Check for updates

STUDY PROTOCOL

REVISED Improving hospital-based opioid substitution therapy (iHOST): protocol for a mixed-methods evaluation

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

Dan Lewer[1,2], Michael Brown[3,4*], Adam Burns[5*], Niamh Eastwood[6*], Rosalind Gittins[7*], Adam Holland[8*], Vivian Hope[9*], Aubrey Ko[10*], Penny Lewthwaite[5*], Ann-Marie Morris[11*], Adrian Noctor[3*], Andrew Preston[4*], Jenny Scott[8*], Erica Smith[11*], Sedona Sweeney[10*], Nerissa Tilouche[10*], Marisha Wickremsinhe[10*], Magdalena Harris[10]

[1]Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, England, BD9 6RJ, UK
[2]University College London, London, England, WC1E 6AE, UK
[3]University College London Hospitals NHS Foundation Trust, London, NW1 2PG, UK
[4]Exchange Supplies, Dorchester, DT1 1RD, UK
[5]Leeds Teaching Hospitals NHS Trust, Leeds, LS9 7TF, UK
[6]Release, London, E1 8AN, UK
[7]Aston University, Birmingham, England, B4 7ET, UK
[8]University of Bristol, Bristol, England, BS8 1QU, UK
[9]Liverpool John Moores University, Liverpool, England, L2 2QP, UK
[10]London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK
[11]University Hospital of the North Midlands NHS Trust, Stoke-on-Trent, ST4 6QG, UK

* Equal contributors

v2 **First published:** 13 Mar 2024, **4**:10
https://doi.org/10.3310/nihropenres.13534.1
Latest published: 06 Nov 2024, **4**:10
https://doi.org/10.3310/nihropenres.13534.2

Abstract

Background

Opioid substitution therapy (also known as 'opioid agonist therapy' or 'medication treatment of opioid use disorder') is associated with improved health and social outcomes for people who use heroin and other illicit opioids. It is typically managed in the community and is not always continued when people are admitted to hospital. This causes opioid withdrawal, patient-directed discharge, and increased costs. We are establishing a project called iHOST (improving hospital opioid substitution therapy) to address these problems. This is an applied health research project in which we will develop and evaluate an intervention that aims to improve opioid substitution therapy in three acute hospitals in England. The intervention was developed in

Open Peer Review

Approval Status ? ✓

	1	2
version 2 (revision) 06 Nov 2024		
version 1 13 Mar 2024	? view	✓ view

1. **Sandra A Springer**, Yale School of Medicine, Connecticut, USA

2. **Chris Tremonti**, Alcohol and Drug Services St Vincent's Hospital, University of Sydney, Sydney, Australia

collaboration with stakeholders including people who use opioids, hospital staff, and other professionals who work with this group. It includes five components: (1) a card that patients can use to help hospital clinicians confirm their opioid substitution therapy, (2) a helpline for patients and staff, (3) an online training module for staff, (4) a clinical guideline for managing opioid withdrawal in hospital, and (5) 'champion' roles at each hospital.

Methods

We will do a mixed-methods study including a quasi-experimental quantitative study and a qualitative process evaluation. The primary outcomes for the quantitative study are patient-directed discharge and emergency readmission within 28 days. We will do a difference-in-difference analysis comparing changes in these outcomes for patients at iHOST sites with changes for patients at control hospitals. The process evaluation will use in-depth interviews, focus groups, and site observations with people who use opioids and staff. We will assess acceptability of the intervention, barriers and facilitators to implementation, and contextual factors impacting outcomes.

Impact

We anticipate that iHOST will improve care for hospital patients who use illicit opioids and/or are receiving community-based opioid substitution therapy. Depending on the results, we will promote the intervention at hospitals across the UK. Dissemination, including through publication, will inform hospital-based services for people who use drugs both in the UK and other countries.

Any reports and responses or comments on the article can be found at the end of the article.

Plain English Summary

People who use heroin and other illegal opioids can be supported with medically prescribed opioids. These legal medicines, like methadone and buprenorphine, can reduce the need for illegal opioids and improve overall wellbeing. Normally, these treatments are managed in community clinics. They can be provided at stable doses for long periods, sometimes decades.

However, when people are admitted to hospital for treatment of medical problems, they don't always continue receiving these crucial treatments. This happens for various reasons – sometimes hospital staff do not fully understand how the medicines work, or the hospital might have overly strict rules that restrict their use. As a result, patients can experience opioid withdrawal and pain, which can lead them to leave hospital to buy illegal opioids. It might also cause arguments between staff and patients. Hospitals often focus too much on potential risks associated with these medicines, and sometimes forget the needs of patients who depend on them.

We are addressing these issues in three hospitals in England. Our

project consists of five components: (1) a patient card with information about their opioid treatment to speed up prescriptions; (2) a helpline for patients and hospital staff to seek support; (3) an online training module for hospital staff; (4) clinical guidelines for managing opioid withdrawal in hospitals; (5) named 'champions' in each hospital to raise the profile of these resources. These components have been developed together with people who use heroin and hospital staff.

We will study the effect of the project using a combination of quantitative and qualitative methods. The quantitative aspect will assess how the project affects the number of patients leaving against medical advice or returning to hospital in emergencies. The qualitative aspect will involve interviews and focus groups to understand how patients and staff perceive the project.

Keywords
Opiate Substitution Treatment, Methadone, Buprenorphine, Substance-Related Disorders, Opioid-Related Disorders, Heroin Dependence, Hospitals, Staff Development

Corresponding authors: Dan Lewer (dan.lewer@bthft.nhs.uk), Magdalena Harris (magdalena.harris@lshtm.ac.uk)

Author roles: Lewer D: Conceptualization, Funding Acquisition, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Brown M**: Conceptualization, Funding Acquisition, Methodology, Resources, Supervision, Writing – Review & Editing; **Burns A**: Conceptualization, Methodology, Resources, Supervision, Writing – Review & Editing; **Eastwood N**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Gittins R**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Holland A**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Hope V**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Ko A**: Project Administration, Resources, Writing – Review & Editing; **Lewthwaite P**: Conceptualization, Methodology, Resources, Supervision, Writing – Review & Editing; **Morris AM**: Conceptualization, Methodology, Resources, Supervision, Writing – Review & Editing; **Noctor A**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Preston A**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Scott J**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Smith E**: Conceptualization, Methodology, Resources, Supervision, Writing – Review & Editing; **Sweeney S**: Conceptualization, Methodology, Writing – Review & Editing; **Tilouche N**: Conceptualization, Methodology, Writing – Review & Editing; **Wickremsinhe M**: Methodology, Writing – Review & Editing; **Harris M**: Conceptualization, Funding Acquisition, Methodology, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: AH is conducting a PhD funded by the Medical Research Council, grants MR/W006308/1 and MR/X018636/1; he is Co-Chair of the Faculty of Public Health Drugs Special Interest Group; volunteers for the Loop (a drug checking organisation); is a member of the Drug Science Enhanced Harm Reduction Working Group (EHRWG); and in the last three years was Associate Director of International Doctors for Healthier Drug Policies.

Grant information: This project is funded by the National Institute for Health and Care Research (NIHR), a 'Health and Social Care Delivery Research' award to Professor Magdalena Harris (Improving Hospital Opiate Substitution Therapy (iHOST), Grant Reference Number NIHR133022). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2024 Lewer D *et al*. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Lewer D, Brown M, Burns A *et al.* **Improving hospital-based opioid substitution therapy (iHOST): protocol for a mixed-methods evaluation [version 2; peer review: 1 approved, 1 approved with reservations]** NIHR Open Research 2024, **4**:10 https://doi.org/10.3310/nihropenres.13534.2

First published: 13 Mar 2024, **4**:10 https://doi.org/10.3310/nihropenres.13534.1

REVISED **Amendments from Version 1**

In the revised version, we have:

1. Updated terminology following advice from peer reviewers, including the use of the term "patient-directed discharge".

2. Clarified limitations regarding the evaluation methodology, including the possible differing use of ICD-10 codes between intervention and control sites.

3. General improvements to the clarity of the text.

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

Introduction

People who use illicit opioids such as heroin have a high rate of hospital admission, particularly due to injecting-related and respiratory infections, exacerbations of chronic respiratory diseases, and gastrointestinal problems related to hepatitis and comorbid alcohol dependence[1–3]. In the UK the population using illicit opioids is ageing due a peak in initiation of heroin use in the 1980s and 1990s[4,5]. Management and acute treatment of long-term conditions is therefore becoming a more important issue in this population.

Many people who use illicit opioids report poor experiences when admitted to hospital. Qualitative research has found evidence of stigma among hospital staff, diagnostic overshadowing (in which symptoms are attributed to drug use and not investigated to the same extent as other patients), poor pain relief, and limited availability of opioid substitution therapy (OST)[6–10]. OST (also known as 'opioid agonist therapy' or 'medication treatment of opioid use disorder') is a medical intervention that includes prescription of opioids such as methadone or buprenorphine to alleviate opioid withdrawal, reduce illicit drug use, and help provide stability[11]. In the UK, it is typically managed in community-based clinics, and at the time of writing (2024), methadone is the most prescribed medicine, and buprenorphine is less commonly used. While data on the relative use of methadone and buprenorphine in OST in the UK is not readily available, some hospital guidelines for management of substance dependence do not mention buprenorphine[12]. Research in the UK and internationally shows that lack of OST in hospitals is a key barrier to hospital care and means that people are reluctant to go to hospital until symptoms are severe, or may leave hospital before completing treatment to access illicit opioids (a scenario called 'patient-directed discharge)[8,13,14].

Outcomes for this patient group are poor. For example, approximately 10% of inpatient admissions among people with a history of using illicit opioids end in patient-directed discharge (compared to approximately 1% of all admissions)[15–17]; 80% of admissions are unplanned (compared to 50% for all hospital inpatients of the same age[18]); and the risk of fatal opioid overdose is four times greater in the two weeks after hospital discharge than at other times[15].

Various initiatives have been established to improve OST and care for hospital patients who use illicit drugs[19]. These include addiction liaison teams, in which multidisciplinary specialists support ward staff to care for patients who use drugs and alcohol; bridge clinics, which aim to link patients with community addiction services and provide addiction treatment while these linkages are being made; and training for general medical staff[19,20]. These initiatives have mostly been studied in North America. The 'Improving Hospital Opioid Substitution Treatment' (iHOST) project is working with three acute hospitals in England to develop, test, and evaluate an intervention to improve opioid withdrawal management and OST provision in acute NHS Hospitals.

Protocol

Patient and public involvement

The project stemmed from community-identified need, and intervention components were co-produced with people who use heroin and/or receive OST. Our advisory board members, peer researchers, and investigators also include people with past and current experience of opioid use to ensure community accountability. Some of authors listed on the present paper have past or current experience of opioid use.

In quarterly workshops throughout the project we will work with a group of 'peer experts' (people who currently use opioids or are on OST) to discuss project progress and findings and iteratively co-create a cultural safety framework to inform hospital care for people who use opioids in England. This participatory approach is core to the iHOST project.

Cultural safety principles focus on the way dominant cultural expectations of healthcare can be experienced as unsafe by marginalised groups[21–24]. Cultural safety principles aim to reduce health care practices that cause marginalised patients to feel unsafe and powerless. Developed by nurse academics working with Maori patients in New Zealand, this approach has been translated widely, including for practitioners working with people who use drugs in North America.

Aims and objectives

iHOST aims to improve OST in hospital settings to: (1) reduce barriers to hospital presentation and reduce delayed presentations, (2) improve care, (3) reduce patient-directed discharges, and (4) reduce emergency readmissions. The research objectives are to: (1) optimise iHOST components and test feasibility in a London hospital and associated local drug services; (2) evaluate intervention acceptability, fidelity, reach, costs, and impact; (3) develop and disseminate toolkits for national implementation.

The intervention

We will develop and evaluate an intervention (iHOST) to improve OST in acute hospital settings. iHOST will be implemented at three acute hospitals in England: University College London Hospital, St. James University Hospital Leeds, and Royal Stoke University Hospital. The project will be developed in

partnership with local drug treatment services. The intervention primarily aims to improve continuation of OST from community to hospital settings but will also inform OST initiation and discharge planning for patients who were not already in receipt of community-based OST. The programme phases are shown in Figure 1, and launch dates are currently anticipated to be:

- University College London Hospital: November 2022 (already launched at the time of publication)
- St James University Hospital Leeds: January 2024
- Royal Stoke University Hospital: January 2024

iHOST is designed to be pragmatic and work in real-world hospitals and drug treatment services. It consists of five components, which are listed below. More information is available at https://www.lshtm.ac.uk/research/centres-projects-groups/ihost.

a) My Meds Card: A patient advocacy card designed for hospital patients who receive OST in the community. This includes information about the importance of timely OST on hospital admission, a space for prescriber and community pharmacy contact details to enable verification of the patient's OST dose, and an advocacy helpline number (see below). Patients can give the card to hospital clinicians to facilitate OST. The card was co-produced in workshops with people who use opioids and refined in collaboration with hospital clinicians, pharmacy, and drug treatment service providers.

b) A helpline for patients and hospital staff run by the drugs advocacy charity Release (https://www.release.org.uk/). The helpline supports patients in advocating for OST access and supports hospital staff who have questions about OST.

c) An online training module for hospital staff working in acute admissions and key specialties such as infection control and hepatology. The module aims to improve knowledge about opioid dependency and withdrawal and develop non-stigmatising care and communication practices. The e-learning module will be hosted on the Exchange Supplies training site with embedded attitude and knowledge evaluation measures assessed at pre- and post-completion. The module will draw on cultural safety principles to

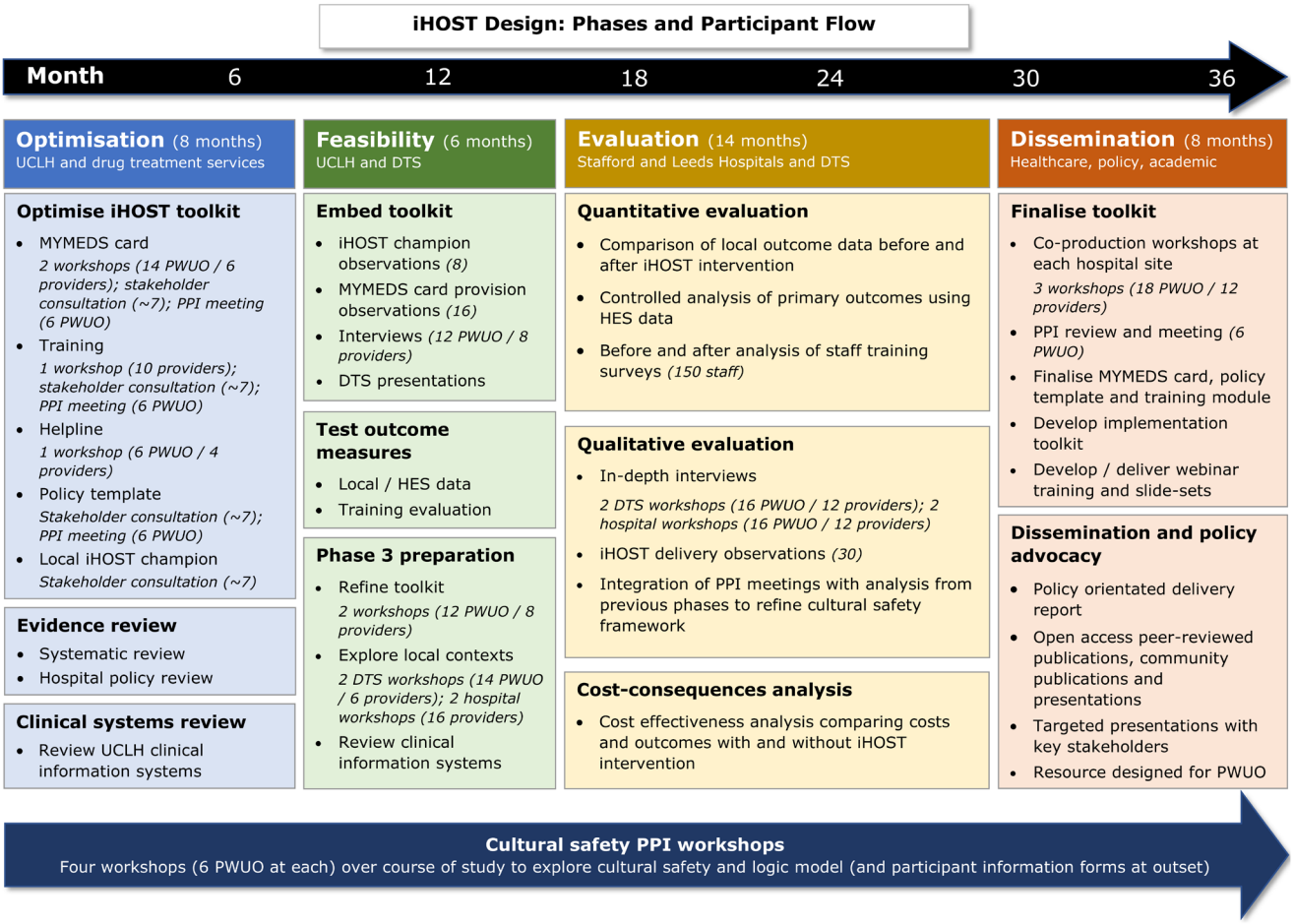

Figure 1. Programme phases.

encourage practitioners to reflect on how power relations, social norms and inequity can impact health care opportunity and outcomes, including through the expression of their personal attitudes and beliefs.

d) A clinical guideline for managing opioid withdrawal, including continuity of care between community and hospital prescribers, and where necessary initiation or retitration of OST. The guideline will be developed through consultations with stakeholders, including people who use drugs, hospital staff, and representatives of national organisations, and will seek to reduce procedural barriers identified through a review of existing hospital policies[12].

e) An iHOST 'champion' role to support implementation of iHOST. The champion will support colleagues to adopt iHOST principles. iHOST champions will receive a role description, dedicated training in addition to the online module described above, and an 'iHOST champion' badge.

Systematic review

We will do a systematic review of published studies that evaluate projects aiming to improve OST in acute hospital settings. This will include a structured search for studies using any design to evaluate relevant interventions and a narrative review of findings. The protocol is published on PROSPERO[25].

Process evaluation

We will conduct a process evaluation at each site to examine intervention fidelity, acceptability, and perceived impact on practice. We will primarily use qualitative methods to explore implementation processes, intervention mechanisms and how these vary between sites.

The methods comprise:

1. Focus groups. These will be conducted before iHOST implementation with people who use opioids and hospital staff. The aim will be to develop a baseline understanding of each local context, including drug market dynamics, service accessibility for people who use drugs, hospital opioid withdrawal management practice and perceived quality of relationships between drug treatment and hospital services. One group will be held at each local community drug treatment service and intervention hospital (ie. a total of six groups).

2. In-depth interviews. These will be conducted at least two months after iHOST is launched, with hospital staff and inpatients who use opioids. The aim will be to assess acceptability and fidelity of implementation. Interviews will be informed by a topic guide including perceptions of the hospital culture, experiences of the intervention, care for patients who use opioids, communications between hospital and community services, and perceptions/experiences of opioid toxicity risk.

3. Observations. These will be conducted in each hospital site both prior to and during iHOST implementation. We will shadow clinical staff to observe the dynamics of care for people who use opioids in practice, and conduct observations during interview, training and focus group visits. Observations will be recorded as ethnographic field notes, with a focus on conveying detailed information about the context and culture of each hospital site and how this interacts with the iHOST implementation process.

4. Measuring intervention reach. We will get the number of advocacy cards distributed from local drug treatment services, numbers accessing the helpline, and numbers accessing the online module. The champions will be asked to keep a log of activities they carry out in support of intervention delivery (with support from the local iHOST lead).

Analysis. We will transcribe all audio-recorded interviews and focus groups. Transcripts, interview field notes, and ethnographic observations will be uploaded into NVivo 12 for qualitative data management and analysis. We will conduct a thematic analysis, informed by constructivist grounded theory[26] principles. Grounded theory is an analytic method for studying processes, particularly useful for generating theory that can be applied in other sites and conditions. Coding will be implemented in a stepwise process, comprising open inductive coding, focused coding, category mapping, and theme development.

Qualitative data generated will take a number of forms (interviews, focus groups, ethnographic field notes), capture multiple perspectives (people who use drugs in and out of hospital, drug treatment and hospital care providers) and reflect different contexts (the three sites). We will 'triangulate' (compare/contrast)[27] these data to explore how and in what way the iHOST intervention works, for whom and in what context.

Measures of intervention reach will be described and assessed alongside the qualitative data to inform understandings of iHOST implementation in context, including barriers and facilitators to uptake of different intervention components, how this is reflected in patient and provider perceptions of the intervention and outcome measures for each site.

Difference-in-difference study

Study design. We will do a controlled study that will use data from iHOST hospitals and control hospitals (where iHOST is not implemented) to estimate the effect of iHOST on two outcomes: patient-directed discharge and emergency readmission within 28 days.

The study will use a difference-in-difference method[28,29]. This is a quasi-experimental design that aims to measure the effect of a change in clinical practice when the change in practice was not randomised. The method works by measuring

patient outcomes in two groups (iHOST hospitals and control hospitals) and at two points in time. At the first point in time iHOST is not implemented in either group. At the second point in time, iHOST is only implemented in one group. The design is based on comparing the change in outcomes.

The purpose of including control hospitals is to account for background trends in outcomes that are common across hospitals. Examples include changes in the population (such as ageing), national policies, national restrictions related to COVID-19, and changes in drug supply. The design is more robust than an uncontrolled pre-post study, but less robust than a randomised experiment.

A central assumption of the difference-in-difference method is that there are common trends in the outcome across participants. In the absence of the intervention, we assume that the change in outcome observed in the control group would have happened in the intervention group. In Figure 2, the 'counterfactual iHOST' risk is estimated using the trend in the control group, and the estimated effect of iHOST is the difference between the observed and counterfactual iHOST risks.

Population. The study will use the Hospital Episode Statistics database, which includes all inpatient, outpatient, and A&E episodes at NHS hospitals in England[30].

The target population is hospital admissions for patients who may benefit from OST. Hospital Episode Statistics does not include records of OST (either in the community or in hospitals), and therefore the study will use a proxy of patients with records of opioid dependence. This will be defined as emergency hospital admissions (i.e., where the field ADMIMETH is 21-25, 2A, 2B, 2C, 2D, or 28) at acute hospitals in England, where the patient was (a) aged 18–64 years at admission; (b) the date of admission was between 12 months before and 12 months after the iHOST site's implementation dates; and (c) the ICD-10 code F11 ('mental and behavioural disorders due to use of opioids') was recorded either at that admission or at another hospital episode for that patient in the preceding 12 months.

We will include patients from the three iHOST sites and from the 50 largest acute hospitals in England where iHOST is not being implemented (when size is defined by the number of patients meeting the criteria listed above). The reason for limiting the control group to the 50 largest hospitals is to exclude small hospitals that may have volatile trends in patient characteristics or outcomes.

Analysis. iHOST will be implemented at different times at each of the three participating hospitals. This means that background trends in outcomes could be different, and the analysis will therefore be done separately for each hospital.

For analysis of patient-directed discharge, study entry will be at hospital admission. For analysis of readmission, study entry will be at discharge, such that patients who died during the index admission are excluded. We will use a mixed (hierarchical) linear model in which the dependent variable is a binary indicator of the outcome, and independent variables are an interaction term between two binary outcomes: time (i.e., before/after iHOST implementation) and iHOST site or control; a random intercept for the hospital site; and patient-level confounders/covariates. This approach to modelling is known as a 'linear probability model', and we have selected it to allow

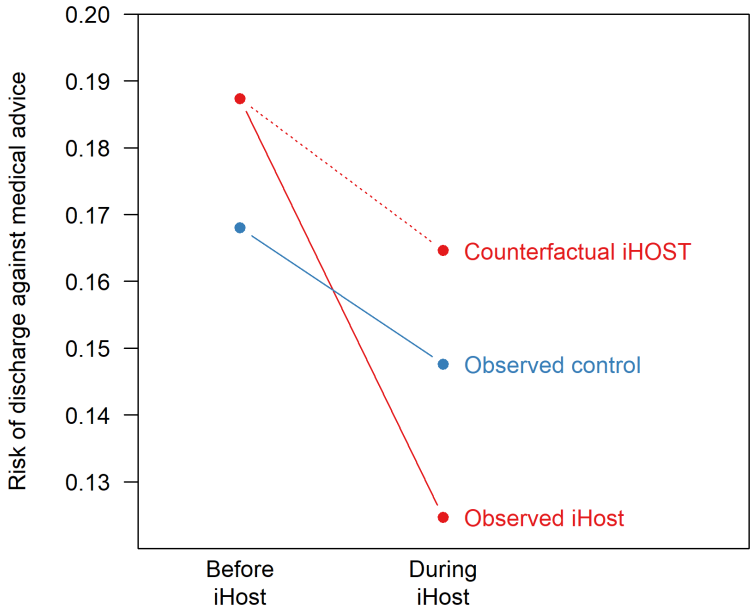

Figure 2. Illustrative difference-in-difference analysis.

estimation of absolute difference in the risk of outcomes. Confounders will be age, sex, season, primary cause of admission, number of comorbidities, proportion of patients at the hospital who have COVID-19. We will fit the model using a restricted maximum likelihood method implemented in the R package lme4[31]. The effect of iHOST will be interpreted from the interaction between time and the control/intervention indicator. Definitions of study variables are included in Extended Data[32].

Baseline data analysis. We extracted data from Hospital Episode Statistics for the calendar year 2021 to estimate the number of eligible patients and understand their characteristics. The results are summarised in Table 1. Hospitals are anonymised.

Power. To estimate power, we simulated the study assuming that iHOST reduces the risk of each outcome by 5 percentage points (for example from 20% to 15%). For the "pre iHOST" data, we used the calendar year 2021 (summarised in Table 2). For the "post iHOST" data, we used same dataset; but with outcomes randomly generated where the risk of each outcome was the hospital-specific risk from 2021, reduced by 5 percentage points for the iHOST sites. An example of a single simulation is shown in Figure 3. We repeated this simulation 1,000 times and calculated the proportion of simulations in which a significant result was found (ie. $p < 0.05$). This suggested good power to detect a risk reduction of 5 percentage points when results from the three hospitals are pooled, but low power at individual sites. Code for the power analysis is available at https://github.com/danlewer/ihost/tree/main/power.

OST process measures

Participating hospitals will use local clinical data to report measures of the quality of OST provision ('process measures'). We have worked with information specialists and clinicians at University College London Hospital NHS Foundation Trust to develop the following measures:

1. The number of patients administered methadone. Most patients provided with OST in acute hospitals in the UK are given methadone; and additionally, methadone

Table 1. Number and characteristics of patients with recent diagnoses of opioid dependence in the calendar year 2021, based on preliminary analysis of Hospital Episode Statistics.

Site	Number of patients	Patient-directed discharge N (%)	28-day readmission N (%)	Age (IQR)	Male N (%)	5+ comorbidities N (%)	% patients at hospital with COVID-19
iHOST sites							
A	349	70 (20.1)	101 (28.9)	46 (36-54)	244 (69.9)	143 (41.0)	10.1
B	662	149 (22.5)	214 (32.3)	43 (38-47)	489 (73.9)	195 (29.5)	6.9
C	624	116 (18.6)	148 (23.7)	43 (37-50)	392 (62.8)	182 (29.2)	4.8
Control hospitals							
All	24604	4048 (16.5)	7001 (28.5)	43 (37-50)	16425 (66.8)	6718 (27.3)	7.9
1	893	61 (6.8)	322 (36.1)	42 (35-49)	535 (59.9)	97 (10.9)	6.1
2	818	102 (12.5)	156 (19.1)	40 (35-47)	584 (71.4)	138 (16.9)	8.3
3	728	103 (14.1)	183 (25.1)	45 (37-52)	458 (62.9)	134 (18.4)	9.0
4	732	191 (26.1)	265 (36.2)	45 (38-50)	533 (72.8)	208 (28.4)	6.7
5	739	92 (12.4)	249 (33.7)	43 (37-50)	445 (60.2)	185 (25.0)	5.8
Etc ...							

Table 2. Power of the iHOST study to detect an absolute reduction in outcomes of five percentage points.

	Patient-directed discharge	28-day emergency readmission
Site A	0.475	0.228
Site B	0.839	0.442
Site C	0.837	0.376
Pooled effect	>0.999	0.921

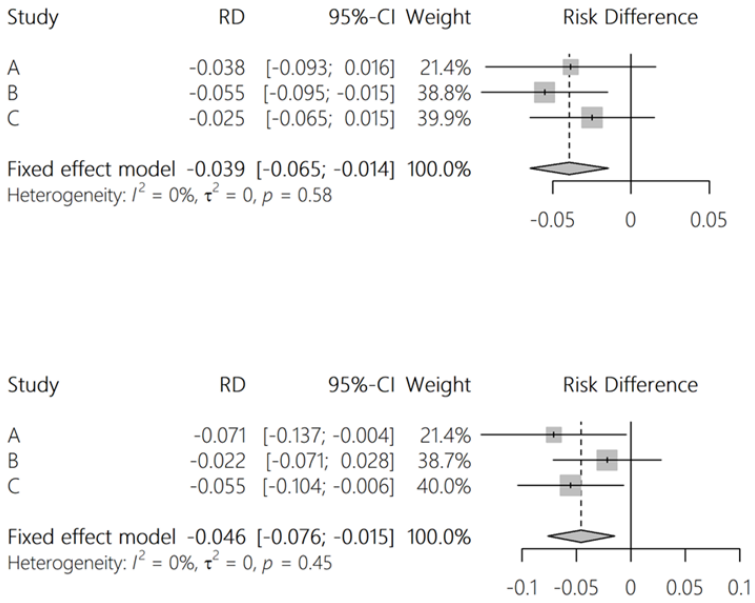

Figure 3. Example results from a single simulation of the difference-in-difference study.

is rarely given for other indications. Therefore, it is a useful indicator of the quantity of OST provided; while avoiding the need to consider the indication and formulation.

2. Duration between decision to admit and administration of methadone, reported as (a) the proportion that is 24 hours or greater; and (b) the median and interquartile range.

3. The dose, defined as (a) the proportion of patients administered at least 20mg of methadone in one 24-hour period; reported as a proportion of patients who are administered methadone and admitted for at least 24 hours, and (b) the mean and distribution of administered doses across 24-hour intervals following admission.

4. The proportion of potentially eligible patients who are provided with OST, defined as the proportion of inpatients with a discharge diagnosis of ICD-10 F11 ('opioid related disorders') who were administered methadone or buprenorphine during their admission.

5. The proportion of patients who are potentially eligible for OST who have a patient-directed discharge, defined as the proportion of inpatient admissions with discharge diagnosis of ICD-10 F11 ('opioid related disorders') that end in patient-directed discharge.

6. Possible OST-associated overdoses, defined as inpatients who are administered naloxone after an administration of methadone or buprenorphine.

Depending on the feasibility of extracting these data, each iHOST site will calculate each measure for quarterly periods (i.e., every three months) for time periods before and during iHOST implementation. The sites will nominate a group of staff (for example medical staff, pharmacists, and information specialists) to review the indicators every three months. We will also do an uncontrolled before/after analysis to test if the indicators change after implementation of iHOST.

Health economic study

We will perform a cost-consequence analysis of the iHOST intervention compared to not using it, in terms of cost per OST prescription, cost per patient-directed discharge prevented and cost per 28-day emergency readmission prevented. Analysis will use an NHS cost perspective and include each of the main elements of the intervention (MyMedsCard, helpline, OST champion and the e-learning module) as well as the costs of OST prescription within the hospital setting. As the opioid withdrawal management policy guideline will not need to be developed again on roll-out of the intervention, we assume this cost to be negligible and will therefore not conduct a detailed cost estimate of the policy development. We will include the cost savings for 28-day emergency visits prevented, but will exclude the costs of unrelated hospital visits.

Safety

iHOST may involve changes to OST prescribing in participating hospitals. Changes to guidelines and clinical processes will be agreed through existing clinical governance structures at participating hospitals and will become part of usual care. Potential safety issues will be identified through these processes. Where events occur that may be related to the safety of new OST pathways, the events will be reviewed by the participating hospital. If the participating hospital assesses that the event was at least partly attributable to the new protocol,

all partner hospitals together with the iHOST team will together review whether changes across all iHOST sites are necessary.

Ethics and approvals

Ethical approvals have been received from the NHS Health Research Authority on 8 September 2022 [Ref 133022], the Camden and Islington NHS Research Ethics Committee on 31 May 2022 [Ref 22/LO/0370] and the LSHTM Observational Research Ethics Committee on 18 July 2022 [Ref 27895]. Local research and development approvals have been obtained from each hospital site and participating drug treatment service.

The difference-in-difference study was approved by the UK Health Security Agency Research Ethics and Governance Group on 29 March 2022 [R&D ref 497].

Discussion

Poor OST in acute hospitals is a barrier to effective care for patients who use illicit opioids. This is clear from our research in the UK[33–35], engagement with affected groups, and international evidence[8,13,14,23,36,37]. Poor OST can cause physical and psychological distress and result in treatment interruption or patients leaving hospital to obtain illicit drugs[8,13]. People experiencing opioid withdrawal can be perceived as challenging by healthcare workers. Improving care for patients who use illicit opioids and their feeling of safety could be beneficial for both patients and hospital staff. Although there are well-documented problems with OST in hospitals[6–10], this has not led to evaluated interventions in the UK.

Barriers to better OST have been investigated, and qualitative evidence has found procedural and attitudinal barriers. For example, medical professionals often have negative attitudes towards patients who use opioids, which may impact care[10,38]. Fear and experience of drug withdrawal are key risk factors for patient-directed discharge[13,39], which is associated with hospital readmission and increased mortality risk[40–44].

iHOST is designed to address these barriers using a multicomponent intervention that addresses procedures, knowledge, and attitudes. It is an applied research project in which the intervention is developed in a real-world setting. If successful, it should improve management of withdrawal and reduce delays in the prescription of OST. We anticipate that improvement of OST will lead to improved patient care, improved patient experiences, a reduction in patient-directed discharge, and reduced re-admissions.

We will evaluate the intervention using a pragmatic mixed-methods approach. This will provide a holistic understanding of the intervention's costs and benefits. We chose this approach over a cluster randomised trial for three reasons. First, such a trial would be expensive. Second, the barriers to implementation are different in each hospital and iHOST is focused on developing an intervention that is suitable for each site, rather than a consistent intervention. Third, we do not necessarily expect a clear effect on a single primary outcome. Given the marginalisation of the patient group and the long histories of adversity that many have experienced, it is possible that many patient-directed discharges will occur despite better OST and better patient care. Our engagement with patients and staff suggests that better OST could reduce suffering and increase trust between staff and patients even if primary outcomes in our quantitative study do not appear to change significantly. We wanted to capture these holistic outcomes.

Key limitations are:

1. **Process evaluation.** (a) The research team involved in intervention development will also oversee the process evaluation. This might inhibit some staff and stakeholders from expressing robust critique of the intervention, particularly if interviewed by researchers recognisable from e-learning training videos. A different team member will, therefore, conduct most of the qualitative interviews after the intervention has launched at the evaluation sites. (b) We will recruit inpatients who use opioids through hospital staff. This is crucial to ensure patients are well enough to consent, are present on the ward, and meet inclusion criteria (ie, use opioids). This can however, facilitate 'gatekeeping', whereby patients likely to provide a favourable impression of the hospital or intervention are selected for interview. In building relationships with hospital staff, we will stress the need to talk with a diversity of patients and the learning to be gained from understanding less positive experiences. (c) Observations include active shadowing of hospital staff on ward rounds. The presence of the researcher, and their association with the intervention, can impact staff-patient dynamics observed. Detailed field notes will be taken for all site visits, including interviews and staff training sessions, to provide additional context. (d) The three hospitals participating in iHOST may be more motivated or otherwise optimised for successful implementation. Recommendations for roll-out will need to account for potential additional barriers such as the absence of a motivated senior 'champion'.

2. **Controlled difference-in-difference study.** (a) No data will be available on OST prescriptions, either in the community or in hospital. Ideally, our study would include patients who had a community OST prescription prior to admission. Instead, we will use patients with a diagnosis of 'opioid dependence' as a group that may benefit from iHOST. This may dilute the effect of iHOST because some participants will not have prescriptions of OST; (b) the study will not capture any effect on patients' propensity to seek treatment. Part of the rationale for iHOST is that people who are dependent on opioids avoid or delay hospital treatment because they anticipate poor

OST. This study investigates outcomes after admission and will not capture any effect on patients' propensity to seek treatment in hospital. If iHOST leads to more patients seeking hospital care or presenting earlier, this may cause residual confounding because patients after implementation will differ from those before; (c) The study will only estimate effects on patient-directed discharges and readmissions. These outcomes are based on previous research, patient and public involvement, and the availability of data in HES. Other important outcomes may be affected by iHOST, such as the quality of medical treatment, patient satisfaction, continuation of OST in the community, and use of illicit drugs. Other parts of the evaluation seek to understand broader outcomes. A more detailed list of limitations for the difference-in-difference study is provided in Extended Data[32].

3. **OST process measures**. These measures are intended to support iHOST sites to learn about the quality of OST in their setting and identify opportunities for ongoing improvement. They are not a robust approach to estimating the impact of the intervention, as a change in these measures could be attributed to many factors other than the intervention, such as changing patient demographics, changing use of OST (eg. if iHOST leads to different types of patients being given OST), and wider healthcare policies.

4. **Health economic study.** We may not be able to accurately estimate the difference in methadone prescriptions. In many cases methadone may have been prescribed without the iHOST protocol, but having the protocol in place may mean that it is prescribed more quickly. We will do sensitivity analysis around this, assuming ranges in counterfactual prescription rates without the iHOST protocol in place. Costs included in the economic evaluation will be specific to sites where the study is operating and may not be generalisable to other settings or implementation of iHOST at large scale. We are unable to do any modelling of long-term outcomes, and therefore cost and effect estimates may not include important future events.

Conclusions

This work aims to recognise that patients who use illicit opioids are often vulnerable and require support in their journey through the healthcare system. iHOST aims to promote a culture change in which patients who use opioids feel confident to access medical care. This can also benefit providers and staff who sometimes feel unconfident working with this group and may consider them 'challenging'. iHOST training will provide skills in de-escalation strategies and culturally safe communication. The work with clinical policies will address procedural barriers to OST provision. We hope these changes will improve medical care and reduce health inequality.

Data availability

Underlying data

No data are associated with this article.

Extended data

LSHTM Research Online: Extended data for 'Improving hospital-based opioid substitution therapy (iHOST): protocol for a mixed-methods evaluation', https://doi.org/10.17037/PUBS.04671913[32]

This project contains the following extended data:

- Definitions of variables for difference-in-difference study
- Limitations for difference-in-difference study

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0)

References

1. Lewer D, Freer J, King E, *et al.*: **Frequency of health-care utilization by adults who use illicit drugs: a systematic review and meta-analysis.** *Addiction.* 2020; **115**(6): 1011–1023.
PubMed Abstract | Publisher Full Text | Free Full Text

2. Nambiar D, Stoové M, Hickman M, *et al.*: **A prospective cohort study of hospital separations among people who inject drugs in Australia: 2008–2013.** *BMJ Open*. 2017; **7**(8): e014854.
PubMed Abstract | Publisher Full Text | Free Full Text

3. van Hest N, Brothers TD, Williamson A, *et al.*: **Health-care resource use among patients who use illicit opioids in England, 2010-20: a descriptive matched cohort study.** *Addiction.* 2024; **119**(4): 730–740.
PubMed Abstract | Publisher Full Text

4. Lewer D, Croxford S, Desai M, *et al.*: **The characteristics of people who inject drugs in the United Kingdom: changes in age, duration, and incidence of injecting, 1980-2019, using evidence from repeated cross-sectional surveys.** *Addiction.* 2022; **117**(9): 2471–2480.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Morgan N: **The heroin epidemic of the 1980s and 1990s and its effect on crime trends - then and now**. 2014; (accessed 12 September 2019).
Reference Source

6. Strike C, Robinson S, Guta A, *et al.*: **Illicit drug use while admitted to hospital: patient and health care provider perspectives.** *PLoS One.* 2020; **15**(3): e0229713.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Neale J, Tompkins C, Sheard L: **Barriers to accessing generic health and social care services: a qualitative study of injecting drug users.** *Health Soc Care Community.* 2008; **16**(2): 147–54.
PubMed Abstract | Publisher Full Text

8. McNeil R, Small W, Wood E, *et al.*: **Hospitals as a 'risk environment': an ethno-epidemiological study of voluntary and involuntary discharge from hospital against medical advice among people who inject drugs.** *Soc Sci Med.* 2014; **105**: 59–66.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Chan Carusone S, Guta A, Robinson S, *et al.*: **"Maybe if I stop the drugs, then**

maybe they'd care?"-Hospital care experiences of people who use drugs. *Harm Reduct J.* 2019; **16**(1): 16.
PubMed Abstract | Publisher Full Text | Free Full Text

10. van Boekel LC, Brouwers EPM, van Weeghel J, *et al.*: **Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: systematic review.** *Drug Alcohol Depend.* 2013; **131**(1–2): 23–35.
PubMed Abstract | Publisher Full Text

11. Connock M, Juarez-Garcia A, Jowett S, *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.
PubMed Abstract | Publisher Full Text

12. Harris M, Holland A, Lewer D, *et al.*: **Barriers to management of opioid withdrawal in hospitals in England: a document analysis of hospital policies on the management of substance dependence.** *BMC Med.* 2022; **20**(1): 151.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Simon R, Snow R, Wakeman S: **Understanding why patients with substance use disorders leave the hospital against medical advice: a qualitative study.** *Subst Abus.* 2020; **41**(4): 519–525.
PubMed Abstract | Publisher Full Text

14. Marks LR, Munigala S, Warren DK, *et al.*: **Addiction Medicine Consultations Reduce Readmission Rates for Patients With Serious Infections From Opioid Use Disorder.** *Clin Infect Dis.* 2019; **68**(11): 1935–7.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Lewer D, Eastwood B, White M, *et al.*: **Fatal opioid overdoses during and shortly after hospital admissions in England: a case-crossover study.** *PLoS Med.* 2021; **18**(10): e1003759.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Ti L, Ti L: **Leaving the hospital against medical advice among people who use illicit drugs: a systematic review.** *Am J Public Health.* 2015; **105**(12): e53–9.
PubMed Abstract | Publisher Full Text | Free Full Text

17. Smith MW, Stocks C, Santora PB: **Hospital readmission rates and emergency department visits for mental health and substance abuse conditions.** *Community Ment Health J.* 2015; **51**(2): 190–7.
PubMed Abstract | Publisher Full Text

18. Lewer D, Padmanathan P, Qummer ul Arfeen M, *et al.*: **Healthcare Use by People who use Illicit Opioids (HUPIO): development of a cohort based on electronic primary care records in England [version 1; peer review: 1 approved].** *Wellcome Open Res.* 2020; **5**: 282.
PubMed Abstract | Publisher Full Text | Free Full Text

19. Englander H, Jones A, Krawczyk N, *et al.*: **A taxonomy of hospital-based addiction care models: a scoping review and key informant interviews.** *J Gen Intern Med.* 2022; **37**(11): 2821–33.
PubMed Abstract | Publisher Full Text | Free Full Text

20. French R, Aronowitz SV, Brooks Carthon JM, *et al.*: **Interventions for hospitalized medical and surgical patients with opioid use disorder: a systematic review.** *Subst Abus.* 2022; **43**(1): 495–507.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Gerlach AJ: **A critical reflection on the concept of cultural safety.** *Can J Occup Ther.* 2012; **79**(3): 151–8.
PubMed Abstract | Publisher Full Text

22. Ramsden I: **Cultural safety in nursing education in Aotearoa (New Zealand).** *Nurs Prax N Z.* 1993; **8**(3): 4–10.
PubMed Abstract

23. McCall J, Pauly B: **Sowing a seed of safety: providing culturally safe care in acute care settings for people who use drugs.** *JMHAN.* 2019; **3**(1): e1–7.
Publisher Full Text

24. Pauly BB, McCall J, Browne AJ, *et al.*: **Toward cultural safety: nurse and patient perceptions of illicit substance use in a hospitalized setting.** *ANS Adv Nurs Sci.* 2015; **38**(2): 121–35.
PubMed Abstract | Publisher Full Text

25. Lewer D, Harris M, Scott J, *et al.*: **PROTOCOL: opioid agonist therapy for management of opioid dependence in acute hospital settings: a systematic review and narrative synthesis**. 2022.
Reference Source

26. Charmaz K: **Constructing Grounded Theory.** 2nd ed. London: Sage, 2014.
Reference Source

27. Farmer T, Robinson K, Elliott SJ, *et al.*: **Developing and Implementing a triangulation protocol for qualitative health research.** *Qual Health Res.* 2006; **16**(3): 377–94.
PubMed Abstract | Publisher Full Text

28. Dimick JB, Ryan AM: **Methods for evaluating changes in health care policy: the difference-in-differences approach.** *JAMA.* 2014; **312**(22): 2401–2.
PubMed Abstract | Publisher Full Text

29. Wing C, Simon K, Bello-Gomez RA: **Designing difference in difference studies: best practices for public health policy research.** *Annu Rev Public Health.* 2018; **39**: 453–69.
PubMed Abstract | Publisher Full Text

30. Herbert A, Wijlaars L, Zylbersztejn A, *et al.*: **Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC).** *Int J Epidemiol.* 2017; **46**(4): 1093–1093i.
PubMed Abstract | Publisher Full Text | Free Full Text

31. Bates D, Mächler M, Bolker B, *et al.*: **Fitting linear mixed-effects models using lme4.** *J Stat Softw.* 2015; **67**(1)1–48.
Publisher Full Text

32. Lewer D, Brown M, Burns A, *et al.*: **Extended data for 'Improving Hospital-based Opioid Substitution Therapy (iHOST): protocol for a mixed-methods evaluation'**.
http://www.doi.org/10.17037/PUBS.04671913

33. Harris M: **Normalised pain and severe health care delay among people who inject drugs in London: adapting cultural safety principles to promote care.** *Soc Sci Med.* 2020; **260**: 113183.
PubMed Abstract | Publisher Full Text | Free Full Text

34. Wright T, Hope V, Ciccarone D, *et al.*: **Prevalence and severity of abscesses and cellulitis, and their associations with other health outcomes, in a community-based study of people who inject drugs in London, UK.** *PLoS One.* 2020; **15**(7): e0235350.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Doran J, Harris M, Hope VD, *et al.*: **Factors associated with skin and soft tissue infections among people who inject drugs in the United Kingdom: a comparative examination of data from two surveys.** *Drug Alcohol Depend.* 2020; **213**: 108080.
PubMed Abstract | Publisher Full Text

36. Englander H, Collins D, Peterson-Perry S, *et al.*: **"We've learned it's a medical illness, not a moral choice": qualitative study of the effects of a multicomponent addiction intervention on hospital providers' attitudes and experiences.** *J Hosp Med.* 2018; **13**(11): 752–758.
PubMed Abstract

37. Jicha C, Saxon D, Lofwall MR, *et al.*: **Substance use disorder assessment, diagnosis, and management for patients hospitalized with severe infections due to injection drug use.** *J Addict Med.* 2019; **13**(1): 69–74.
PubMed Abstract | Publisher Full Text

38. Eaton EF, Westfall AO, McClesky B, *et al.*: **In-hospital illicit drug use and patient-directed discharge: barriers to care for patients with injection-related infections.** *Open Forum Infect Dis.* 2020; **7**(3): ofaa074.
PubMed Abstract | Publisher Full Text | Free Full Text

39. McNeil R, Small W: **' Safer environment interventions': a qualitative synthesis of the experiences and perceptions of people who inject drugs.** *Soc Sci Med.* 2014; **106**: 151–8.
PubMed Abstract | Publisher Full Text | Free Full Text

40. Southern WN, Nahvi S, Arnsten JH: **Increased risk of mortality and readmission among patients discharged against medical advice.** *Am J Med.* 2012; **125**(6): 594–602.
PubMed Abstract | Publisher Full Text | Free Full Text

41. Hwang SW, Li J, Gupta R, *et al.*: **What happens to patients who leave hospital against medical advice?** *CMAJ.* 2003; **168**(4): 417–20.
PubMed Abstract | Free Full Text

42. Tawk R, Freels S, Mullner R: **Associations of mental, and medical illnesses with against medical advice discharges: the national hospital discharge survey, 1988-2006.** *Adm Policy Ment Health.* 2013; **40**(2): 124–32.
PubMed Abstract | Publisher Full Text

43. Tan SY, Feng JY, Joyce C, *et al.*: **Association of hospital discharge against medical advice with readmission and in-hospital mortality.** *JAMA Netw Open.* 2020; **3**(6): e206009.
PubMed Abstract | Publisher Full Text | Free Full Text

44. Alfandre DJ: **"I'm going home": discharges against medical advice.** *Mayo Clin Proc.* 2009; **84**(3): 255–60.
PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ? ✓

Version 1

Reviewer Report 08 October 2024

https://doi.org/10.3310/nihropenres.14692.r33051

© **2024 Tremonti C.** This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

✓ **Chris Tremonti**
[1] Alcohol and Drug Services St Vincent's Hospital, University of Sydney, Sydney, Australia
[2] Alcohol and Drug Services St Vincent's Hospital, University of Sydney, Sydney, Australia

Thank you to the authors for the opportunity to review this article, which is in fact indexing of a study protocol. As a consequence, it is somewhat unusual to review as the authors will no doubt have undergone extensive review of their protocol during the process of seeking ethics. I am also unqualified to review some of the more novel statistical methodologies employed for the study. While this does appear scientifically robust, I would suggest if the journal had concerns to seek review from a biostatician, but I suspect one has been involved in the write-up, and likely review the protocol during the ethics process.

I do not think it is worth a significant reevaluation of the protocol here. Nonetheless I will mention some minor limitations that may be worth commenting upon, and could be added under the limitations already listed:

1. 'Patients who may benefit from OST' – a limitation of using the ICD-11 diagnostic criteria of opioid use disorder is that that those not forthcoming in their opioid use may not be captured. In hospitals without ihost – where stigma may be higher against those who use opioids – there may therefore be less people captured by this criteria, and a 'falsely high' proportion of people receiving appropriate treatment. I'm unsure if I have a solution to that problem, it may just be worth discussing.

2. I am unclear why the authors are only capturing those administer methadone. I do appreciate that buprenorphine is now commonly being used for pain management, but not typically at the doses seen in OST. Furthermore in my jurisdiction it is commonly used in the form of suboxone or subutex, while temgesic is used for pain. I do wonder if patients on buprenorphine could be captured, perhaps with a criteria of it needing to be in a specific form, or on a daily dose >8mg (which would be unusual in pain management).

3. The limitation of treatment bias warrants a small discussion too - those hospitals with iHOST may be geared towards the success of its implementation.

In spite of these pedantic points, this is a very worthy and ambitious study being undertaken, and I wish the authors the best with it.

I would add to the journal that given my lack of expertise with both lived experience and biostatistics, it may be worth review from those with expertise in these areas

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

Is the study design appropriate for the research question?
Yes

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

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

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Addiction medicine

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

Author Response 04 Nov 2024

Dan Lewer

11. 'Patients who may benefit from OST' – a limitation of using the ICD-11 diagnostic criteria of opioid use disorder is that that those not forthcoming in their opioid use may not be captured. In hospitals without ihost – where stigma may be higher against those who use opioids – there may therefore be less people captured by this criteria, and a 'falsely high' proportion of people receiving appropriate treatment. I'm unsure if I have a solution to that problem, it may just be worth discussing.

*Response: We agree, this is a potential source of bias. We have added the following text to the list of limitations in our supplementary file: "**Use of ICD-10 codes may differ between iHOST and control sites**. We will use ICD-10 diagnoses (F11, Mental and behavioural disorders due to use of opioids) to identify eligible patients. The use of these codes may differ between hospitals. Bias may occur if iHOST sites become more likely to identify opioid dependence after implementation of the intervention. For example, this scenario may lead to a lower average severity of opioid dependence because the hospital may have a lower threshold for identifying opioid dependence, and therefore an inflated effect estimate. This is just an example of a potential bias resulting from changing use of ICD-10 codes."*

12. I am unclear why the authors are only capturing those administer methadone. I do appreciate that buprenorphine is now commonly being used for pain management, but not

typically at the doses seen in OST. Furthermore in my jurisdiction it is commonly used in the form of suboxone or subutex, while temgesic is used for pain. I do wonder if patients on buprenorphine could be captured, perhaps with a criteria of it needing to be in a specific form, or on a daily dose >8mg (which would be unusual in pain management).

Response: Please also see comments #7 and #8. In our context, buprenorphine is rarely used for OST, and in addition detailed prescribing data is typically difficult to capture in a structured format. In our partner hospitals it would likely require reading free-text notes for each patient prescribed buprenorphine. ie. The information specialists at the hospitals can query a database to identify patients prescribed buprenorphine, but they cannot determine what product and dose was used. The majority who are prescribed buprenorphine probably would not be receiving OST.

13. The limitation of treatment bias warrants a small discussion too - those hospitals with iHOST may be geared towards the success of its implementation.

Response: We agree and have added the following text under Limitations/process evaluation: "(d) The three hospitals participating in iHOST may be more motivated or otherwise optimised for successful implementation. Recommendations for roll-out will need to account for potential additional barriers such as the absence of a motivated senior 'champion'."

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 June 2024

https://doi.org/10.3310/nihropenres.14692.r31990

© 2024 A Springer S. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

?

Sandra A Springer
[1] Yale School of Medicine, Connecticut, USA
[2] Yale School of Medicine, Connecticut, USA

This is a protocol paper for a mixed methods evaluation to improve "Opioid substitution treatment (OST)" in 3 acute hospitals in England.
Importantly this study was informed by discussions with key collaborators that included persons who use opioids as well as hospital staff.
This study aims to establish an identification card for patients to give to hospital clinicians to confirm their OST, a helpline for patients and staff, an online training module for staff, a clinical guideline for managing opioid withdrawal in the hospital and will develop roles for a champion at each hospital. Primary outcome is "discharge against medical advice and emergency readmission within 28days .'
The investigators plan to do a comparison of changes in outcomes for patients at iHOST hospital sites with changes in outcomes from patients at control hospital sites.

The importance of the subject matter and study aims are well delineated. Many persons admitted to hospitals with OUD are not identified and can go without treatment for OUD and lead to withdrawal from opioids and early discharges as well as increases in death from overdose and readmissions as well related to poorly treated/untreated other medical problems such as serious injection related infections.
Here the authors use the term 'opioid substitution treatment' (OST), however in the United States the terms are not used any more as it has perpetuated myths of treatment of OUD with opioid agonists as a substitution of one opioid for another. Thus, American Society of Addiction medicine (ASAM) and SAMHSA and NIDA and other groups now refer to OUD medication treatment as medication treatment of OUD (MOUD) and sub-categorizes the forms of MOUD as opioid agonist-based treatments, methadone and buprenorphine, and opioid antagonist treatments, extended-release naltrexone. I understand this is a UK specific study, but is a concern I voice for all persons globally and is in particular for those in the U.S.

Outcomes of interest are patient self- discharges and readmissions. The authors use the term 'leaving against medical advice (AMA)' and this term is also stigmatizing and not used in the literature any longer in the U.S., it is described as' patient self-discharge'.

Strength of this proposed study is that it was informed by persons with lived experience including those with OUD on MOUD or here opioid agonists (or what authors report as OST) and staff as well as with culturally specific safety principles .

The overall aims are to improve OST use in hospital settings and reduce "delayed presentation". I found this term a bit difficult to understand- the authors mean delayed treatment with OST or delayed specifically continuation of OST as they are specifically only identifying persons with OUD on OST in community who are admitted to hospitals thus Would suggest possibly editing this term or meaning of term under Aims and Objectives.

The study is focusing on those who are on 'OST in the community' and helping them ensure their caregivers in the hospital are aware – hence the ID card. I wonder however if more could be done here including identifying persons with OUD who have not been started on OST or those who previously had been but were no longer retained on OST. Hospitalizations are reachable moments where persons can be initiated or reinitiated on treatment for OUD . In the U.S there is no universal diagnosis of SUD/OUD and many are admitted and OUD is not identified leading to missed opportunities to engage/ initiate MOUD and link to care in the community and thus with goal to reduce overdose and other associated harms like HIV, HCV , injection related infections, depression/ suicide etc.
Concerns about the ID card proposed in this study I have are the potential for staff/ patients misplacing it and leading to confidentiality breaches. Is it possible to make electronic for persons smart phones or other way to assure decreasing chance of loss of confidentiality?

'Difference in difference Study 'section:
Authors plan to do a 'controlled study'design using data from iHOST hospitals and control hospital to estimate the effect of iHOST on AMA discharge and ER readmission within 28 days.
Concerns for this design, is that there will be significant intra-group and inter-group differences that could affect the outcomes. For example, staff differences (bias, experience etc) and hospital/ setting differences. Is it possible instead to compare the intervention to treatment as usual in the

3 hospitals?
I am not familiar with this type of study design and thus would request a person with such design familiarity to review this section as well as the power analysis. My concerns are: the many differences of the particular patients at each sites as well as staff and hospital settings/ experience etc with addiction and support services . The analysis of the data from this study will have to balanced as much as possible for such differences and acknowledge this as a limitation of the final analysis as of course not everything will be able to be accounted for. Would suggest a statistician who has familiarity with this type of evaluation / study design/ analytic plan to comment on this concern.

'Ost process measures' section: .
Not clear but seems like only methadone is to be evaluated , not buprenorphine. Not explained why hospitals in UK use methadone more than buprenorphine. Would make this more clear in the intro/ abstract and methods sections as instead of what they call 'OST" it is only methadone.
For methadone, would evaluate the mean dose of methadone. 40 mg is sufficient to treat some forms of opioid withdrawal but higher doses are needed for fentanyl withdrawal and of course for maintenance treatment and reduction in craving .Much higher doses over 90 and 100 mg are required to treat heroin and fentanyl addiction . We do know that persons who are not adequately dosed will be more likely to experience craving/ withdrawal and leave against medical advice. Thus the dose of methadone could affect the planned primary outcomes of ' patient leaving against medical advice'. If buprenorphine is also included as I would suggest, then also the mean dose should be evaluated and at least 16 mg is recommended to reduce craving etc and up to 32 mg ; also include long acting injectable buprenorphine monthly formulations now available that could be started in hospital settings or may have started in the community setting and continued in the hospital setting especially upon discharge (sublocade 300mg and 100mg doses where 300 mg continuation has been found to improve retention among those who inject heroin/ fentanyl; and now Brixadi available at different doses and weekly/ monthly injections that are similar to the SL doses).

Other factors that could affect outcomes include comorbid other substance use like stimulants that can interfere with MOUD /OST use/access/ continuation/ retention as well as lead to withdrawal along with withdrawal from alcohol that if undiagnosed could lead to leaving against medical advice and increase hospital readmissions .. thus there needs to be a careful understanding of the population characteristics to see if persons enrolled in the trial have co-occurring other su/ sud that could affect their primary outcomes . Further, other factors that may lead to a difference in outcomes include other comorbid psychiatric conditions, severity of illness upon hospital admission (Elixhauser severity index could be added); pain ; housing status etc that could impact ability to stay in hospital outside of whether on MOUD or not (or here OST)- and specifically especially for pain - is there a difference in opioid agonist methadone versus partial agonist buprenorphine , dose etc and change in pain .. acute pain possibly related to hospital medical condition that may affect management of the treatment of OUD as well.

Safety
Highly recommend that the investigators assess adverse events and serious adverse events as is standard in NIH reporting / etc .

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

Yes

Is the study design appropriate for the research question?
Partly

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

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: I have received paid scientific consultation from Alkermes Inc and have received study drug donation in-kind for Sublocade from Indivior Pharmaceutical Company and Vivitrol from Alkermes Inc for NIH-funded research. I have received NIH grant support from NIDA, NIAAA and NCATS and the Veterans Administration Healthcare system.

Reviewer Expertise: Opioid use disorder treatment in hospital, community and carceral systems including buprenorphine both sublingual and injectable forms as well as extended-release naltrexone; access to services via linkage care models including patient navigators and mobile health unit provision of care for persons who use drugs ; HIV prevention and treatment; Infectious disease integrated with SUD care; mobile pharmacies.

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

Author Response 04 Nov 2024

Dan Lewer

1. Here the authors use the term 'opioid substitution treatment' (OST), however in the United States the terms are not used any more as it has perpetuated myths of treatment of OUD with opioid agonists as a substitution of one opioid for another. Thus, American Society of Addiction medicine (ASAM) and SAMHSA and NIDA and other groups now refer to OUD medication treatment as medication treatment of OUD (MOUD) and sub-categorizes the forms of MOUD as opioid agonist-based treatments, methadone and buprenorphine, and opioid antagonist treatments, extended-release naltrexone. I understand this is a UK specific study, but is a concern I voice for all persons globally and is in particular for those in the U.S.

Response: We are aware of these developments in language and perceptions about the term "substitution". We named our project "iHOST" (improving hospital opiate/opioid substitution therapy" together with patients and clinicians. This reflects historical terminology and vernacular in these groups, with "OST" remaining the best-recognised term in the UK. While we would be very willing to change the terminology in this article, it would make the text inconsistent with the project name. We also note that no term for these medicines is universally acceptable, for example some people consider the word "disorder" to be pejorative and therefore prefer not to use "medication treatment of opioid use disorder". For consistency with the project name "iHOST",

we have retained the use of "OST" in this article, however in the abstract and at the start of the introduction we have added: "Opioid substitution therapy (also known as opioid agonist therapy and medication treatment of opioid use disorder)".

1. Outcomes of interest are patient self- discharges and readmissions. The authors use the term 'leaving against medical advice (AMA)' and this term is also stigmatizing and not used in the literature any longer in the U.S., it is described as' patient self-discharge'.

Response: We agree and have changed our terminology to "patient-direct discharge".

1. The overall aims are to improve OST use in hospital settings and reduce "delayed presentation". I found this term a bit difficult to understand- the authors mean delayed treatment with OST or delayed specifically continuation of OST as they are specifically only identifying persons with OUD on OST in community who are admitted to hospitals thus Would suggest possibly editing this term or meaning of term under Aims and Objectives.

Response: Our sentence as originally written was confusing, and we have changed it to "iHOST aims to improve OST in hospital settings to: (1) reduce barriers to hospital presentation and reduce delayed presentations, (2) improve care, (3) reduce patient-directed discharges, and (4) reduce emergency readmissions." The first aim relates to patients who should go to A&E/ED but do not because they believe they will not be treated well. Our qualitative and patient engagement work suggests this happens often. A typical scenario would be a patient with a skin and soft tissue infection waiting until they have symptoms of systemic infection before going to hospital. We are only able to evaluate aims 3 and 4 quantitatively, and other aspects of the projects consider the other aims. Hopefully this is clearer, but please let us know if you have further feedback.

1. The study is focusing on those who are on 'OST in the community' and helping them ensure their caregivers in the hospital are aware – hence the ID card. I wonder however if more could be done here including identifying persons with OUD who have not been started on OST or those who previously had been but were no longer retained on OST. Hospitalizations are reachable moments where persons can be initiated or reinitiated on treatment for OUD . In the U.S there is no universal diagnosis of SUD/OUD and many are admitted and OUD is not identified leading to missed opportunities to engage/ initiate MOUD and link to care in the community and thus with goal to reduce overdose and other associated harms like HIV, HCV , injection related infections, depression/ suicide etc.

Response: This is a fair observation, and iHOST does largely focus on continuity of OST. The UK context is different to North America since between half and three-quarters of patients who are dependent on opioids already have OST prescriptions and hospital staff can have difficulty determining the daily dose and when the next dose is due. Therefore, medicine reconciliation and continuity of doses is a major consideration in the UK. iHOST does also aim to improve initiation of OST, and the text under the section "The Intervention" says that iHOST "primarily aims to improve continuation of OST from community to hospital settings but will also inform OST initiation and discharge planning for patients who were not already in receipt of community-based OST." The specific approaches are not detailed in the protocol, however the policies/protocols and training materials at participating hospitals address initiation of OST and these will be published in due course.

1. Concerns about the ID card proposed in this study I have are the potential for staff/ patients misplacing it and leading to confidentiality breaches. Is it possible to make electronic for persons smart phones or other way to assure decreasing chance of

loss of confidentiality?

Response: This issue was also raised when we developed the card. The card does not include the patient's details, and only includes information about the importance of timely OST, and contact details for the patient's prescriber. You can see images of the card here: https://www.lshtm.ac.uk/research/centres-projects-groups/ihost#about. We did explore electronic versions but could not design a feasible solution – problems included the fact that many patients do not have the same phone / online accounts over time, and technical integration with prescribers' clinicals systems was challenging.

1. (Concerning the difference-in-difference analysis) Concerns for this design, is that there will be significant intra-group and inter-group differences that could affect the outcomes. For example, staff differences (bias, experience etc) and hospital/ setting differences. Is it possible instead to compare the intervention to treatment as usual in the 3 hospitals? [...] My concerns are: the many differences of the particular patients at each sites as well as staff and hospital settings/ experience etc with addiction and support services . The analysis of the data from this study will have to balanced as much as possible for such differences and acknowledge this as a limitation of the final analysis as of course not everything will be able to be accounted for. Would suggest a statistician who has familiarity with this type of evaluation / study design/ analytic plan to comment on this concern.

Response: The design is observational and there is always the possibility of residual confounding. In the difference-in-difference design, the control group (ie. hospitals that did not implement iHOST) are intended to control background time trends in the outcome that are common across all hospitals. Differences in the baseline outcome rate (eg. if hospitals in the control group have lower overall rates of patient-directed discharge) would not bias the study. A bias would occur if the trend in outcomes over time was different; for example if patient-directed discharge increased in the control hospitals, but would not have increased in the iHOST hospitals in the counterfactual scenario that we did not implement iHOST. In this scenario, the estimated effect of iHOST would be overestimated. The assumption that the time trends are the same in the iHOST and control groups is known as the "parallel trends assumption". The robustness of this assumption cannot be directly observed, since that would require observation of the counterfactual scenario in which iHOST hospitals did not implement iHOST. However, this design does mean that more general differences in patient profiles, availability of addiction and support services, etc., should not cause major bias. This is in fact the case, and our baseline data suggest that patient-directed discharge is more common in iHOST hospitals than in control hospitals (see our presentation of the design to the NIHR Statistics Conference - https://www.youtube.com/watch?v=rC9GJya6h6Y&list=LL&index=9). If these factors change differentially between the iHOST and control groups, that could cause bias. Changes over time in measured factors are controlled. For example, if the patient age, primary reason for admission, or comorbidities change in one group, that would be controlled. Similarly, if some hospitals are more affected by COVID-19, that would also be controlled. The design was developed by methodologists on the study team and reviewed by an independent statistician (Professor Ben Armstrong at LSHTM) as part of our study approvals.

1. 'Ost process measures' section: Not clear but seems like only methadone is to be evaluated, not buprenorphine. Not explained why hospitals in UK use methadone more than buprenorphine. Would make this more clear in the intro/ abstract and methods sections as instead of what they call 'OST" it is only methadone.

Response: buprenorphine is used as OST in the UK, but much less frequently than in North

*America. The reasons for this include: (1) the cohort in treatment for opioid dependence in the UK is older and many started treatment before buprenorphine was available; (2) there are fewer regulatory barriers to using methadone in the UK. We do not have data on the proportion of individuals who have methadone vs. buprenorphine prescriptions, but anecdotally very little buprenorphine is currently prescribed for OST in our participating hospitals. In many UK hospital policies on management of substance dependence, buprenorphine is not even mentioned (https://pmc.ncbi.nlm.nih.gov/articles/PMC9007696/). We have added the following sentence to the introduction: "*While data on the relative use of methadone and buprenorphine in OST in the UK is not readily available, some hospital guidelines for management of substance dependence do not mention buprenorphine."

1. For methadone, would evaluate the mean dose of methadone. 40 mg is sufficient to treat some forms of opioid withdrawal but higher doses are needed for fentanyl withdrawal and of course for maintenance treatment and reduction in craving .Much higher doses over 90 and 100 mg are required to treat heroin and fentanyl addiction . We do know that persons who are not adequately dosed will be more likely to experience craving/ withdrawal and leave against medical advice. Thus the dose of methadone could affect the planned primary outcomes of ' patient leaving against medical advice'. If buprenorphine is also included as I would suggest, then also the mean dose should be evaluated and at least 16 mg is recommended to reduce craving etc and up to 32 mg ; also include long acting injectable buprenorphine monthly formulations now available that could be started in hospital settings or may have started in the community setting and continued in the hospital setting especially upon discharge (sublocade 300mg and 100mg doses where 300 mg continuation has been found to improve retention among those who inject heroin/ fentanyl; and now Brixadi available at different doses and weekly/ monthly injections that are similar to the SL doses).

Response: This is a good idea and we will do it if possible, however in practice we are not able to estimate the mean dose at our pilot site (University College Hospital, London). Reporting the dose per patient seems straightforward, however there are various factors that make it difficult: (1) patients often receive multiple doses per day, so the dose must be calculated over an arbitrary period, eg. 24-hour intervals after their admission time; (2) the admission time can have a number of definitions, and the dose is sensitive to the choice; (3) the prescribed and administered schedule may differ, for example some doses may be late; (4) the prescribed schedule may only be available in free-text notes; (5) some patients have duplicate dose data that is difficult to validate. Although similar challenges are likely to arise at our two other sites, we will report summary measures of the dose if possible, and have edited the text to say: "3. The dose, defined as (a) the proportion of patients administered at least 20mg of methadone in one 24-hour period; reported as a proportion of patients who are administered methadone and admitted for at least 24 hours, and (b) the mean and distribution of administer doses across 24-hour following admission."

1. Other factors that could affect outcomes include comorbid other substance use like stimulants that can interfere with MOUD /OST use/access/ continuation/ retention as well as lead to withdrawal along with withdrawal from alcohol that if undiagnosed could lead to leaving against medical advice and increase hospital readmissions .. thus there needs to be a careful understanding of the population characteristics to see if persons enrolled in the trial have co-occurring other su/ sud that could affect their primary outcomes . Further, other factors that may lead to a difference in

outcomes include other comorbid psychiatric conditions, severity of illness upon hospital admission (Elixhauser severity index could be added); pain ; housing status etc that could impact ability to stay in hospital outside of whether on MOUD or not (or here OST)- and specifically especially for pain - is there a difference in opioid agonist methadone versus partial agonist buprenorphine , dose etc and change in pain .. acute pain possibly related to hospital medical condition that may affect management of the treatment of OUD as well.

Response: We agree – these are all important factors that could affect patient-directed discharge and readmission. From a quantitative perspective, these are potential confounders and may affect the study if time-trends in these factors differ between iHOST and control sites (please see comment #6). From a qualitative perspective, we will be gathering evidence about factors that affect access to OST and patient outcomes via interviews with staff and clinicians.

1. Highly recommend that the investigators assess adverse events and serious adverse events as is standard in NIH reporting / etc .

Response: iHOST works with partner hospitals to develop new protocols for treatment of opioid withdrawal. It is not developing new treatments, rather it aims to reduce barriers to evidence-based treatments that are already recommended. The new protocols are agreed through the hospitals' existing clinical governance structures and the hospitals remain responsible for the protocols and for identifying and investigating events that may be related to the safety of new protocols. An example of a relevant event might be a patient experiencing an opioid overdose after being administered OST in the hospital. Where such an event occurs and partner hospital assesses that the event was at least partly attributable to the new protocol, all partner hospitals together with the iHOST team will together review whether changes across all iHOST sites are necessary. We have clarified this procedure under the section "safety".

Competing Interests: No competing interests were disclosed.