throughout the manuscript,

defining it as death directly due to the toxic effect of methadone. In polydrug poisoning deaths, all drugs recorded on the death certificate have equal weight in relation to the cause of death i.e. there is not one main drug and then additional drugs. The drugs implicated on the death certificate are transcribed verbatim to the NDRDI database and then assigned ICD codes, unique NDRDI codes and ATC codes (where applicable) by NDRDI researchers. Up to 15 drugs implicated in drug poisoning deaths by the Coroner are included in the NDRDI. If methadone is deemed implicated we consider it a methadone-related death, even if other substances are also present/implicated, consistent with standard reporting practices for the NDRDI. We added a clarification to the definition of the outcome:
"***Outcome.*** *The primary outcome will be the bi-monthly number of methadone-related deaths, defined as deaths directly due to the toxic effect of methadone, alone or in combination with other substances, as directed by the Coroner on the certificate of death registration and/ or the record of verdict, between January 2018 and December 2023."*

1. In the statistical analysis of study 3, the authors mention again that the increase in methadone-related deaths after the expansion in take-home dispensations, implying causation, citing Aldabergenov et al., offering no evidence of such connection. This is particularly relevant when the authors indicate that there is no linkage between prescribing practices and mortality data. Therefore, it is important to exercise caution particularly when writing about structurally disadvantage populations to avoid re-stigmatizing them with between the lines' assumptions.

Response:
We have now have removed reference to Aldabergenov et al in the statistical analysis section, and as clarified in response to question 8, treatment status at time of death is determined by the National Drug Related Death Index which captures data across multiple datasets, including the national OAT treatment register (CTL):

"We will conduct a stratified analysis for (1) deaths among people on OAT at time or death and (2) deaths among those not in treatment at time of death."

1. Discussion (cont.)

The authors, also in the discussion, imply that they can offset the challenge to establish causation with their robust methodology. This sentence needs to be corrected. The present study design does not allow proving causal relationships.

Response:
It was certainly not our intention to imply our study design can offset the challenge of establishing causation or prove causal relationships and we acknowledged that this work remains hypothesis generating. We have revised this statement to remove any doubt for the reader.

"Furthermore, while the studies employ robust methods like ITSA and comparative trend analysis of non-methadone-related deaths to explore the relationship between the intervention and

observed outcomes, the study designs cannot establish causality. The Bradford Hill criteria can be used to assess causal inference; nonetheless any observed associations will remain hypothesis generating."

1. Dissemination: Regarding the dissemination in the UISCE magazine, can the authors elaborate a bit on this? Will this publication be led or co-led with people with lived/ing experience?

Response:
We have an ongoing and active collaboration with UISCE for both research and educational activities. UISCE was involved in the development of this research grant, study design and the writing of the study protocol. The UISCE publication will be co-led with people with lived/living experience who are linked in with UISCE. We will organise meetings with UISCE/people who use opioids and those with experience of OAT services, and discuss how best to design/ write this piece. We will be flexible in the process of writing the magazine article, and remain open to different ideas from experts with lived experience.

References:
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Hanrahan, M. T., Millar, S., Phillips, K. P., Reed, T. E., Mongan, D., & Perry, I. J. (2022). *Problematic opioid use in Ireland, 2015–2019.* [Report]. Health Research Board. https://www.drugsandalcohol.ie/35856/
Kelleher, C., Carew, A. M., & Lyons, S. (2021). *National Drug Treatment Reporting System 2014 – 2020 drug treatment data.* [Report]. Health Research Board. https://www.drugsandalcohol.ie/34162/

Competing Interests: No competing interests were disclosed.

Reviewer Report 05 March 2025

https://doi.org/10.21956/hrbopenres.15418.r46011

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Kristen A Morin
Northern Ontario School of Medicine University, Sudbury, Ontario, Canada

Thank you for the opportunity to review this protocol paper on changes in prescribing patterns after take-home dose policy changes. This is a very important topic and a very well designed study. I have a few specific suggestions below.
INTRODUCTION
I really like how the first paragraph is framed
I think there's a paragraph missing before the last paragraph. This is usually the "hook" the so what and why the research is needed after summarizing the literature and the rationale. Please refer to this article for more details. [Ref 1]
METHODS
Add a section named "setting" to describe the OAT climate in Ireland for the international reader. Describe the drug supply, how OAT is typically dispensed (i.e. primary care or specialty clinics like in North America) and differences in patients between both settings. Also describe the health care system in Ireland briefly (i.e. private like US or public like Canada; talk about coverage for prescription drugs like methadone and buprenorphine, etc.)
In study 2, Can authors describe if they are only looking at one treatment window (i.e. first window as many other have done in previous studies) or considering all windows in a repeated measures model. If only looking at one window, are they adjusting for multiple treatment attempts.
Can authors describe how or if they addressed switching between methadone and suboxone within treatment windows.
Limitations

The limitation that only 40% of OAT patients (primary care patients that are more stable) should be stated earlier in the methods in the "setting" section suggested above.

References

1. Lingard L: Joining a conversation: the problem/gap/hook heuristic.*Perspect Med Educ*. 2015; **4** (5): 252-253 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Opioid agonist treament (OAT), epidemiology, health services research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Apr 2025

Louise Durand

INTRODUCTION: I really like how the first paragraph is framed. I think there's a paragraph missing before the last paragraph. This is usually the "hook" the so what and why the research is needed after summarizing the literature and the rationale. Please refer to this article for more details. [Ref 1]
Response: Thank you for this useful reference and for the suggestion. We have added a paragraph introducing more explicitly the need for the proposed studies:
"*Although guidance regarding OAT take-home dosing changed in Ireland in 2020, there is no evidence published on the actual changes in prescribing practices of take-home dosing in Ireland, and whether any such changes were sustained over time. In addition, it is important to assess any potential impacts of changes to take-home dosing on patient outcomes, including treatment discontinuation, a known risk factor for mortality, and overdose deaths. We will address these questions through three interlinked objectives*"

METHODS: Add a section named "setting" to describe the OAT climate in Ireland for the international reader. Describe the drug supply, how OAT is typically dispensed (i.e. primary care or specialty clinics like in North America) and differences in patients between both

settings. Also describe the health care system in Ireland briefly (i.e. private like US or public like Canada; talk about coverage for prescription drugs like methadone and buprenorphine, etc.)
Response: Thank you for this suggestion. We included a setting section which provides a detailed description of the delivery of OAT in Ireland:

"Methadone and buprenorphine are available free of charge to all persons undergoing OAT for opioid use disorder in Ireland. In 1998 the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations were introduced in Ireland, which involved the establishment of a national register, the Central Treatment List (CTL). The Misuse of Drugs Regulations were updated in 2017 to authorise access to buprenorphine or buprenorphine/naloxone for OAT on the same statutory basis as methadone. All individuals in receipt of OAT are registered on the CTL, with each person linked to one specific prescriber and a single pharmacy dispensing site. A total of 10,251 people were in receipt of OAT in 2019 (Durand et al., 2023). OAT is provided in specialist outpatient addiction clinics or primary care settings, with approximately 60% of people in treatment in specialist addiction clinics (Delargy et al., 2019; Durand et al., 2021). Previous studies of OAT in Ireland suggest that access to take-home doses is greater in primary care than in outpatient clinics (Cousins et al., 2017; Durand et al., 2020). "

In study 2, Can authors describe if they are only looking at one treatment window (i.e. first window as many other have done in previous studies) or considering all windows in a repeated measures model. If only looking at one window, are they adjusting for multiple treatment attempts.
Response: Consistent with previous studies (Gomes et al., 2022), we plan to look at one exposure window and whether THD regimen changed during this time. We are not planning to include further treatment episodes after the first dropout in the analysis, as we consider further episodes may not be comparable to those ongoing at the time of the guidelines introduction, due to variations in public health restrictions.

Can authors describe how or if they addressed switching between methadone and suboxone within treatment windows.
Response: Thank you for highlighting this point. Most people receive methadone in Ireland, with low numbers receiving buprenorphine. While we do anticipate a small increase in buprenorphine, the numbers are likely to be very small. This is based on our previous analysis of the national treatment register, where we identified that 2% of the 10,251 people on OAT were prescribed buprenorphine (n=178) in March 2020 (Durand et al., 2023). We would be underpowered to examine switching. We plan to exclude patients who switched between treatments from the main analysis. However, we will report on the numbers to describe the level of switching:
" People who had their OAT drug changed (from methadone to buprenorphine or vice versa) during the accrual or exposure windows will be excluded."

Limitations: The limitation that only 40% of OAT patients (primary care patients that are more stable) should be stated earlier in the methods in the "setting" section suggested above.
Response: Thank you for this suggestion, we have included this detail in the setting section

as you recommended.
"Methadone and buprenorphine are available free of charge to all persons undergoing OAT for opioid use disorder in Ireland. In 1998 the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations were introduced in Ireland, which involved the establishment of a national register, the Central Treatment List (CTL). The Misuse of Drugs Regulations were updated in 2017 to authorise access to buprenorphine or buprenorphine/naloxone for OAT on the same statutory basis as methadone. All individuals in receipt of OAT are registered on the CTL, with each person linked to one specific prescriber and a single pharmacy dispensing site. A total of 10,251 people were in receipt of OAT in 2019 (Durand et al., 2023)*. OAT is provided in specialist outpatient addiction clinics or primary care settings, with approximately 60% of people in treatment in specialist addiction clinics* (Delargy et al., 2019; Durand et al., 2021)*. Previous studies of OAT in Ireland suggest that access to take-home doses is greater in primary care than in outpatient clinics* (Cousins et al., 2017; Durand et al., 2020)*."*

References:
Cousins, G., Boland, F., Barry, J., Lyons, S., Keenan, E., O'Driscoll, D., Bennett, K., & Fahey, T. (2017). J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study. *Drug and Alcohol Dependence*, *173*, 126–131. https://doi.org/10.1016/j.drugalcdep.2016.12.009
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Competing Interests: No competing interests were disclosed.