Evaluating the Public Health Impact of Interventions for the Prevention of Drug-related Deaths in the Population: in Scotland [EPHESUS] – Research Protocol

Chief Investigators:
Dr Jack Stone, University of Bristol
Professor Matthew Hickman, University of Bristol

Version: 0.3

Date: 13/11/2025

Project Number: NIHR160569

IRAS Number: 338482

Sponsor: University of Bristol

Funder: This study is funded by the NIHR PHR (NIHR160569)

Approvals: Ethical approval was obtained from the University of Bristol Faculty of Health Sciences Research Ethics Committee (FREC) on 11th June 2025 (reference 26008). We are awaiting approvals from the Public Benefit and Privacy Panel for Health and Social Care to access specific datasets for this project.

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

.....

Name (please print):

.....

.....

Position:

.....

.....

Chief Investigator:

Signature: Date:

..../...../.....

.....

Name: (please print):

.....

.....

List of Contents

Key Study Contacts

Principal Investigators	Dr Jack Stone, Bristol Medical School, University of Bristol, Jack.stone@bristol.ac.uk, +441174559043 Prof. Matthew Hickman, Bristol Medical School, University of Bristol, matthew.hickman@bristol.ac.uk, +441174552480
Project Manager	Clare Jarvis, Bristol Medical School, University of Bristol, clare.jarvis@bristol.ac.uk, + 441174557959
Sponsor	University of Bristol
Funder(s)	National Institute for Health and Care Research, Public Health Research (NIHR160569)

Investigators

Principal Investigators: Dr Jack Stone[1], Prof. Matthew Hickman[1]

Co-Investigators: Dr Adelina Artenie[1], Mr Lee Barnsdale[2], Dr Rosie Cornish[1], Prof Neil Craig[3], Dr Elinor Curnow[1], Dr Hannah Fraser[1], Dr Haley Jones[1], Ms Katy MacLeod[4], Prof Catriona Matheson[5], Prof Andrew McAuley[3], Dr Saket Priyadarshi[6], Dr Jennifer Scott[1], Dr Tara Shivaji[2], Mr Wez Steele[4], Dr Kirsten Trayner[3], Prof Peter Vickerman[1]

UK and International collaborators: Prof John Macleod[1], Prof Natasha Martin[7], Prof Louisa Degenhardt[8], Prof Paul Dietze[9]

Affiliations
1. University of Bristol
2. Public Health Scotland
3. Glasgow Caledonian University
4. Scottish Drugs Forum
5. University of Stirling
6. Greater Glasgow and Clyde NHS board
7. University of California San Diego
8. National Drug and Alcohol research Centre, University of New South Wales Sydney
9. Burnet Institute

Sponsor and Funder Detail

Sponsor: University of Bristol

Funder: National Institute for Health and Care Research, Public Health Research (NIHR160569)

The funder and sponsor have not or will not be involved in the study design, conduct, data analysis and interpretation, manuscript writing or dissemination of results.

Protocol Version

Version	Purpose/Change	Date
V0.1	Draft version for funder approval	**01/10/2024**
V0.2	Added Section on Dissemination, research reference numbers, Signature Page, list of contents, key study contacts, list of investigators	**22/11/2024**
V0.3	Edited section 7 on Ethical Approvals.	**13/11/2025**

	Updated throughout the name of the linked dataset - from " Scottish Public Health Drug Linkage Programme (SPHDLP) " to "Substance Use and Health Intelligence Linked Dataset (SHIeLD)" Included information about ethics and information governance approvals on title page	

1. Scientific Abstract

Background

Drug-related mortality is a public health crisis in the UK; drug-related deaths (DRD) in Scotland have doubled in last decade. Opioid agonist therapy (OAT) reduces DRD risk by over 50%. Periods of elevated mortality risk when starting and leaving OAT combined with poor retention, as well as increased risk associated with poly-drug use (especially with street benzodiazepines (BZD)), may reduce population benefits of OAT. New long-acting formulations of OAT (la-bup) could increase retention and so improve effectiveness. Since 2011, Scotland's National Naloxone program (NNP) has distributed >150,000 naloxone kits, which can be administered after someone uses opioids to prevent fatal overdose. Plans for safer drug consumption facilities (SDCF) and safer BZD prescribing will be piloted during our study.

Aim

To evaluate the population-level impact of existing and novel interventions for reducing DRD in Scotland.

Methods

Objective 1: We will analyse Scotland's Substance Use and Health Intelligence Linked Dataset to determine: DRD mortality rates at critical risk periods in and out of OAT; individual and programmatic factors associated with OAT retention and time to re-engagement; if DRD risk changed during COVID-19; if OAT retention and outcomes improved after implementation of new drug treatment standards; impact of OAT on re-incarceration and DRD after prison release; effectiveness of la-Bup. An individual-based model of OAT and DRD among people with opioid dependence will be developed, parameterised and calibrated primarily using the linked data. The model will be used to evaluate how many DRD have been averted by OAT as delivered in Scotland. Objective 2: The model will be extended to include non-fatal overdoses and naloxone distribution. The model will be parameterised and calibrated using NNP data, data on ambulance callouts for overdoses and survey estimates of the prevalence of non-fatal overdose among people who inject opioids. The model will estimate the additional number of DRD averted by NNP. We will estimate costs of the NNP and incorporate these into the model to estimate NNP cost-effectiveness. Objective 3: Projecting forwards, the model will be used to evaluate how changes to OAT delivery could increase the impact of these interventions. Finally, the model will be extended to evaluate the potential impact of introducing novel interventions, including SDCFs and BZD safer prescribing, and consider the impact and costs of alternative DRD prevention strategies as proposed by our stakeholders. Throughout, people with lived experience and other stakeholders will advise on project priorities, model scenarios for objective 3, interpretation and implications of the research findings.

Timelines for delivery

Model findings for objective 1 will be available in Year 1-2; objective 2 in Year 2-3, and objective 3 during Years 3 and 4.

Anticipated impact & Dissemination

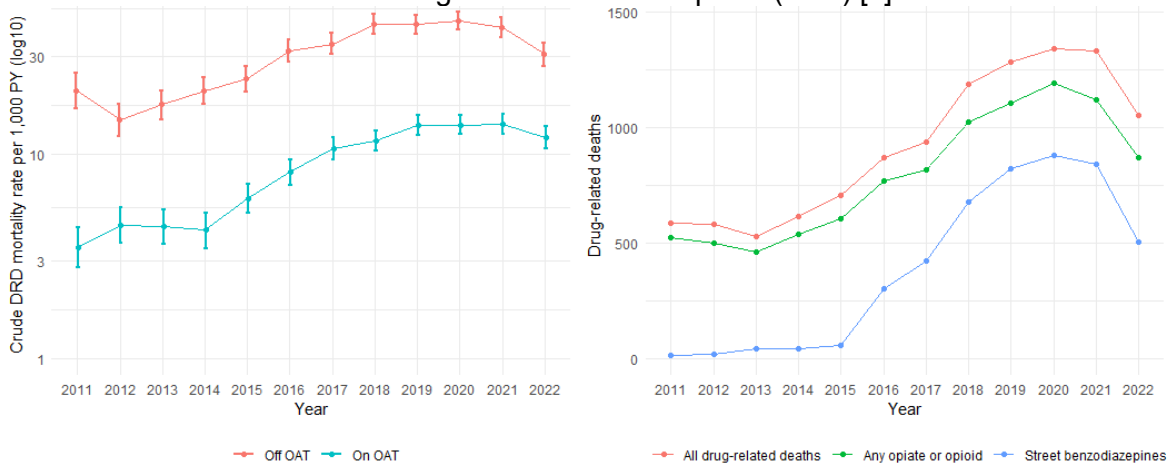
Our key aim is to improve the evidence on what actions can be taken to reduce DRD in the population, informing changes to drug policy and public health guidance in UK and internationally. Through Co-Is and stakeholder meetings, findings will be shared with Scottish Government, drug treatment providers in Scotland and England, public health director leads and other stakeholders. Model code and dummy data sets will be available. Lay summaries and infographics of key outputs will be coproduced with our PPI advisory group, Scottish Drugs Forum and Policy Bristol.

2. Background and rationale

The Problem

The record rise in drug-related mortality, primarily opioid-related poisoning, is a public health crisis in the UK, especially in Scotland with Scottish Parliament declaring it a “public health emergency” in 2021. In England & Wales there were 4,859 drug poisonings in 2021, approximately ½ involving opioids. In Scotland, opioid drug-related deaths (DRD) are the leading cause of death in people aged 15-54. Scotland has the highest recorded DRD population rate in Europe, at 250-300 (2021-22) per million population - sixteen times the EU average, nearly 4 times higher than England and Finland (next highest countries in EU [1]), and on par with North America [2] where overdose deaths now exceed 100,000 per year [3]. The below figure illustrates the problem in Scotland. Opioid DRD (right panel) doubled in ten years to 1,087 in 2021 with a fall in 2022 to 881 [1]. The risk of DRD in opioid dependent people in Scotland increased over three-fold in the last 10 years (overall from 0.6% in 2011/12 to 2.1% in 2019/20) [4] with equivalent increases for people both in and out of Opioid Agonist Treatment (OAT) (left panel). OAT is the prescription of substitute opioids such as methadone or buprenorphine to people dependent on illegal supplies of opioids such as heroin. OAT is considered an essential medicine and the most effective treatment for opioid dependence by WHO, but also is an essential public health or harm reduction intervention for reducing drug related harm. In Scotland, despite the rise in DRD risk in the community, OAT remained strongly protective [4].

Figure: Drug Related Death Time Trends: (Left Panel) DRD Risk in Cohort of people with opioid dependence in and out of Opioid Agonist Treatment (OAT) (updated from [4]); (Right Panel) Total Number of DRD in Scotland and number involving street Benzodiazepines (BZD) [1]



Analyses in England and Scotland do not support initial hypotheses (proposed in government reports [5, 6]) that the increase in the number of DRD are due to an ageing cohort [4, 7, 8]. There is no evidence either for an increase in the size of the underlying population of people dependent on opioids[9] . Instead, we see that the increase in the number of DRD in the population closely correlates with the risk of death experienced by people who are opioid dependent (including latest unpublished DRD risk estimates which fell in 2021/22 corresponding with the recent fall in the number of recorded DRD). Other hypotheses include changing patterns of polydrug use (i.e. use of multiple drugs in combination with opioids which may increase risk of overdose) and greater comorbidity [10, 11]. In Scotland, the rise in the number of DRD is strongly correlated with exposure to street benzodiazepines (BZD) as detected in post-mortem samples [12]. It will be important to see if the decline in DRD in Scotland in 2021-22 is sustained – provisional reports [13] are not promising – making it all the more important that we determine what modifiable factors could be enhanced to further reduce DRD in the population.

Why Important

DRD are preventable [2]. Opioid dependence is a chronic relapsing problem which may persist for several decades. OAT is central to the prevention of DRD as well as other causes of mortality and drug-related harm – such as prevention of HIV and hepatitis C virus (HCV) infection [2, 14]. Other harm reduction interventions available in the UK include needle and syringe programmes (NSP) and distribution of take-home naloxone (THN), with drug checking facilities, "safer supply" to reduce more toxic combinations of illicit drugs and Safer Drug Consumption Facilities (SDCF) being introduced or ready to be piloted [2, 15, 16]. Coverage of OAT and THN in UK is among the highest in the world [17] – yet DRD remain high. The importance of improving the response to DRD and reversing current trends has been recognised by the Scottish Drug Death Taskforce initiatives and the National Mission in Scotland. We propose transforming the evidence base on DRD prevention so that policymakers, practitioners, and citizens. We have transformed the prevention of HCV in PWID combining public health surveillance data, systematic review evidence and modelling e.g. see [18-20]. In this project we aim to transform strategies and policies to prevent DRD in Scotland in ways applicable to the rest of the UK and elsewhere.

Existing Evidence

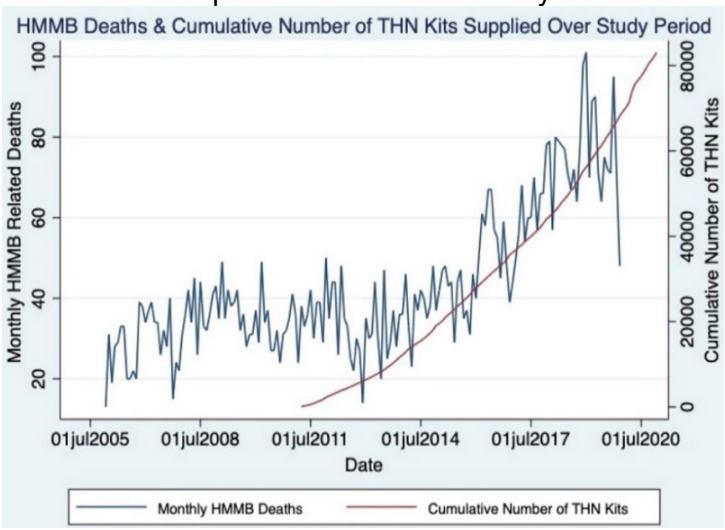
There is strong evidence from global reviews, including UK evidence, that OAT can reduce overdose by over 50% and can also reduce suicide, other causes of death and all-cause mortality. This evidence comes from observational cohort studies that link people in OAT treatment with mortality registers – as historically randomised controlled trials were underpowered to measure mortality [14]. Observational studies have also shown that OAT reduces HIV and HCV transmission by 50% [21]. In Scotland, we showed that DRD risk was reduced by 70% for people on OAT compared to being not on OAT [4]. However, UK and international evidence also show that DRD and self-harm are elevated in the first month of starting and ceasing OAT [11, 14, 22] so population benefits of OAT, irrespective of high coverage, may be reduced or lost if people frequently cycle in and out of OAT and are not retained in OAT for a sustained period [23]. In Scotland, new guidance on Medication-Assisted Treatment (MAT) standards [13] were issued in 2021, which have been raised as one potential explanation for the recent fall in DRD.

There is evidence that mortality risk in the first month of treatment is lower for patients on buprenorphine compared to methadone, but global reviews show slightly better retention on methadone compared to buprenorphine [11, 24]. It has been argued that new long-acting formulations (prolonged-release injection) of buprenorphine - which can be taken weekly or monthly - could increase retention and reduce DRD [2]. However, real-world evidence is limited and NICE noted that long-acting injectable buprenorphine (la-bup) is more expensive than traditional OAT [25]. In Scotland la-bup was introduced in prison during the COVID-19 pandemic and extended to the community following MAT standards and by 2022 had increased to ~9% of OAT community-based prescriptions in Scotland.

There is a substantial increased risk of DRD in the first month people leave prison – as risk of overdose is heightened when people who have lost tolerance to opioids relapse and begin use again. Australian and English evidence have shown the benefits of people maintained on OAT in prison, with reductions in mortality risk during imprisonment and the critical first month after leaving prison by 85% [26, 27].

Naloxone is an opioid antagonist that can reverse the effects of a fatal opioid overdose. The distribution of naloxone to those at risk of overdose or likely to witness an overdose ('take-home naloxone' - THN) can reduce DRD [28]. There is a strong association between THN programmes and overdose survival, with THN estimated to reverse overdoses in ≥96.3% administrations [29]. Multiple theoretical models have suggested that THN is highly cost-effective [30, 31], including a model partly parameterised for the UK [32]. However, these are not based on actual inputs from its implementation or mortality risk experienced recently. In April 2011, Scotland implemented a national naloxone programme (NNP), the first of its kind globally [33]. Following brief training, THN kits are issued to those at risk of opioid overdose,

their friends and family, and service workers. Overall, the program has distributed over 150,000 kits by March 2023, with approximately 8% of those given to prisoners upon release [34]. The effectiveness and cost-effectiveness of the national THN programme has not been fully evaluated. Opioid-related deaths in the month after prison release reduced by a third after the first two years of the programme and halved after 5 years [35]. However, at the same time there was a scale-up of OAT in prison so any reduction in DRD in the period immediately following release may not be simply attributed to the naloxone programme [26, 36]. Previous research to evaluate the impact of the programme as a natural experiment, using interrupted time-series methods, were not successful and could not tease out changes in other exposures occurring during the period of THN scale-up. The figure on the left illustrates the problem, with scale-up of THN (in maroon) occurring at the same time as the substantial increase in DRD (in blue). The research team leading the analyses reported to Scottish Government that mathematical modelling is required to evaluate the programme's impact [37].



Safer Drug Consumption Facilities (SDCF) are supervised facilities where people can consume drugs in a safe environment and directly prevent DRD onsite as well as indirectly through THN and OAT referral [38]. International evidence has shown that the introduction of SDCF has reduced DRD in the vicinity compared to other neighbourhoods [38, 39], and have been shown to attract a population of underserved people at higher risk of drug-related harm [40-43]. Although existing estimates suggest each SDCF may prevent a low number of DRD each year [44, 45], the accumulated effects of multiple SDCFs over time could be substantial [45]. Currently, 12 countries operate SDCFs with at least 88 SDCFs in Western Europe. Following advice from Scotland's Lord Advocate, Glasgow City Health and Social Care Partnership will be opening a pilot SDCF (funded by Scottish Government) in Glasgow in 2024, in response to a recent HIV outbreak and ongoing problem with public injecting [46, 47]. The ENACT (Evaluating the impact of the UK's first saNctioned sAfer drug Consumption faciliTy: A mixed-methods natural experiment study) NIHR Programme Grant (co-led by EPHESUS CoI Sharon Hutchinson) will evaluate the pilot SDCF and will use the model proposed here to evaluate long-term cost-effectiveness and consider the wider population-level benefits of their introduction nationally or at increased scale.

In addition, in Scotland, there has been a pilot study of introducing safer prescribing of BZD to reduce street BZD use during OAT [48]. The IN-BOAT Trial (A RCT of a Diazepam Maintenance Intervention versus Standard Care of Tapering Diazepam to Reduce Dependent Street Benzodiazepine Use in Adults Receiving OAT) – a NIHR HTA funded study (led by EPHESUS coI Catriona Matheson) - will also use our model to evaluate long-term cost-effectiveness. In UK primary care data, co-prescription of BZD during periods both off and on OAT was associated with a two-fold increased risk in DRD [10]. Scotland, however, has a particular problem with exposure to street BZD, which is also of increasing concern in North America [12, 16]. Provisional analysis of the Substance Use and Health Intelligence Linked Dataset (SHIeLD) [4] suggests that there is an excess risk of DRD in people that report street BZD use both in and out of OAT, while the increased risk associated with prescribed BZD occurs predominantly for patients in Scotland out of OAT (further justifying the trial of safer BZD prescribing).

Evaluating how effective a multi-component national programme to reduce DRD is and determining what needs to change cannot be done through an RCT. Mathematical modelling has an important role in informing public health action and national and international policies for averting drug related harms [49, 50]. This can create the counterfactuals (control conditions) necessary to evaluate current public health programmes as well as project potential impact of new interventions. Our models have demonstrated that OAT coverage, and retention in community and prison OAT, are important factors in determining the population-level impact of OAT (with case studies in rural US, Tehran and Kyiv) [51]. We evaluated the OAT programme in New South Wales, finding that it halved DRD over 2001-2019 [52]. Modelling for British Columbia found that OAT, naloxone and SDCFs averted half of all overdose deaths that would have otherwise occurred [45]. No similar studies have been conducted in the UK.

3. Research Questions

We aim to evaluate the population-level impact of Opioid Agonist Treatment (OAT), the national naloxone programme (NNP) and novel interventions for the prevention of drug-related deaths (DRD) in Scotland. The project will provide the evidence for policymakers on what changes to existing interventions and extra interventions are needed to sustain a reversal in the alarming DRD trends. We propose 3 work packages (WP) that combine a series of policy-relevant statistical analyses of the performance of OAT in Scotland (mostly in WP1) with developing a modelling framework (figure below) that simulates trends in DRD and builds in complexity, from evaluating OAT in WP1, additional benefit of THN in WP2, to projecting impact of future prevention strategies in WP3. The work packages (WP) and research questions (RQs) are:

WP1: Evaluating the impact of OAT as delivered in Scotland.

Statistical Evidence

RQ1: What are the DRD mortality rates at critical risk periods in and out of OAT in Scotland and do these vary between methadone and buprenorphine?

RQ2: What individual and programmatic factors are associated with OAT retention and time to reengagement in Scotland, and do these vary by OAT modality?

RQ3: Was there a change in DRD risk during the COVID-19 pandemic and has it been sustained?

RQ4: Has the implementation of Medication-Assisted Treatment (MAT) standards had any impact on OAT retention and other outcomes (non-fatal and fatal opioid overdose)?

RQ5: Does long-acting buprenorphine (la-bup) (compared to prescription of methadone and/or buprenorphine) improve OAT outcomes (retention and non-fatal and fatal opioid overdose during OAT)?

RQ6: Is retention on OAT associated with rates of (re-/)incarceration?

RQ7: What is the impact of OAT exposure in prison on DRD after prison release?

Modelling Evidence

RQ8: What are the OAT retention thresholds for preventing DRD in the population?

RQ9: How many deaths have been averted by Scotland's OAT programme?

WP2: Evaluate the National Naloxone Programme (NNP) in Scotland.

RQ10: What is the coverage, carriage and use of take-home naloxone among people who inject drugs (PWID) in Scotland and what is the contribution of community and prison supply to coverage?

RQ11: How many DRD have been averted by the NNP, accounting for changes in DRD epidemiology and other programmatic changes?

RQ12: What is the average cost of the NNP per PWID covered in the community and what is its incremental cost-effectiveness?

WP3: Evaluate the potential impact on DRD of changes to existing interventions and implementing novel interventions.

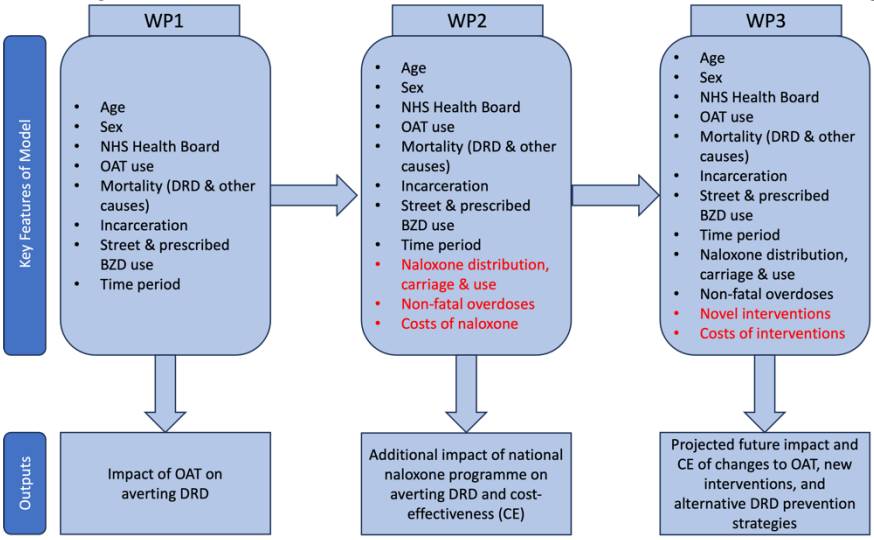
RQ13: To what extent can the population-level impact of OAT on DRD be improved?

RQ14: What coverages of novel interventions (Safer Drug Consumption Facilities (SDCF); safer prescribing of benzodiazepines (BZD), other novel interventions proposed by stakeholders) are needed to achieve measurable impact on DRD?
RQ15: What is the likely impact of alternative strategies (implementing changes to existing and introducing novel interventions) for reducing DRD?
RQ16: What are the potential costs and cost-effectiveness of alternative strategies to reduce DRD?

4. Research plan/methods

The research will focus on Scotland which has the greater public health problem and already established linked drug treatment and health outcomes administrative datasets (Substance Use and Health Intelligence Linked Dataset - SHIeLD). However, the methods, models developed, and policy recommendations will be adaptable to the rest of the UK. We will generate Scotland-specific estimates of how Opioid Agonist Treatment (OAT) reduces rates of incarceration and mortality in the high-risk periods and examine changes in OAT outcomes and risk of drug-related deaths (DRD) during and since the COVID-19 pandemic, following implementation of Medication-Assisted Treatment (MAT) standards, and increased availability of long-acting buprenorphine (la-bup). These analyses, alongside others already done or synthesised, will inform – and update as the evidence becomes available – our model of DRD in Scotland. For Scotland, the model (as shown in figure) will: evaluate how many DRD were prevented by OAT (WP1); evaluate how many DRD were prevented by national naloxone programme (NNP) and its incremental cost-effectiveness (WP2); and then project the future impact on DRD and cost-effectiveness of implementing changes to OAT, introducing new interventions, and comparing alternative DRD prevention strategies as proposed by policymakers, practitioners, and people with living/lived experience.

Figure: Key features and outputs of the model across work packages.



WP1: Evaluate the impact of Opioid agonist treatment (OAT) as delivered in Scotland

I Statistical Evidence from Substance Use and Health Intelligence Linked Dataset (SHIeLD)

The below table shows the current linked dataset – from 2011-2022 with planned annual updates to 2028. Key data sources include (i) Prescribing Information System (PIS), providing data on key exposures and confounders - OAT and other prescription drug exposure (such as BZD, z-drugs (zopiclone and others), gabapentinoids); (ii) Drug and Alcohol Information System (DAISy) and Scottish Drug Misuse Database (SDMD), providing self-reported data on key confounders such as drug and injecting history, homelessness, prison history; (iii) Scottish Morbidity Record (SMR) giving outcome data on admissions

for overdose and measures of comorbidity; (iv) National Records of Scotland deaths giving outcome data on DRD and other causes of death. New datasets from Prison/Scottish Criminal Justice and Prison Health are being linked and will be available in 2024/25 generating key confounder (prison history) and exposure (prison OAT) and outcome ((re)-incarceration) data. The total cohort of people who have been in OAT 2011-22 is approximately 45,000 with 10,000 deaths (5,800 DRD) and over 13,000 non-fatal opioid overdose admissions. The cohort has approximately 50% of all opioid poisonings registered in Scotland 2011-22. This rich dataset has been used previously to estimate DRD in and out of OAT over time [4] and was fundamental to new estimates of the prevalence of people who use opioids and inject drugs [9]. These analyses found that 75% of people with opioid dependence had been on OAT within the last five years. All non-fatal and fatal opioid and other overdoses are recorded within SHIeLD and through the linkages we can determine what proportion were exposed to OAT and potentially other interventions – which with the population size estimates will feed into the mathematical modelling. In addition, estimates of the impact of OAT on suicide, effect of co-prescription of OAT and z-drugs or gabapentinoids on DRD, and effect of co-prescription of OAT, BZD, and street BZD use on DRD are underway and will be submitted in 2024.

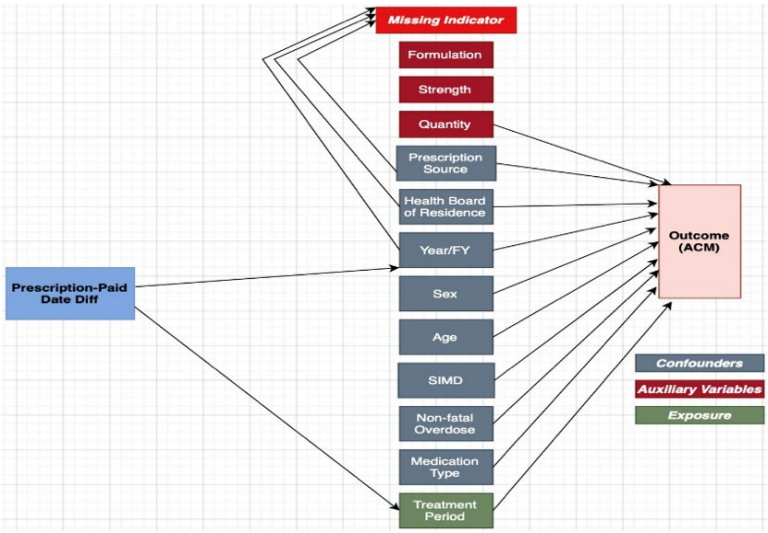
Table: Substance Use and Health intelligence Linked Dataset (SHIeLD) – data sources and summary of variables available for analysis

Dataset/source name	Key Variables (Age/Sex on all datasets)
Prescribing Information System (PIS)	NHS Board, prescription date, re-imbursement-date, OAT type and quantity of prescribed methadone/buprenorphine/long-acting buprenorphine, derived duration of prescription, prescriber type, dispenser type. Other drugs prescribed (eg BZD, other antidepressants, anxiolytics, sleeping tablets and pain medication).
Scottish Drugs Misuse Database (SDMD) & Drug and Alcohol Information System (DAISy)	Date of current contact with drug treatment services, year of last contact with drug treatment services, age started using illicit drugs, drug use profile (frequency, type and route of illicit drugs use), history of injecting (ever and last month), homelessness, self-report prison history, drug treatments received
Scottish Morbidity Record (SMR) 01/04	NHS Board, hospital admission date and type, hospital discharge date and type
National Records of Scotland (NRS) Deaths (SMR99)	NHS board and area of residence, NHS Board and council area of death, date of event, primary and secondary causes of death
National Drug-Related Deaths Database (DRDD)	Additional information on whether DRD known to be drug user, injecting drug user, date last contact with a drug treatment service, contact with other NHS service, date of last release from prison
Prison Service	Dates of incarceration, criminal offences related to incarceration, OAT in prison through linkage to DAISY/SDMD4/PIS

Methods/Statistical Approach (RQ1-7)
We will pre-register all of our analysis plans. We will curate and publish our code and dummy datasets in collaboration with PHS. We will use “causal inference” methods where appropriate.

RQ1&2: OAT 2011-2022. In previous analyses in England we have shown that people offered and entering different forms of OAT (methadone and buprenorphine) differ according to multiple characteristics of the patient and prescriber [11]. It is critical, therefore, that we describe and take account of these potential differences in our analyses in Scotland – in general we will do so by deriving propensity scores and using these to incorporate Inverse Probability Weights (IPW) into our analyses outlined below. We know also there are missing data on specific OAT prescription end dates in Scotland (with full information on date of re-imbursement but 60% missing an exact date of last prescription). In analyses

to date, an algorithm was used estimating the end date as on average 12 days before last paid date with prescription start on average 60 days before paid date [4]. This algorithm is not, however, sufficiently refined for measuring risk in critical OAT periods which is required for modelling OAT.



We will use a multiple imputation analysis approach, imputing date OAT ended (if missing) from information on date dispensed, date of re-imbursement and other information (see Directed Acyclic Graph (DAG) below) so additional analyses on time varying exposure to OAT defined by periods of risk can be undertaken. There are two critical periods of elevated risk: (i) the first 4 weeks of treatment, and (ii) the first 4 weeks after treatment cessation. To investigate these periods, we will divide OAT exposure periods into four categories: weeks 1-4 in OAT; weeks 1-4 out of OAT; remainder time (5+ weeks) in OAT; and 5+ weeks out of OAT. In primary analyses we will censor at 24 months after end of OAT prescription to address the potential issue of survivor bias (given variable follow-up of people off OAT and its positive association between probability of cessation from drug use over time). This will be varied in sensitivity analyses. In general, we will estimate adjusted mortality rates and rate ratios using generalized estimating equations (GEE), and according to primary characteristics and OAT exposure periods. GEEs adjust for multiple observations per participant using a working correlation structure, providing robust parameter estimates. We will fit Poisson, quasi-Poisson and negative binomial distribution models, assessing models for best fit using appropriate methods (e.g. AIC, BIC). As a sensitivity analysis, we will also fit a time-to-event model (e.g. Cox proportional hazards model). In all DRD analyses, we will use a 'cause-specific' approach to account for the competing risk of other cause mortality, censoring individuals whose cause of death is not drug-related, at time of death. Key confounders for propensity score matching include – previous history of OAT, geographical area, age, sex, comorbidity, poly-drug use, co-prescription, homelessness, prison history, overdose history and prescriber (primary care or specialist drug agency). We will test for differences in DRD and all-cause mortality by medication type (methadone vs buprenorphine) and whether there is evidence that the risks between critical risk periods have varied over time and are comparable to England and International evidence.

We will use the same model to estimate retention (expressed as median, IQR, and % of people that have been retained for 3 months, 6 months and for longer than one year, and mean). We will test for differences in retention by calendar period (2011-22), OAT modality, prescriber type; age, sex, geographical area; homelessness and prison history; poly-drug use; and comorbidity.

RQ3: OAT before/during and after COVID-19 Angus et al have shown that the number of opioid DRD per 100,000 fell during the COVID-pandemic in Scotland compared to US [53] whereas in both countries alcohol-related causes of death increased. Once linked data for 2024/25 are incorporated we can also track the risk of DRD within the cohort and examine whether it follows the same trends in the number of DRD as seen in the population. We will also test for differences in OAT retention during the COVID-pandemic period compared to the pre-pandemic period. We will use the same modelling approach as outlined above.

Natural Experiments

RQ4: Medication-Assisted Treatment (MAT) standards (see box on following page) have been implemented at different periods over time (Standards 1-5 below in 2021-2023 and Standards 6-10 on trauma informed care, primary care, and additional advocacy later). Adoption speeds also have varied by region. We will focus on Standards 1-5 including steps to reduce time between OAT episodes and increase OAT retention. We will use a regression discontinuity design to evaluate whether there is evidence that the implementation of these standards impacted OAT retention rates, re-engagement rates and DRD within OAT.

Medication-Assisted Treatment (MAT) Standards (1-5)

1: All people accessing services have the option to start MAT/OAT same day of presentation.
2: All people supported to make an informed choice on dose and type of medication.
3: All high risk people proactively identified and offered support to commence or continue MAT.
4: All people are offered evidence-based harm reduction at point of MAT delivery.
5: All people will receive support to remain in treatment for as long as requested.

RQ5: Once the cohort has been updated to include 2025/26 data we will quantify exposure to la-bup, methadone and buprenorphine and carry out a target trial emulation [54, 55] to compare OAT outcomes (retention and non-fatal and fatal overdose during OAT) among those prescribed la-bup and those prescribed methadone and/or buprenorphine as OAT. We will use DAG to specify common causes (confounders) between la-bup exposure and outcomes and use statistical model approach outlined in RQ1 including use of marginal structural models to generate intervention effect estimates.

RQ6: Reducing drug-related crime and imprisonment are key social and population benefits of OAT and can be a critical contribution to OAT cost benefit and cost-effectiveness analyses [56]. In UK cost-effectiveness analysis OAT dominates no treatment when the costs of crime are included and no longer dominates no treatment, though still highly cost-effective, if they are excluded from analyses [56]. Evidence from causal modelling, however, is weak [57, 58]. By mimicking aspects of a trial (since OAT retention cannot be randomised), we will aim to overcome some of the limitations of previous analyses. We will identify all individuals who cease OAT and match them 1:1 with a control individual who has been retained in OAT and has been on treatment for the same amount of time. Individuals will be matched on several characteristics associated with retention on OAT (informed by RQ2). We will follow up matched pairs for 36 months and compare (re)incarceration rates among those who ceased OAT to those continuing treatment. Follow-up for matched pairs will be censored if the matched control ceases OAT or if the individual who originally ceased resumes treatment.

OAT in Prison: Scottish Evidence

RQ7: There have been multiple studies in Scotland assessing DRD and other causes of death in periods following prison release [59-61] – but no estimates for prisoners with documented evidence of a history of injecting/Opioid dependence that were (or not) maintained and released on OAT. The key outcome is DRD rate in the month leaving prison. We will quantify exposure to OAT in prison to replicate analyses undertaken in England and Australia [26, 27]. These fitted a Cox proportional hazards model, stratified by post-release period for DRD during days 1–28, months 2–4 and months 5–12 after prison release. Prison of release random-effects (shared frailty) terms were included. In addition to confounders (RQ1) we will include length of time in prison and prison history. In addition, admission to community drug treatment during the first 4 weeks will be incorporated as a time-varying covariate to test whether any effect of OAT exposure at release could be accounted for by subsequent treatment.

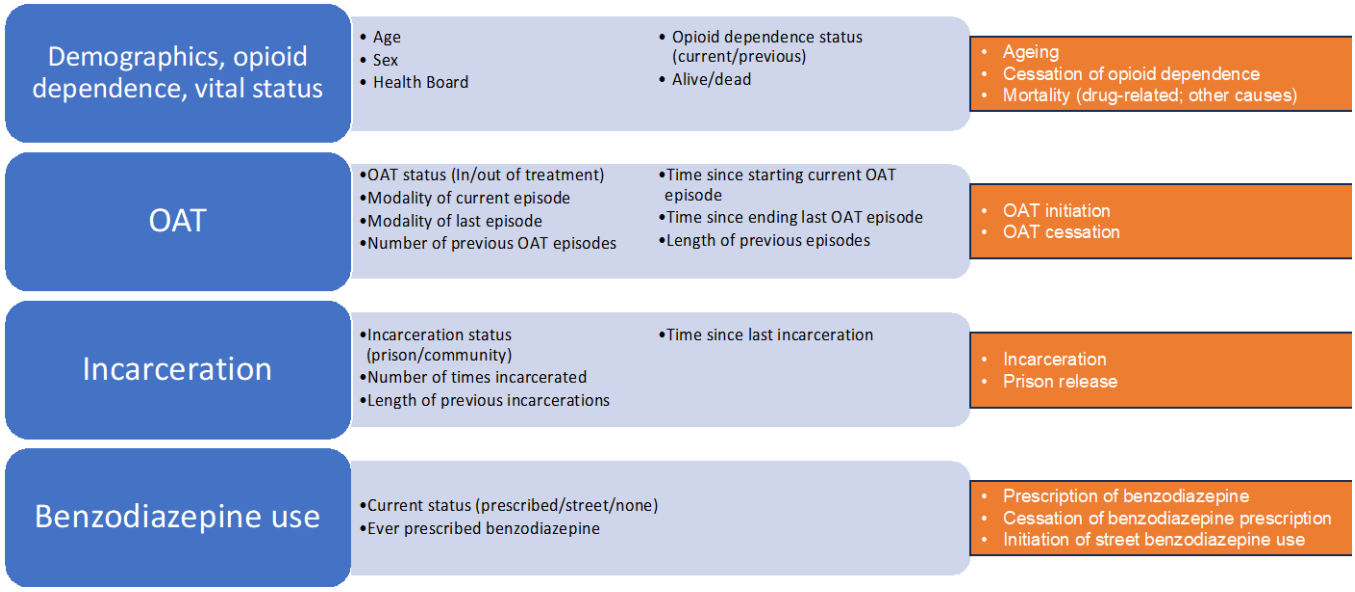
II Modelling

RQ8: OAT retention thresholds for preventing DRD. Following earlier analyses for England[11], we will develop a simple model that considers OAT retention and differences in mortality risk immediately after starting or ceasing OAT and by modality (methadone/buprenorphine) [11, 14]. Using information from analyses in Scotland [4] and Global reviews [14], we will sample model parameters on the differences in mortality risk related to OAT and calculate the probability that a treatment episode of a given duration will reduce mortality (mortality ratio<1; 'probability of benefit'). Through this, we will estimate the minimum treatment duration needed for each OAT modality such that the probability of benefit exceeds key values (e.g.50%, 80%, 95%). We will then consider different distributions of OAT retention to inform how this distribution can affect the overall probability of benefit and impact (mean of mortality ratios across treatment episodes, weighted by duration). This model will be developed as a web-based calculator for use by patient groups, policymakers and practitioners (See Dissemination section).

RQ9: How many deaths have been averted by Scotland's OAT programme

Individual-Based Model Description

We will develop a model of OAT initiation and retention, incarceration, aging, and mortality (drug-related and other causes). This model will not include naloxone, which will be included in an extended version of the model (WP2). Instead, the model will include changes in the rates of DRD over time, which will implicitly capture effects of the national naloxone programme. The model will simulate the population of people who are opioid dependent (primarily people who inject drugs - PWID) and trends in DRD in Scotland from 2011-22. The model will include geographical heterogeneity based on NHS Board to capture variations in rates and trends of DRD and provision of OAT. The model consists of individuals with *characteristics* that are tracked over time and *events* that can occur to these individuals, changing their *characteristics*. The risk of an *event* happening to an individual depends on their *characteristics* and may differ over time. Modelled *characteristics and events* are summarised in below figure.



The model will be open, such that individuals enter through initiation of opioid dependence, and leave through mortality (drug-related or other causes) or progress to a stage of long-term cessation of opioid dependence. Those with long-term cessation will only be exposed to other cause mortality and are retained in the model to allow estimation of life-years saved by OAT. Individuals enter the model without a history of OAT use or BZD use (prescribed or street) and are probabilistically assigned an age, NHS

board, sex and incarceration history. Official size estimates show that, despite high mortality rates, the size of population at risk has remained stable [9] – which with other evidence (e.g. from NESI which also shows ageing population) we will use to simulate trends in prevalence by age over time.

Individuals transition between periods on and off OAT. When individuals initiate an OAT episode, the modality of OAT for that OAT episode is assigned probabilistically. The probability for each modality will change over time (e.g. to reflect increase in buprenorphine vs methadone over time and introduction of la-bup) and may differ based on an individual's OAT history (e.g. modality of last treatment) and other characteristics, as informed by RQ2. Being on OAT affects an individual's risk of mortality (drug-related, and other causes) and, possibly, incarceration. Upon initiating OAT, individuals experience a period of elevated risk of DRD, which may differ based on modality (RQ1). After this period of elevated risk, individuals have a reduced risk of DRD whilst on OAT. Risk of mortality through other causes is reduced during time on OAT. Individuals are retained on OAT for durations that depend upon the modality of treatment, OAT history, and other characteristics, as informed by RQ2. Retention may also change over time (e.g. following implementation of MAT standards or during COVID-19). Upon ceasing OAT, individuals experience a period of elevated risk of DRD, which may differ based on modality (RQ1).

Individuals can be incarcerated, the risk of which depends upon their characteristics (informed by preliminary analyses for RQ6). It is hypothesised, that age, sex, OAT status and incarceration history (e.g. time since last incarceration, and previous number of incarcerations) will affect risk of incarceration. Individuals that were on OAT in the community have a probability of immediately ceasing OAT. Individuals can start and discontinue OAT in prison as in the community. The time from incarceration to prison release is determined based on their characteristics at time of incarceration (e.g. age, sex and incarceration history). Individuals on OAT at the time of release have a probability of ceasing OAT. Upon release, individuals experience a period of elevated risk of DRD, which may be reduced if they left prison in receipt of OAT (preliminary analyses for RQ7).

The model tracks an individual's use of benzodiazepines (BZD), whether prescribed or street. Individuals can initiate or cease use of prescribed or street BZD, the risk of which will differ by time (to capture reductions in prescribing and increases in street use) and individual's characteristics. Initiation of street BZD use will also be higher among individuals with a history of prescribed use, as suggested by analyses for Scotland [62]. Use of BZD will affect an individual's risk of DRD, differing between prescribed or street use and OAT status. The model will also incorporate other factors, where data are available, identified as important by our PPI advisory groups and statistical analyses (e.g. cocaine use and homelessness).

Model Parameterisation & Calibration

The model will be parameterised and calibrated using Scottish data, from 2011-2022, stratified by NHS Board. We will utilise aggregated and/or anonymised data from the following datasets managed by PHS:

- The Substance Use and Health Intelligence Linked Dataset (described above)
- The Needle Exchange Surveillance Initiative (NESI) is a biennial national cross-sectional voluntary anonymous survey of people who inject drugs in Scotland since 2008 (n=2,435 in 2019-2020). Participants are recruited from ~100 (50%) agencies and pharmacies that provide injecting equipment, and may also provide other harm reduction services, such as prescribed OAT and THN. NESI will provide key data on additional variables not captured in SHIELD and/or how key parameters may differ for those that have never been on OAT.
- National Records of Scotland (NRS) which produces annual reports of the number of DRD in Scotland and their distribution by age, sex, drugs-implicated and NHS board.
- The National Drug-Related Deaths Database (NDRDD**)** collects detailed information regarding the health and social circumstances of people with DRD in Scotland annually since 2009.

Ongoing analyses by coIs will also feed into model parameterisation and calibration and validation. This includes analyses to: (i) estimate mortality risks associated with benzodiazepine co-prescription and street benzodiazepine use; (ii) estimate the number of people who use opioids and inject drugs in Scotland. Because of uncertainty in the data used to parameterise and calibrate our model, prior distributions will be assigned to all important model input parameters, and Bayesian methods will be used to generate multiple model fits to available data as outlined below. Data used for model calibration will be stratified by NHS Board and age (using 10-year age-bands. Most parameters will have informative priors based on data estimates (either existing or estimated using data from the Substance Use and health Intelligence Linked Dataset – "SHIELD") while others will be estimated through the model fitting, with calibration targets informed by the above data sources. These data sources will also provide estimates for model validation.

Analyses of the SHIELD data will directly feed into model parameterisation. They will inform prior distributions for the: rates of OAT initiation and discontinuation and characteristics that affect these; effects of OAT (including at critical times starting/leaving OAT or leaving prison) on risk of DRD and incarceration; estimates of DRD mortality rates and differences over time and by individual characteristics (including prescribed and street BZD use) and NHS board; estimates of incarceration rates and durations of each incarceration and how they differ by individual characteristics and NHS board; rates of BZD prescribing and lengths of prescriptions.

The model will be initialised with an initial population size with characteristics distributed stochastically based on characteristics in the SHIELD and NESI in 2011. The size of the initial population at risk will be calibrated to the overall number of DRD (by NHS Board), assuming that those have never been on OAT have similar mortality rates to those out of OAT with the same characteristics (parameterised using SHIELD data), and NESI estimates of the coverage of OAT (current, past 6 months and ever). Reflecting the uncertainty in the rates of long-term cessation of opioid dependence, this parameter will be given a wide prior and calibrated to trends in the age distribution in NESI and SHIELD.

Similar to previous work in Scotland[63], the incarceration aspect of the model will be calibrated to age-stratified data from NESI on the proportion of community PWID who have ever been incarcerated, the number of times they have been incarcerated, and the average lengths of time spent incarcerated in the past year to calibrate rates of incarceration. Rates of initiating street and prescribed BZD use will be calibrated to NESI estimates on the prevalence of street BZD use by history of prescribed use (available from 2019-22[62]) and the proportion of PWID who have ever been prescribed BZD and trends in the proportion of DRD with street and prescribed BZD implicated.

As in previous analyses [51, 63], including in our recent evaluation of OAT in New South Wales which used linked data similar to SHIELD [52], we propose using Approximate Bayesian Computation for model calibration. This algorithm uses multiple rounds of parameter selection and filtering to approach the posterior parameter distributions through successive improvements in goodness of model fits until further iterations do not meaningfully improve the goodness of fits ('there is convergence'). The calibrated model will be validated by comparing model outputs to the distributions of DRD by age, sex and NHS board and NDRDD data on the percentage of people with DRD prescribed OAT at time of death, the proportion of people with DRD that had ever been in prison and the distribution of DRD by length of time between prison release and death. Additionally, modelled population sizes will be compared to upcoming population size estimates including estimates of people out of OAT (led by coI Jones).

Model changes based on feedback from PPI, stakeholders and analyses in WP1 would be parameterised and calibrated using additional data from the SHIELD and NESI. For instance, the SHIELD could parameterise DRD risk in those who are homeless or injecting cocaine. Whilst NESI estimates of the prevalence of past 6 month cocaine injecting and current, past 6 month, and lifetime homelessness and

difference by characteristics could be used to calibrate transitions between homeless and cocaine injecting states.

To account for model stochasticity, model outputs for each proposed parameter set will be averaged over multiple simulations, with the number of simulations based on an initial assessment of the stochastic variability between model simulations and typical model runtimes. Model calibration will be computationally intensive and require use of high-performance computing facilities at the University of Bristol which the team has experience of. Bayesian calibration methods typically require a high number (hundreds of thousands or millions) of model simulations and so model emulation (use of a statistical representation of the model outputs) may be utilised during the calibration process if model run-times are sufficiently large. If required, we will build different types of model emulators (artificial neural networks, Gaussian processes) using the same training set of model runs and choose the emulator for use based on performance on the same validation set of model runs. The emulator would be used only during calibration and so developed to only represent the model outputs needed for model calibration. Model fits arising from use of an emulator would be validated through directly running the main model.

Model Analyses

The model will then be used to determine the number of DRD and all-cause deaths have been averted by OAT as delivered in Scotland. This will be done through comparing the number of DRD and total deaths in the baseline model fits with a counterfactual scenario in which the effects of OAT on mortality and incarceration are removed. Analyses will also consider removing the effects of each type of OAT (methadone/buprenorphine) or in each delivery setting (prison/community). The model will be run multiple times for each model fit to account for stochasticity. We will also estimate the number and proportion of DRD averted in each NHS board and each year. If the model suggests that OAT may have had an adverse population-level impact, the model will estimate the probability that OAT has had a beneficial impact on DRD in each NHS Board and nationally. Uncertainty analyses will be undertaken to determine which parameters are most important for determining the impact of OAT on DRD. These analyses will also inform how much of the variability in model projections is contributed by uncertainty in each parameter, thus informing what future data collection efforts are most needed to refine our model projections.

WP2: Evaluate the existing impact of the national naloxone programme (NNP) on DRD

I Quantitative Data Analysis/parameters

RQ10: We will generate key parameter estimates for the modelling. These include NNP coverage in terms of the number of take-home naloxone (THN) kits given per person with opioid dependence/who injects drugs with a THN kit and where they obtained the kit (from prison or community), and proportion of overdoses where naloxone has been used. Evidence will be combined from the NNP programme (total kits issued in community and prison), ambulance call-out, PWID prevalence estimates, self-report THN use and data from Needle Exchange Surveillance Initiative (NESI). Descriptive analyses of the NNP programme and distribution of THN from different settings (prison, pharmacies and drug treatment services) and its association with promotion campaigns and trends in DRD is underway.

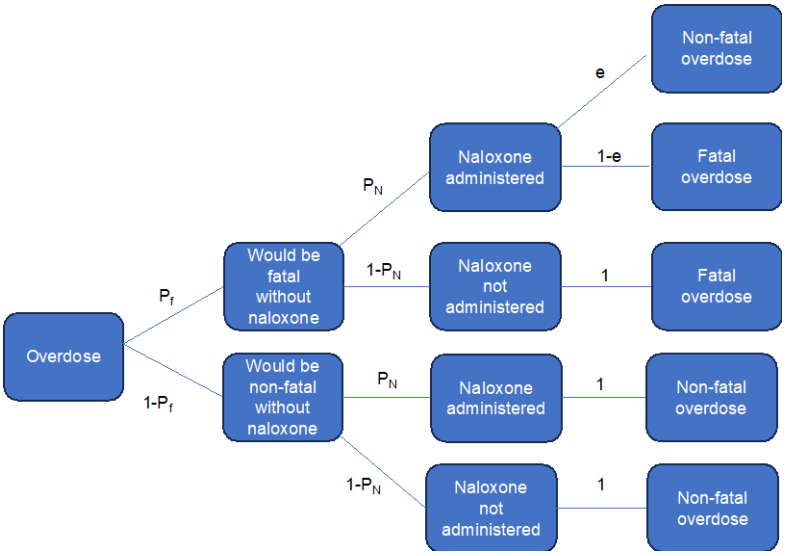
II Modelling

The model from WP1 will be extended (RQ11/12) to include all overdoses (non-fatal and fatal) and the distribution, carriage and use of THN kits. The model will incorporate rates of overdose (fatal and non-fatal combined), that differ by individual's characteristics. The below figure summarises how we will model non-fatal and fatal overdoses and the effect of naloxone.

The model will utilise programmatic data on naloxone distribution (described below). In the model, individuals in the community will be issued a kit at a time-varying rate which will depend on their age, sex and contact with services. Individuals leaving prison will be issued with a kit with a probability that

changes over time. Individuals issued a kit will have a propensity to carry naloxone - that is the probability that they will have naloxone with them at any given time – which will depend on their characteristics.

When an overdose occurs, naloxone will be administered with a probability that incorporates the propensities of the individual overdosing and others in that NHS Board carrying naloxone (if they have been issued with a kit) and the probability of administering naloxone when available. If naloxone is administered, an individual is selected randomly to have used their kit based on their propensity to carry, and naloxone prevents an otherwise fatal overdose with a probability based on the 'effectiveness' of THN when administered. The model will incorporate the loss and resupply of kits based on programmatic data, with uncertainty incorporated in the rate of kit loss to account for not all lost kits being replaced.



P_f is the probability that an overdose would be fatal without naloxone, which can differ based on an individual's characteristics.

P_N is the probability that naloxone is administered, which will depend upon whether an individual carries naloxone. This probability will be assumed to be independent of whether the overdose would be fatal in the absence of naloxone. This assumption will be varied in sensitivity analyses.

e is the effectiveness of naloxone in preventing an otherwise fatal overdose.

Model parameterisation and calibration

The model will be calibrated using Bayesian methods as in WP1. We will use routine Scottish Ambulance Service data on the monthly number of callouts to drug overdoses by sex, age and NHS board. Since not all overdoses result in an ambulance callout (e.g. ~12% of DRD over 2009-18), NESI will also provide estimates of the proportion of PWID that have experienced a non-fatal overdose in the past year (16% in 2019-20) and the number of times in the past year. Together, with the number of DRD, this data will be used to calibrate rates of overdose, the probability that an overdose would be fatal without naloxone, and differences by characteristics.

The NNP monitoring dataset collates data quarterly from each NHS Board and prison establishment on distribution of take-home naloxone. For each supply, this includes date of issue, source of supply (e.g. drug treatment service, hospital, pharmacy), type of supply (first, repeat, or spare) and reason for a repeat supply (e.g. whether used on self or other, or lost). If consent has been given to the sharing of an individual's personal data (88% of THN recipients), then information on age and gender of the recipient is also known. NESI will provide estimates on the proportion of PWID that have been prescribed THN (to carry) in the last year (63% in 2019-20). We will calibrate rates of naloxone prescription to programmatic data on number of kits distributed by age, sex, source and NHS board and NESI data on proportions of PWID with a prescription. We will calibrate the proportion of people leaving prison given a naloxone kit to trends in the number of kits issued at prison release.

NESI will also provide the proportions of PWID with a THN prescription that carry naloxone at time of interview (21% in 2019-20), which will be used to parameterise levels of THN carriage and how individual

characteristics affect carriage. The probability of THN administration will be calibrated to NESI data on the proportion of PWID that have administered naloxone or had naloxone used on them in the past year and programmatic data on the number of THN kits distributed for re-supply.

The National Drug-Related Deaths Database (DRDD) will provide the annual number of DRD where THN was available and, when available, was administered (data currently being updated to 2022). Historical (2018) data suggests that naloxone was administered to 0.9-8.6% of those that died. Within our approach to modelling overdose and naloxone, this proportion depends only on the probability of THN administration and its effectiveness (i.e. it does not depend on ratios of fatal to non-fatal overdoses). This data will be used to calibrate the effectiveness of THN at preventing an otherwise fatal overdose.

Model analyses (RQ11)
The model will then be used to estimate the number and proportion of DRD that have been averted by the NNP. This will be done by comparing the number of DRD in the baseline model fits with a counterfactual scenario in which naloxone is not distributed. The model will estimate the number of deaths averted nationally and for each NHS Board since the NNP was implemented, in each year and per kit distributed. Uncertainty analyses will determine which model parameters are most important for determining the impact of the NNP.

Cost effectiveness (RQ12)
We will consider cost-effectiveness from both the NHS/PSS perspective and a wider societal perspective which will include criminal justice service (CJS) costs, the societal costs of crime, patient costs, and, if agreeable with our PPI and stakeholder groups, productivity costs. NHS/PSS costs will include prescribing costs, distribution costs, costs of training users and their families, friends or carers in the use of naloxone, ambulance call outs, A&E attendances and potentially drug-related hospital admissions and drug treatment services. Where possible, we will measure the use of these resources using data from administrative sources such as the NNP monitoring data set or NESI (number of THN kits distributed), Scottish Ambulance Service data (ambulance call outs) and the linked dataset (hospital admissions and drug treatment services). To estimate resource use in non-NHS domains, we will use data from SHIELD (incarceration episodes) and NESI (employment, housing, social work, crime). We will then value these resources using unit cost data from UK sources, such as the Unit Costs of Health and Social Care [64] or The Economic and Social Costs of Crime. We will discount costs and health impacts at 3.5% as recommended by NICE [65].

Using cost estimates and model outputs, we will also estimate the cost per DRD averted, cost per life-year gained, and cost per quality-adjusted life-year gained. Quality-adjusted life-years will be calculated using quality of life data measured using the EQ-5D-5L from NESI. Uncertainty analyses will determine which model parameters and costs are most important for determining the cost-effectiveness of the NNP.

WP3: Evaluate the potential impact on DRD of changes to existing interventions and implementing novel interventions.

I Economic Inputs
We will work with policymakers, practitioners and people with living/lived experience through the PPI advisory group to review and finalise the provisional scenarios (outlined below) for changes to OAT delivery and for different combinations of OAT with other interventions. As well as clarifying the services for which cost data need to be gathered, this will inform the incremental cost effectiveness analysis. Most scenarios will involve more than one element of support so it will be important to clarify the *additional* cost and benefit arising from adding a particular intervention to a combination of interventions already in place. We will then estimate the costs of these interventions using a mixture of published and newly collected data. Where available, we will collate cost estimates from existing literature, pilot studies and

international evidence and review the appropriateness of those for use in a Scottish context. Where suitable cost data are not available, including for novel interventions proposed but not yet in place in Scotland, we will estimate the costs based on consultation with colleagues involved in the planning and delivery of services, including Public Health Scotland (PHS), to identify the inputs required to deliver each intervention within the various scenarios and then measure those inputs.

Our approach to generating naloxone costs is given above. We also will coordinate and where appropriate draw on cost data emerging from studies to evaluate the impact of the SDCF (ENACT) currently being planned in Glasgow. This includes an economic evaluation estimating the cost of the facility relative to its impacts. We also collaborate with Health Economists and Trial team evaluating safer BZD supply (IN-BOAT Trial). All costs will be expressed in terms of a common price base, updating costs from the literature with the NHS Cost Inflation Index. Sensitivity analyses will include test of the sensitivity of the cost-effectiveness results to plausible ranges in the estimated costs of the inputs to the different scenarios.

II Modelling

The model from WP1&2 will be updated using data up to 2025/6 and incorporating the evidence generated in RQs3-5. We will first use the model to update our estimates of the population-level impact of OAT and the NNP - including estimates of how many DRD may have been averted by the implementation of MAT standards 1-5 and existing provision of la-bup. The model will then project forwards to evaluate how changes to OAT delivery and OAT in combination with other interventions could increase its population impact following consultation with our PPI advisory group and stakeholder workshops. Provisional scenarios include:

1. **Increasing OAT retention and coverage.** Models will consider the impact of rigorous adoption of MAT standards and other changes (e.g. improving retention, non-fatal overdose pathways into OAT).
2. **Optimising OAT modalities.** Models will consider alternative mixes of buprenorphine, methadone, and long-acting injectable buprenorphine.
3. **Introducing SDCFs.** Model analyses will assume that SDCFs are fully effective at preventing DRD when drugs are consumed on site, with this assumption tested in sensitivity analyses. Impact will therefore be determined based on the population coverage of SDCFs, i.e. the proportion of drug consumptions that occur within SDCFs. Analyses will consider several scenarios in which the population coverage is varied based on capacity and uptake and account for SDCF users having different overdose risks to non-users [40-43]. We will explore the impact of indirect effects of SDCFs, including linkage to OAT and distribution of THN as informed by international evidence.
4. **Safer BZD prescribing**. Models will consider potential impact of BZD prescribing to reduce use of street BZD based partly on pilot evidence and establishing thresholds for reductions in DRD in relation to reductions of poly-drug use and OAT retention.

We will consider each new scenario – co-developed with PPI Advisory Board and Workshops individually and in combination. Workshops will help parameterise feasible coverage levels that could be obtained within each scenario, based on the perspectives of potential users and stakeholders. Pilot studies of introducing SCDF and safer prescribing of BZD will be used to parameterise these interventions, complemented, where needed, with international evidence (e.g. from collaborators). The models will compare impact in terms of number and proportion of DRD that could be averted compared to baseline scenario (continuing current provision of OAT and THN). We will develop a provisional economic model (RQ16) in collaboration with PHS that estimates the incremental costs of each scenario compared to baseline investment in current provision. The model will estimate and compare the incremental cost per additional life saved and incremental costs per quality adjusted life year gained. As for the economic evaluation of the NNP, we will consider both a NHS/PSS perspective and a wider societal perspective.

5. Dissemination/Outputs/Impact

Overview: Our programme of work will generate multiple outputs for use and discussion with UK policymakers, treatment providers, people with lived experience and wider community, as well as contributing to international evidence. The key aim is to improve the evidence and our shared understanding on what actions can be taken to reduce DRD in the population.

By the end of the project there will have been extensive involvement and participation by people with lived/living experience (PWLLE) through our Advisory Group and coordinated by Scottish Drugs Forum (SDF) and PPI co-leads. There will have been two workshops with peer support workers, PWLLE, drug treatment workers, providers and policymakers that will have co-produced scenarios for comparing in work package 3 and considered the implications of findings from each of the work packages.

Our co-investigators will have key roles in communicating findings with specific audiences. PHS coI (T Shivaji (TS), L Barnsdale (LB), S Hutchinson (SH), A MacAuley (AM)) will lead on sharing and communicating findings with Scottish Government, Ministers responsible for drug and health policy, and National Mission within Scottish Government. Clinical coI (S Priyadarshi (SP), J Scott, C Matheson (CM), and collaborator J Macleod) will share and discuss findings with drug treatment providers (including primary care) in Scotland and England. Public Health Leads (M Hickman (MH), TS, SH, AM) will communicate findings with Directors of Public Health in Scotland, England, Northern Ireland and Wales.

We will also draw on our excellent working relationships with our steering group and international collaborators, to get their support and advice on relevance and dissemination of findings. They will have a brokerage role in organising meetings with key stakeholders – including Drug Policy Makers in UK governments, , ACMD, , Royal College Psychiatrists Addiction Specialist Group and Faculty of Public Health Drug Harms Special Interest Group, European Union Drugs Agency (EUDA), National Institute Drug Abuse (NIDA) and WHO. We also will discuss with our steering group any implications for current NICE guidance. Our Knowledge Mobilisation and and communications strategy will be supported by PolicyBristol and Bristol's NIHR infrastructure (ARCWest and HPRU). We illustrate our approach to key messages below.

I) Web-based interactive tool

Influencing Goal: to highlight how critical OAT duration is to reducing the number of DRD in the population. *Target Stakeholders:* PH directors and commissioners in local government, drug treatment agencies, national policymakers (OHID, PHE, PHW), organisations and NGOs representing people with lived and living experience, EUDA and drug policymakers in Europe. *Timing and Activities:* We will promote and make the tool available on UoB NIHR websites and seek release or promoted links on other sites including EUDA evidence portal and Society for the Study of Addiction (SSA) website. We will create digital promotion materials and seek to launch the tool through UK public health and drug conferences and through networks and target stakeholders as advised by our coI and steering group.

II) OAT and DRD in Scotland

Influencing Goal: ensuring that drug policy and OAT delivery in UK is as evidence-based as possible. Positive findings will show how many deaths have been averted by OAT programme – which can act as springboard to next phase of project on what else needs to be done to reduce drug-related harm. They may show also that population benefit of OAT has improved after MAT standards. Negative findings, however, also are conceivable, potentially showing that population benefits of OAT are outweighed by sub-optimal delivery (e.g. poor retention) that need to be addressed urgently. *Target Stakeholders:* Drug treatment agencies and commissioners, national policymakers, organisations and NGOs representing people with lived and living experience. *Timing and Activities:* Model findings will be available by year 2. We will arrange expert meetings with policymakers in Scotland, England, Northern Ireland and Wales to discuss findings supported by our coI and Steering Group. We will discuss findings with national treatment

agencies – and prepare lay summary and policy implications based on academic paper for circulation to local government and public health commissioners. SDF will prepare briefings for NGOs.

III) Evaluation of THN in Scotland
Influencing Goal: underpin drug policy and public health guidance in UK, Europe and globally. We expect to show added value of THN in averting DRD and provide further evidence of its cost-effectiveness. *Target Stakeholders:* Policymakers in UK, international organisations developing public health guidance on preventing drug-related harm, NGOs representing people with lived and living experience. *Timing and Activities:* Model and cost-effectiveness findings will be available in year 3. We will prepare expert and policy meetings in the UK, promoting findings through our public health and user networks in the UK, and ensure that the work is presented and discussed with officials representing EUDA, and WHO.

IV) DRD Policy Model
Influencing Goal: drug policy and guidance in UK, research priorities in UK and internationally. Our model will show potential benefits of expanding OAT and other interventions to reduce DRD and compare cost effectiveness of alternative strategies that will require testing empirically and could be adapted for use in England and other countries. *Target Stakeholders:* Policymakers in UK, funding agencies in UK, Europe and US, NGOs representing PWLLE. *Timing and Activities:* Final models will be available towards the end of the project (Year 4) and will have been refined at a workshop with PPLE, treatment providers and policymakers. We will prepare additional expert and policy meetings with UK government officials on the implications of our model for harm reduction in the UK. We will promote our approach and policy model at European and other international meetings with organisations that set priorities for research funding.

There will also be statistical and model code and opportunities to share code and our learning with researchers and policymakers in England and Wales so that the models and analyses developed during this project can be replicated directly or motivate additional funding and grants to generate the datasets and analytic capacity in England and Wales. Model code and dummy datasets will be publicly archived in Github and we will develop a series of seminars/webinars for researchers at UKHSA/OHID/PHW/PHS to discuss and get training on our resources. We will support exchanges between coI in PHS and officials in OHID and PHW to determine how similar linked datasets can be established.

Academic outputs
In addition, there will be >10 academic papers plus comparative and joint papers with collaborators. These will be submitted to general medical, public health and addiction journals that support open access publication. Provisional and completed work also will be presented at national and international conferences (eg. SSA, Drugs Research Network for Scotland, Lisbon Addictions, CPDD). Lay summaries (policy briefings, blogs, and infographics) of all research academic outputs will be coproduced with our PPI advisory group, SDF and Policy Bristol.

6. Patient and Public Involvement (PPI)

We have planned meaningful PPI, co-working with community networks of people with lived and living experience (PWLLE) and peer workers at each stage. We will support a PPI advisory group – comprising people of lived/living experience of opioid use and/or DRD in a loved one – facilitated by SDF peer research network. The PPI Advisory Group will contribute to project management (including and supported by WS), interpretation and coproduction of content and dissemination plans. We will draw on the learning from our previous and ongoing NIHR funded studies (EPITOPE [RP-PG-0616-20008] and NIHR128513, in which PPI has directly informed our research, including complex mathematical modelling) to ensure we communicate the complexities of the modelling in plain English and being inclusive to those for whom literacy is a barrier. Before consulting wider stakeholders, we will work with the Scottish Drugs Forum (SDF) core peer researcher group to develop summaries, scenarios and case studies to illustrate the findings from each work package. We will co-produce these in plain English

language, then sense check their understanding with a wider group of peers using a 'Think Aloud' technique. The Co-PPI leads JScott and K Macleod (KM) at SDF will then draw on effective risk communication from the pharmacovigilance literature to present these findings at our community network meetings e.g. using visual representation tools. We have budgeted as recommended by our current PPI group for creating visual summaries of the main outputs. Our online model will be shared and tested with non-medical technicians at UoB, again using 'Think Aloud', ahead of testing with PWLLE. In addition, the PPI Advisory Group will co-organize with SDF and JScott two workshops with policymakers, practitioners, and PWLLE consulting on findings from WP1&2 and co-producing the scenarios modelled in WP3. We propose bi-monthly PPI advisory group.

7. Ethics

Ethical approval was obtained from the University of Bristol Faculty of Health Sciences Research Ethics Committee (FREC) on 11th June 2025 (reference 26008). We have applied to the Public Benefit and Privacy Panel for Health and Social Care for access to the SHIELD data to conduct analyses for this project.

8. Success criteria and barriers to proposed work

Measures of success:

- Effective and impactful involvement of people with lived experience measured through our impact log.
- Effective stakeholder buy-in and engagement and high-level discussions with Scottish government.
- Motivating changes to drug policy and OAT and harm reduction provision to reduce DRD as key public health priority.
- Dissemination of policy briefings.
- New grants and projects to replicate modelling and statistical analyses in England and Wales in collaboration with PHW and OHID.
- Presentation of research findings at national and international conferences.
- Multiple high impact academic outputs.

Potential Barriers:

- Exposure to OAT in prison will be identified through linkage to other data sources if specific prison health data are unavailable. We will explore whether this introduces bias compared to other studies in the literature – and if required in the modelling use parameters informed by literature.
- Time needed to calibrate complex models can be substantial and increases with model complexity. In anticipation of such difficulties, we have budgeted for a high-performance laptop capable of simulating multiple model runs simultaneously during model testing prior to use of Bristol's High performance computing facilities.
- Models may require simplifying if there are difficulties calibrating them. Any such changes would be discussed with the project steering group and stakeholders to ensure key features are still modelled.

9. References

1. National Records of Scotland. Drug-related Deaths in Scotland in 2022. Available at https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2022.
2. Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet. 2019;394(10208):1560-79. https://doi.org/10.1016/S0140-6736(19)32229-9
3. Ahmad FB CJ, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2023. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

4. McAuley A, Fraser R, Glancy M, Yeung A, Jones HE, Vickerman P, et al. Mortality among individuals prescribed opioid-agonist therapy in Scotland, UK, 2011-20: a national retrospective cohort study. Lancet Public Health. 2023;8(7):e484-e93. https://doi.org/10.1016/S2468-2667(23)00082-8
5. House of Commons Scottish Affairs Committee. Problem drug use in Scotland. 2019. Available at: https://publications.parliament.uk/pa/cm201919/cmselect/cmscotaf/44/44.pdf.
6. Advisory Council on the Misuse of Drugs. Ageing cohort of drug users. 2019. Available at: https://assets.publishing.service.gov.uk/media/5d037c2ee5274a0b8016b395/Ageing_cohort_of_drug_users.pdf.
7. Lewer D, Brothers TD, Van Hest N, Hickman M, Holland A, Padmanathan P, et al. Causes of death among people who used illicit opioids in England, 2001-18: a matched cohort study. Lancet Public Health. 2022;7(2):e126-e35. https://doi.org/10.1016/S2468-2667(21)00254-1
8. McDonald SA, McAuley A, Hickman M, Bird SM, Weir A, Templeton K, et al. Increasing drug-related mortality rates over the last decade in Scotland are not just due to an ageing cohort: A retrospective longitudinal cohort study. Int J Drug Policy. 2021;96:103286. https://doi.org/10.1016/j.drugpo.2021.103286
9. Public Health Scotland. Estimated Prevalence of Opioid Dependence in Scotland. 2024. Available at: https://www.drugsandalcohol.ie/40706/1/opioid-prevalence-report.pdf.
10. Macleod J, Steer C, Tilling K, Cornish R, Marsden J, Millar T, et al. Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records. PLoS Med. 2019;16(11):e1002965. https://doi.org/10.1371/journal.pmed.1002965
11. Hickman M, Steer C, Tilling K, Lim AG, Marsden J, Millar T, et al. The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom. Addiction. 2018;113(8):1461-76. https://doi.org/10.1111/add.14188
12. McAuley A, Matheson C, Robertson JR. From the clinic to the street: the changing role of benzodiazepines in the Scottish overdose epidemic. Int J Drug Policy. 2022;100:103512. https://doi.org/10.1016/j.drugpo.2021.103512
13. Scottish Government. Suspected drug deaths in Scotland: July to September 2023. Available at: https://www.gov.scot/publications/suspected-drug-deaths-scotland-july-september-2023/documents/.
14. Santo T, Jr., Clark B, Hickman M, Grebely J, Campbell G, Sordo L, et al. Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021;78(9):979-93. https://doi.org/10.1001/jamapsychiatry.2021.0976
15. Rao IJ, Humphreys K, Brandeau ML. Effectiveness of Policies for Addressing the US Opioid Epidemic: A Model-Based Analysis from the Stanford-Lancet Commission on the North American Opioid Crisis. Lancet Reg Health Am. 2021;3. https://doi.org/10.1016/j.lana.2021.100031
16. Zhu DT, Friedman J, Bourgois P, Montero F, Tamang S. The emerging fentanyl-xylazine syndemic in the USA: challenges and future directions. Lancet. 2023;402(10416):1949-52. https://doi.org/10.1016/S0140-6736(23)01686-0
17. Colledge-Frisby S, Ottaviano S, Webb P, Grebely J, Wheeler A, Cunningham EB, et al. Global coverage of interventions to prevent and manage drug-related harms among people who inject drugs: a systematic review. Lancet Glob Health. 2023;11(5):e673-e83. https://doi.org/10.1016/S2214-109X(23)00058-X
18. Martin NK, Vickerman P, Dore GJ, Grebely J, Miners A, Cairns J, et al. Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation. J Hepatol. 2016;65(1):17-25. https://doi.org/10.1016/j.jhep.2016.02.007
19. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, et al. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. Addiction. 2018;113(3):545-63. https://doi.org/10.1111/add.14012
20. Palmateer NE, McAuley A, Dillon JF, McDonald S, Yeung A, Smith S, et al. Reduction in the population prevalence of hepatitis C virus viraemia among people who inject drugs associated with scale-up of direct-acting anti-viral therapy in community drug services: real-world data. Addiction. 2021;116(10):2893-907. https://doi.org/10.1111/add.15459
21. Palmateer N, Hamill V, Bergenstrom A, Bloomfield H, Gordon L, Stone J, et al. Interventions to prevent HIV and Hepatitis C among people who inject drugs: Latest evidence of effectiveness from a systematic review (2011 to 2020). Int J Drug Policy. 2022;109:103872. https://doi.org/10.1016/j.drugpo.2022.103872
22. Padmanathan P, Forbes H, Redaniel MT, Gunnell D, Lewer D, Moran P, et al. Self-harm and suicide during and after opioid agonist treatment among primary care patients in England: a cohort study. Lancet Psychiatry. 2022;9(2):151-9. https://doi.org/10.1016/S2215-0366(21)00392-8

23. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010;341:c5475. https://doi.org/10.1136/bmj.c5475
24. Degenhardt L, Clark B, Macpherson G, Leppan O, Nielsen S, Zahra E, et al. Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomised and observational studies. Lancet Psychiatry. 2023;10(6):386-402. https://doi.org/10.1016/S2215-0366(23)00095-0
25. National Institute for Health and Care Excellence. ES19: Opioid dependence: buprenorphine prolonged-release injection (Buvidal)/ 2019 https://www.nice.org.uk/advice/es19/chapter/Factors-for-decision-making.
26. Marsden J, Stillwell G, Jones H, Cooper A, Eastwood B, Farrell M, et al. Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England. Addiction. 2017;112(8):1408-18. https://doi.org/10.1111/add.13779
27. Degenhardt L, Larney S, Kimber J, Gisev N, Farrell M, Dobbins T, et al. The impact of opioid substitution therapy on mortality post-release from prison: retrospective data linkage study. Addiction. 2014;109(8):1306-17. https://doi.org/10.1111/add.12536
28. Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ. 2013;346:f174. https://doi.org/10.1136/bmj.f174
29. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction. 2016;111(7):1177-87. https://doi.org/10.1111/add.13326
30. Nielsen S, Scott N, Tidhar T, Quiroga MDM, Lenton S, Dietze P. The cost and impact of distributing naloxone to people who are prescribed opioids to prevent opioid-related deaths: findings from a modelling study. Addiction. 2022;117(4):1009-19. https://doi.org/10.1111/add.15727
31. Cherrier N, Kearon J, Tetreault R, Garasia S, Guindon E. Community Distribution of Naloxone: A Systematic Review of Economic Evaluations. Pharmacoecon Open. 2022;6(3):329-42. https://doi.org/10.1007/s41669-021-00309-z
32. Langham S, Wright A, Kenworthy J, Grieve R, Dunlop WCN. Cost-Effectiveness of Take-Home Naloxone for the Prevention of Overdose Fatalities among Heroin Users in the United Kingdom. Value Health. 2018;21(4):407-15. https://doi.org/10.1016/j.jval.2017.07.014
33. McAuley A, Best D, Taylor A, Hunter C, Robertson R. From evidence to policy: The Scottish national naloxone programme. Drugs: Education, Prevention and Policy. 2012;19(4):309-19. https://doi.org/10.3109/09687637.2012.682232
34. Public Health Scotland. National Naloxone Programme Scotland Quarterly Monitoring Bulletin January to March (Q4) 2022/23. https://publichealthscotland.scot/publications/national-naloxone-programme-scotland-quarterly-monitoring-bulletin/national-naloxone-programme-scotland-quarterly-monitoring-bulletin-january-to-march-q4-202223/.
35. Bird SM, McAuley A. Scotland's National Naloxone Programme. Lancet. 2019;393(10169):316-8. https://doi.org/10.1016/S0140-6736(18)33065-4
36. Bird SM, McAuley A, Perry S, Hunter C. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison. Addiction. 2016;111(5):883-91. https://doi.org/10.1111/add.13265
37. A McAuley et al. (2022) Evaluating the impact of Public Health interventions in reducing harms related to Substance Use in Scotland (EPHeSUS): final report to Drug Death Task Force.
38. Marshall BD, Milloy MJ, Wood E, Montaner JS, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. Lancet. 2011;377(9775):1429-37. https://doi.org/10.1016/S0140-6736(10)62353-7
39. Poschadel S, Höger R, Schnitzler J, Schreckenberger J. Evaluation der Arbeit der Drogenkonsumräume in der Bundesrepublik Deutschland: Endbericht im Auftrag des Bundesministeriums für Gesundheit. Baden-Baden, Germany: Nomos. 2003.
40. Wood E, Tyndall MW, Li K, Lloyd-Smith E, Small W, Montaner JS, et al. Do supervised injecting facilities attract higher-risk injection drug users? American journal of preventive medicine. 2005;29(2):126-30. https://doi.org/10.1016/j.amepre.2005.04.011
41. Van Den Boom W, Del Mar Quiroga M, Fetene DM, Agius PA, Higgs PG, Maher L, et al. The Melbourne Safe Injecting Room Attracted People Most in Need of Its Service. American journal of preventive medicine. 2021;61(2):217-24. https://doi.org/10.1016/j.amepre.2021.02.018

42. Scheim AI, Bouck Z, Tookey P, Hopkins S, Sniderman R, McLean E, et al. Supervised consumption service use and recent non-fatal overdose among people who inject drugs in Toronto, Canada. Int J Drug Policy. 2021;87:102993. https://doi.org/10.1016/j.drugpo.2020.102993
43. Kennedy MC, Hayashi K, Milloy MJ, Compton M, Kerr T. Health impacts of a scale-up of supervised injection services in a Canadian setting: an interrupted time series analysis. Addiction. 2022;117(4):986-97. https://doi.org/10.1111/add.15717
44. Kennedy MC, Karamouzian M, Kerr T. Public Health and Public Order Outcomes Associated with Supervised Drug Consumption Facilities: a Systematic Review. Curr HIV/AIDS Rep. 2017;14(5):161-83. https://doi.org/10.1007/s11904-017-0363-y
45. Irvine MA, Kuo M, Buxton JA, Balshaw R, Otterstatter M, Macdougall L, et al. Modelling the combined impact of interventions in averting deaths during a synthetic-opioid overdose epidemic. Addiction. 2019;114(9):1602-13. https://doi.org/10.1111/add.14664
46. McAuley A, Palmateer NE, Goldberg DJ, Trayner KMA, Shepherd SJ, Gunson RN, et al. Re-emergence of HIV related to injecting drug use despite a comprehensive harm reduction environment: a cross-sectional analysis. Lancet HIV. 2019;6(5):e315-24. https://doi.org/10.1016/S2352-3018(19)30036-0
47. Trayner KMA, McAuley A, Palmateer NE, Goldberg DJ, Shepherd SJ, Gunson RN, et al. Increased risk of HIV and other drug-related harms associated with injecting in public places: national bio-behavioural survey of people who inject drugs. Int J Drug Policy. 2020;77:102663. https://doi.org/10.1016/j.drugpo.2020.102663
48. Berry K, Matheson C, Schofield J, Dumbrell J, Parkes T, Hill D, et al. Development of an intervention to manage benzodiazepine dependence and high-risk use in the context of escalating drug related deaths in Scotland: an application of the MRC framework. BMC Health Serv Res. 2023;23(1):1205. https://doi.org/10.1186/s12913-023-10201-7
49. O. U. D. Modeling writing group. How simulation modeling can support the public health response to the opioid crisis in North America: Setting priorities and assessing value. Int J Drug Policy. 2021;88:102726. https://doi.org/10.1016/j.drugpo.2020.102726
50. Martin NK, Vickerman P. The use of mathematical modeling to inform drug policy making. Int J Drug Policy. 2021;88:102759. https://doi.org/10.1016/j.drugpo.2020.102759
51. Stone J, Degenhardt L, Grebely J, Larney S, Altice FL, Smyrnov P, et al. Modelling the intervention effect of opioid agonist treatment on multiple mortality outcomes in people who inject drugs: a three-setting analysis. Lancet Psychiatry. 2021;8(4):301-9. https://doi.org/10.1016/S2215-0366(20)30538-1
52. Chaillon A, Bharat C, Stone J, Jones N, Degenhardt L, Larney S, et al. Modeling the population-level impact of opioid agonist treatment on mortality among people accessing treatment between 2001 and 2020 in New South Wales, Australia. Addiction. 2022;117(5):1338-52. https://doi.org/10.1111/add.15736
53. Angus C, Buckley C, Tilstra AM, Dowd JB. Increases in 'deaths of despair' during the COVID-19 pandemic in the United States and the United Kingdom. Public Health. 2023;218:92-6. https://doi.org/10.1016/j.puhe.2023.02.019
54. van Santen DK, Boyd A, Matser A, Maher L, Hickman M, Lodi S, et al. The effect of needle and syringe program and opioid agonist therapy on the risk of HIV, hepatitis B and C virus infection for people who inject drugs in Amsterdam, the Netherlands: findings from an emulated target trial. Addiction. 2021;116(11):3115-26. https://doi.org/10.1111/add.15503
55. Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-64. https://doi.org/10.1093/aje/kwv254
56. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technol Assess. 2007;11(9):1-171, iii-iv. https://doi.org/10.3310/hta11090
57. Pierce M, Bird SM, Hickman M, Marsden J, Dunn G, Seddon T, et al. Effect of initiating drug treatment on the risk of drug-related poisoning death and acquisitive crime among offending heroin users. Int J Drug Policy. 2018;51:42-51. https://doi.org/10.1016/j.drugpo.2017.09.017
58. Larney S, Toson B, Burns L, Dolan K. Effect of prison-based opioid substitution treatment and post-release retention in treatment on risk of re-incarceration. Addiction. 2012;107(2):372-80. https://doi.org/10.1111/j.1360-0443.2011.03618.x
59. Bird SM, Hutchinson SJ. Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996-99. Addiction. 2003;98(2):185-90. https://doi.org/10.1046/j.1360-0443.2003.00264.x
60. Seaman SR, Brettle RP, Gore SM. Mortality from overdose among injecting drug users recently released from prison: database linkage study. BMJ. 1998;316(7129):426-8. https://doi.org/10.1136/bmj.316.7129.426

61. Graham L, Fischbacher CM, Stockton D, Fraser A, Fleming M, Greig K. Understanding extreme mortality among prisoners: a national cohort study in Scotland using data linkage. European journal of public health. 2015;25(5):879-85. https://doi.org/10.1093/eurpub/cku252
62. McAuley A, Palmateer N, Goldberg DJ, Shivaji T, Ritchie T, Licence K, et al. Increased risk of non-fatal overdose associated with non-prescribed benzodiazepine use in Scotland, UK. Int J Drug Policy. 2023:104236. https://doi.org/10.1016/j.drugpo.2023.104236
63. Stone J, Martin NK, Hickman M, Hutchinson SJ, Aspinall E, Taylor A, et al. Modelling the impact of incarceration and prison-based hepatitis C virus (HCV) treatment on HCV transmission among people who inject drugs in Scotland. Addiction. 2017;112(7):1302-14. https://doi.org/10.1111/add.13783
64. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit costs of health and social care 2022 manual. 2022. https://doi.org/10.22024/UniKent%2F01.02.100519
65. National Institute of Health and Care Excellence (2023) NICE health technology evaluations: the manual. Process and methods [PMG36]. London: National Institute of Health and Care Excellence. Available at: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation.