

FORWARDS-2: study protocol for a double-blind randomised placebo-controlled feasibility and proof-of-concept trial to evaluate baclofen as an adjunct to support methadone detoxification

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Louise M. Paterson, Suzie Cro, Gemma Leobenber, Lorna Hazell, Amy Bagshaw, Claire Smith, Anne Smith & Anne R. Lingford-Hughes

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FORWARDS-2; study protocol for a double-blind randomised placebo-controlled feasibility and proof-of-concept trial to evaluate baclofen as an adjunct to support methadone detoxification

Author details and affiliations

Louise M Paterson¹

Suzie Cro²

Gemma Loebenberg¹

Lorna Hazell²

Amy Bagshaw¹

Claire Smith²

Anne R Lingford-Hughes¹

1. Division of Psychiatry, Dept of Brain Sciences, Imperial College London, London, UK
2. Imperial College Clinical Trials Unit, Imperial College London, London, UK

Corresponding author:

Dr Louise M Paterson

Assistant Professor

Division of Psychiatry

Department of Brain Sciences

Imperial College London

2nd Floor Commonwealth Building

Hammersmith Campus

Du Cane Road

London W12 0NN

l.paterson@imperial.ac.uk

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Abstract

Introduction

Detoxification from opioid substitution therapy (OST), particularly methadone, is challenging. Although many individuals on OST seek abstinence, withdrawal symptoms such as anxiety and insomnia often undermine these efforts. Baclofen, a GABA-B receptor agonist licensed for spasticity and used off-label in alcohol dependence, has shown promise in alleviating opioid withdrawal symptoms. The FORWARDS-1 trial established that baclofen can be safely co-administered with methadone. FORWARDS-2 now aims to investigate whether baclofen can facilitate methadone dose reduction and thus could be repurposed as a novel adjunct to support opioid detoxification. The protocol for this feasibility and proof-of-concept trial is described.

Methods

FORWARDS-2 is a multi-centre, double-blind, randomised placebo-controlled trial, conducted in UK community addiction services. Participants are adults with DSM-5 severe opioid use disorder (OUD) receiving methadone and seeking dose reduction or detoxification. Participants will be randomised 1:1 to receive either baclofen or placebo (target dose: 10 mg tds; max: 20 mg tds) for up to 12 weeks. Methadone dose reductions will be managed by the addiction service team. The primary outcome measure to assess proof of concept is methadone dose (mg/d) at 12 weeks, or time of abstinence if sooner. The trial's feasibility outcomes will be assessed after an initial internal 6 month feasibility phase and at the end of the study. These include recruitment rate, retention rate, and implementation across NHS and non-NHS (third sector) services. A parallel qualitative substudy will assess barriers and facilitators to detoxification and conduct a process evaluation.

Discussion

This pragmatic trial will represent the first such community-based UK opioid detoxification trial in decades and the first clinical trial of an 'investigational medicinal product (CTIMP) to be delivered within non-NHS community addiction services. If the primary outcome demonstrates that baclofen provides clinically meaningful benefits over placebo, this could offer a new pharmacological tool to support opioid detoxification, marking a significant step forward for OUD treatment. Moreover, the trial will establish new infrastructure for OUD research in UK addiction services, supporting future studies on detoxification pathways,

withdrawal management, and relapse prevention.

Introduction

Background and rationale

Opioid addiction in the UK

Addiction is a huge global challenge. In the UK, opiate addiction is a major contributor to addiction-related costs, estimated at over £10.7 billion per year (1). Drug-related deaths remain high in the UK, and about half the deaths involve an opioid (2).

Approximately 300,000 people in England currently use opiates and/or crack cocaine (3). Opiate users currently make up the largest proportion of those accessing UK drug and alcohol treatment services, with over 160,000 individuals with opiate dependence in contact with treatment services in 2023-2024 (4, 5). Heroin is the most common illicit drug that people seek treatment for. The average age of those using opioids has been steadily rising (4); in 2021-2022 69% of those in treatment started using heroin before 2001. The highest death rates are now observed in those aged 40-49 years old, and continue to rise in older age groups (4) with increasingly complex physical and mental health needs (6, 7).

OST provision

Evidence has established that the provision and delivery of safe, effective opioid substitution therapy (OST, commonly methadone in UK) combined with psychosocial support significantly reduces the impact of health, social and financial burden of opioid dependence and reduces mortality (8-11). Large numbers of individuals receiving OST benefit considerably from their treatment and do not detoxify. Indeed, our clinical experience in the UK is that most remain on OST for years despite many presenting for treatment expressing their aim is to 'get off all drugs'. However, evidence is growing about the detrimental impact of chronic opioid use. Methadone, particularly at high doses, is associated with cardiovascular and respiratory disorders, which contribute to physical frailty, and with increased mortality as well as neurocognitive deficits (12-14). OST also

carries the risk of overdose through respiratory depression. These risks are likely to increase as the proportion of older individuals in treatment grows.

Abstinence as a treatment goal

Provision of OST for maintenance therapy is an important aspect for engaging and retaining people with moderate-to-severe opioid use disorder (OUD) in addiction services (15).

However, many individuals express a desire to become opioid-free. It is vitally important therefore to offer detoxification as a potential treatment goal for those for whom it is appropriate and desired, and evidence-based guidelines for the management of opioid detoxification have been established (8, 16, 17). However, despite desiring abstinence, relatively few initiate and complete detoxification. It is hard to achieve due to a range of factors such as the fear of withdrawal, associated emergent symptoms like poor sleep and anxiety, and a lack of effective treatments to ameliorate these symptoms. This is compounded by lack of research into the structural, social and psychological barriers to opioid detoxification.

Detoxification provision

Limited scientific or clinical attention has been paid to opioid detoxification or relapse prevention in recent years, so innovation has been limited. Remarkably, there have been no new adjunctive licensed medications in the UK to assist with either indication for several decades. Slow tapering of OST can attenuate symptoms, but available adjunctive medications including hypnotics and sedatives have limited efficacy and/or can only be used short-term. Lofexidine was formerly used as an adjunct to support opioid detoxification (8), but since 2018 has been unavailable in the UK, despite more recent approval in the US. So it is more important than ever to establish an evidence base for a non-opioid approach to detoxification. This unmet need is set against a backdrop of low rates of achieving abstinence for those in treatment. Only a minority (~30%) of heroin users who begin treatment achieve stable abstinence in 10 to 30 years (18). In England, 'successful exits' (i.e. leaving treatment opioid-free) have reached a historical low; at 23% for 2023-2024, down from a peak of 37% in 2011-2012 (19).

Detoxification in the community

The vast majority of opioid detoxifications are now undertaken in community-based settings such as clinics, rather than inpatient or residential settings, therefore any development in pharmacological management of opiate detoxification must be suitable for use in community settings. Typically, community OST detoxification involves gradual dose reduction or tapering over a period of 12 weeks to reach abstinence, though methadone dose reduction may also be undertaken with a view to switching to buprenorphine.

The role of baclofen

We propose that baclofen, a GABA-B agonist, has the desired properties to facilitate opiate detoxification. Baclofen is a generic medication currently licensed for spasticity and is well tolerated (20). It is prescribed off-label for alcohol dependence, where it has been shown to support abstinence, and to reduce craving and alcohol intake. Meta-analyses support efficacy at doses of 30 to 60 mg/day (21, 22), and an international consensus endorsed its use in moderate-to-severe alcohol use disorder (23).

Evidence for baclofen's potential efficacy in opiate dependence comes from preclinical studies (24) suggesting it will target dysregulated neurobiology during withdrawal, like lofexidine, but also target anxiety, muscle aches, insomnia, and craving (25). Two clinical trials in opiate withdrawal and one in relapse prevention provide further support. A small open-label inpatient study found that baclofen improved withdrawal symptoms after abrupt cessation of methadone and was well tolerated (26). Another trial of illicit opiate withdrawal found that baclofen compared favourably with clonidine in improving 'mental' and physical withdrawal, with few side-effects (27, 28). In abstinence, a relapse prevention study reported that baclofen (60mg/d) showed no benefit in opiate-positive urinalysis but some improvements in treatment retention and symptoms (29). No particular safety concerns were raised in these or similar studies (30).

Safety of baclofen with methadone

The FORWARDS-1 trial recently established that it was safe to co-prescribe doses of up to 70mg methadone per day with a single dose of up to 60mg baclofen, i.e. doses of methadone that are consistent with current prescribing (8) and doses of baclofen are likely

to be efficacious and well tolerated (22). FORWARDS-1 was an ascending dose-finding study that used an adaptive Bayesian model to determine safety parameters for the use of baclofen in combination with an individual's usual dose of methadone (31, 32).

Rationale for FORWARDS-2

We will now conduct the feasibility, and proof-of-concept trial to determine whether baclofen can assist methadone detoxification. FORWARDS-2 (Facilitating Opiate Recovery: Withdrawal and Abstinence thRough Detoxification Support) will be a pragmatic trial, conducted in community-based settings in UK addiction services. Services are delivered by a combination of both NHS and third sector (non-NHS) organisations. All provide methadone OST and offer a range of detoxification provision and psychosocial interventions. Treatment as usual will continue in parallel alongside the trial, with decisions regarding methadone dose changes resting with the clinical service.

We anticipate that the majority of individuals presenting for treatment will have abstinence as the treatment goal, and therefore a duration of 12 weeks was chosen to reflect UK detoxification guidelines (8). It is noteworthy that the evidence-base for RCTs in support of 12-week detoxification programmes is limited (33), with some evidence suggesting longer tapering periods interspersed with periods of stability may be more effective (34). Some individuals could achieve abstinence before 12 weeks whereas others may not be able to detoxify to 0mg/d within 12 weeks, or instead have dose reduction as the goal. All these projected trajectories are permitted within the pragmatic trial design.

Qualitative sub-study: AWARD

Given the lack of recent innovation in the field, there is a dearth of understanding around the barriers and facilitators that shape both the initiation and successful completion of detoxification. Few qualitative studies have explored attitudes towards tapering and cessation of OST. Knowledge surrounding the social, structural, and psychological barriers to implementing a novel intervention in community settings also remains limited. Process evaluations provide valuable insight into how an intervention works, the reasons why it fails, and whether it would work in real-life settings. This process evaluation will follow the MRC framework, and shed light on the feasibility of the intervention through the

assessment of context, implementation, and mechanisms of impact (35-37).

A parallel qualitative study will therefore be conducted; the AWARD study (Attitudes to Withdrawal and Abstinence thRough Detoxification). This sub-study will comprise two sections. First, an exploration of the barriers and facilitators to detoxification, and second, a process evaluation of the FORWARDS-2 trial to aid interpretation of findings. Together, these will inform how future large-scale clinical trials of novel pharmacological adjuncts should be conducted and optimised for implementation into clinical practice.

Herein we describe the protocol for the FORWARDS-2 trial. Whilst this is a feasibility and proof-of-concept study, we have followed the SPIRIT guidelines throughout (38, 39), see Additional File 1.

Aims & Objectives

Primary Objective

The primary objective is to assess the feasibility and proof-of-concept efficacy of baclofen to facilitate methadone detoxification. The study aims to evaluate whether there is evidence of superiority of baclofen over placebo in facilitating reduction in methadone dose in those who are tapering down their methadone with a view to dose reduction or abstinence.

If a meaningful reduction in methadone dose is observed (defined as an absolute difference of ≥ 10 mg/d methadone dose reduction between baclofen and placebo), alongside acceptable feasibility measures, a comprehensive, sufficiently-powered trial will be designed to further investigate baclofen's efficacy in facilitating detoxification from methadone or other opioid substitution therapies (OST) such as buprenorphine.

Feasibility Objectives

Feasibility will be determined through evaluation of 1) proposed recruitment rate and 2) the retention rate at 12 weeks. Achieving an acceptable recruitment rate will be dependent upon the number of sites open to recruitment, which will also be measured.

Secondary Objectives

The secondary objectives include 1) determining whether participants achieve successful abstinence at or before 12-weeks, 2) evaluating the acceptability, retention in detoxification treatment, tolerability, and medication compliance, and 3) assessing potential improvements in self-reported anxiety, cravings, sleep disturbance, muscle spasms/restless legs, and other substance use.

Exploratory Objectives

Exploratory objectives aim to determine participants' previous experience with detoxification, current treatment goals and trial expectations obtained in an entry interview. An exit interview will assess their experience of the trial including accessibility and acceptability, success of blinding and client satisfaction, using a modified Client Satisfaction Questionnaire (CSQ-8) (40). Sample characteristics will be explored to determine which factors influence feasibility or clinical outcomes in the trial. An out-of-trial follow-up at 3-months post-completion will also be conducted, in person if possible and by reviewing case records, to determine participants' current treatment status (i.e. whether they have maintained, increased or decreased their methadone dose, or reached/continued abstinence, as applicable).

Qualitative sub-study objectives

The AWARD sub-study will undertake interviews with trial participants and those in services who are not participating in the trial, to explicitly explore attitudes, barriers, and facilitators to opioid detoxification, including a more thorough assessment of treatment goals and expectations. AWARD also seeks to include the attitudes of staff working within the drug and alcohol services that are hosting the trial, and funding commissioners who are involved in determining service provision in local areas. Findings will provide data for a process evaluation of the FORWARDS-2 trial to inform the design and optimisation of any future follow-up trial.

Specific objectives are to 1) understand if delivery of the FORWARDS-2 trial was acceptable

to treatment providers and service users, 2) explore treatment provider and service user attitudes towards OST and detoxification from methadone, 3) explore service commissioner attitudes towards OST and detoxification from methadone and where funding is prioritised within addiction services and 4) identify key barriers and facilitators to detoxification from methadone.

Trial Design

FORWARDS-2 is a double-blind, randomised placebo-controlled, parallel group trial. Participants will be randomised to receive baclofen or placebo (oral/tablet daily dosing for up to 12 weeks, with a target dose of 10mg tds and a maximum dose of 20mg tds) in a 1:1 ratio, stratified by sex. This is a feasibility and proof-of-concept trial, and is multi-centre, taking place in UK community drug and alcohol services based in London, Essex and the North West of England. It is planned to open at least 15 sites nationally. The trial includes an internal feasibility phase to closely monitor recruitment and retention rates for 6 months, to ensure adequate rates are achieved for this study.

The target population is people with a current or previous diagnosis of moderate-to-severe opioid use disorder (DSM-5) or opioid dependence (DSM-IV), who are treated with methadone substitution therapy in community-based settings, and who desire or are planning to undergo dose reduction or detoxification. This is a pragmatic trial designed to be flexible and accommodating to the differing needs of both individuals receiving methadone and addiction services. Participants can enter the trial on any dose of methadone that is deemed appropriate by the treating service, in discussion with the trial team as necessary, and can enter with the goal of abstinence or dose reduction. The trial team will provide and monitor the adjunctive baclofen/placebo treatment but will not otherwise interfere with participant's 'treatment as usual'. Any changes in methadone dose that occur during the trial will be decided by the participant and their clinical team.

Procedures:

Potentially eligible participants will be identified by record search and/or review by clinical service staff, and those interested will be given the participant information sheet (PIS), and

invited to attend a screening visit. Screening will include written informed consent, semi-structured interviews to ascertain study eligibility, sociodemographic information (e.g. income, education level, ethnicity) medical, psychiatric and substance dependence history, urine pregnancy test (for women of childbearing potential) and completion of baseline self-report and rater-reported questionnaire measures.

Eligible participants will be randomised, then return to their addiction service to collect trial medication and receive instructions on dosing schedule for take-home consumption. They will also complete further baseline questionnaires and complete a brief entry interview. Following this, participants will complete regular in-person follow-up visits during the titration, maintenance and tapering phases of the trial (Figure 1). At each visit, patient reported outcomes (PRO) will be collected according to the Schedule of Events (Table 1) which provides the participant timeline. Participants will also be asked to complete weekly online questionnaires, collected remotely, for electronic patient reported outcomes (ePRO).

The primary endpoint occurs at the 12-week visit (i.e. following a maximum of 12 weeks' maintenance treatment) or at the time of methadone abstinence if sooner.

After completion of the trial, participants will complete an exit interview. After trial completion, participants' methadone dose status will be recorded at an out-of-trial follow-up at 3-months.

We will employ a mixture of face-to-face, video conferencing and telephone calls to collect source data in paper-based case report forms, as well as using a remote online data collection tool for those who have access to online platforms. This will ensure maximum inclusivity for all participants regardless of their situation e.g. whether they have smart phones and internet access or not. This will be decided on a site-by-site and case-by-case basis for individuals.

The AWARD substudy involves a single visit during which participants will complete a semi-structured interview and brief questionnaire: a substance-use questionnaire for service users, or a work-related questionnaire for treatment providers and funding commissioners.

Visits will last approximately 1.5h and may take place remotely or in-person, dependant on participant preference. AWARD visits will be audio recorded for transcribing (with explicit consent).

[insert Figure 1 near here]

Figure 1: Participant Visit Flow Diagram

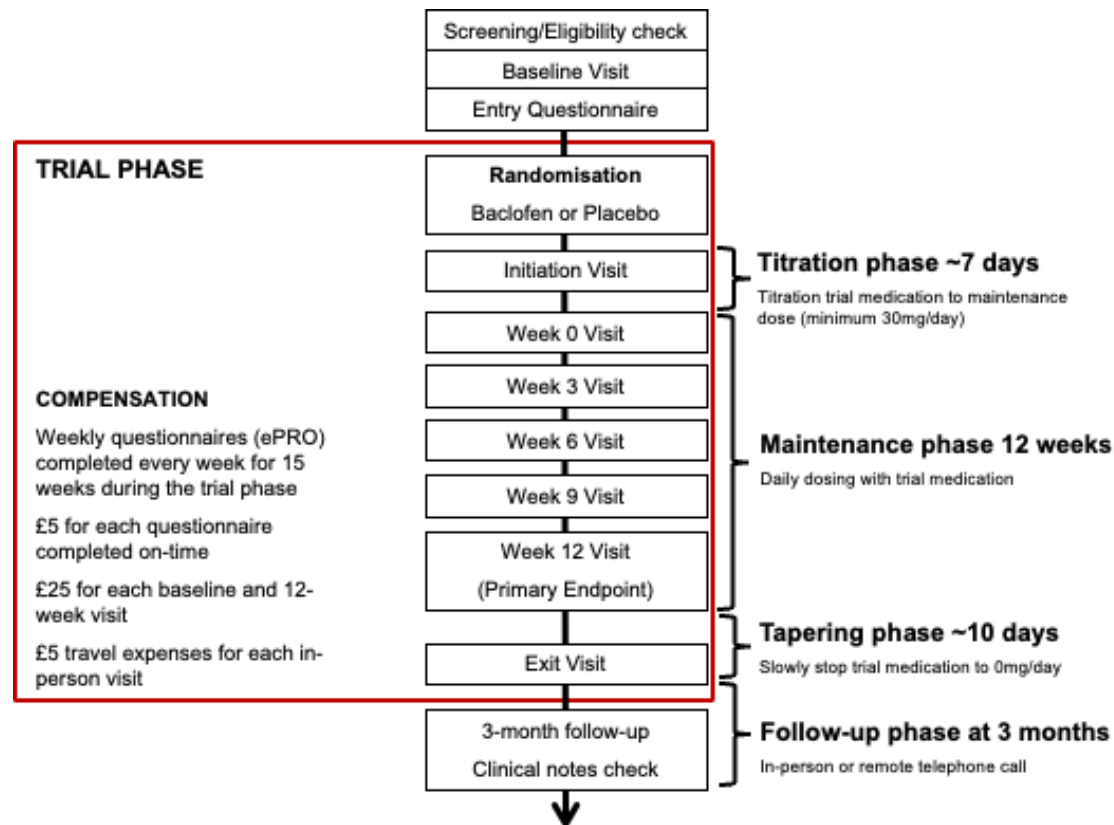


Figure 1. Participant flow diagram.

[insert Table 1 near here]

Study	Scree	Post-			Treatment period and Follow-up												Post-treatment		
Visit & Time-point	P ¹	Initiation P	Titration (extra as	0 P	1	2	3 P	4	5	6 P	7	8	9 P	10	11	12 P	Tapering (extra, as	Exit Visit	3-month
Consent	P																		
DSM-5	P																		
General	P																		X
Demograp	X																		
Pregnancy	P	P		X			X			X			X			X		X ²	
Medical	P																		
Eligibility	P																		
Entry	P ¹	P ¹																	
Baseline	X															X			
TOPS (full)	X															X			X
Medication		P		P			P			P			P			P			
In-person	X			P	(	(	P	(	(	P	(	(	P	(	(	P	X	P	
Feasibility				P	(	(	P	(	(	P	(	(	P	(	(	P	X	P	
Weekly		X		X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	X	
COWS	P ¹															P		P ¹	
Titration		P	X																
Methadon	X	X	X	P	X	X	P	X	X	P	X	X	P	X	X	P	X	X	X
Baclofen/pl			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomita	X	X		X			X			X			X			X	X	X	X
Tapering																P	X		
Exit																		P ¹	
CSQ-8																		P ¹	

Table 1: Schedule of events

P = visit should be in person, X = can be flexible; in-person, phone, electronic, () indicates where data collection will only take place if participants visit weekly. AEs; adverse events. CSQ-8; Client Satisfaction Questionnaire.

¹ visit is ideally in-person,

² optional pregnancy testing will be offered at these visits. At Screening and Initiation visits pregnancy testing is mandatory.

³ Baseline and 12-week Questionnaires: Beck Depression Inventory (BDI), Spielberger Trait Anxiety Index (STAI), Pittsburgh Sleep Quality Index (PSQI), Restless Legs Severity scale (RLS), Assessment of Recovery Capital (ARC), Substance Use Sleep Scale (SUSS), Opioid Use Disorder severity scale (PRO-S; baseline and PRO-I; 12-week).

⁴ In-person repeated Qs: methadone dose (prescribed and actual dose taken), baclofen/placebo dose (prescribed and

actual dose taken), Modified Treatment Outcomes Profile Scale (TOPS, substance use), VAS rating scales for opioid and cocaine need (VAS-N) and want (VAS-W), numerical rating scales for craving (cocaine, opioid), liking, wanting, sleep, anxiety, restless legs, withdrawal.

⁵ Feasibility Questionnaires: Compliance/adherence (pill count), tolerability.

⁶ Weekly Electronic PROMs: methadone dose (prescribed and actual dose taken), baclofen dose (prescribed and actual dose taken), Modified Treatment Outcomes Profile Scale (TOPS, substance use), opioid and cocaine need (VAS-N), want (VAS-W), numerical rating scales for craving (cocaine, opioid), liking, wanting, sleep, anxiety, restless legs, withdrawal), compliance/adherence (pill count), tolerability.

⁷ For those who reach 'early abstinence' (complete detoxification earlier than 12-weeks, defined as reaching 0 mg/d methadone for at least 3 days), these measures will instead be captured at the point at which successful abstinence is achieved.

Methods: Participants, interventions and outcomes

Study Setting

The trial is approved for sites in England, UK. The study will recruit from both NHS and non-NHS third sector addiction services, expected to be in London, Essex and the North West of England.

At the time of writing, 15 community drug and alcohol services had approved the FORWARDS-2 trial and given confirmation of capacity and capability to act as trial sites, with recruitment ongoing. The sites are listed in Acknowledgements.

Eligibility Criteria

Inclusion criteria:

- Current or previous DSM-5 moderate to severe opioid use disorder or ICD10/11 opioid dependence
- Currently treated with methadone substitution therapy
- Ready for dose reduction or detoxification (as determined by their treating addiction service)
- >18 years old
- Individual wishes to undergo methadone detoxification and/or dose reduction

Exclusion criteria

- Lack of capacity to consent
- Unable to take oral medication
- Contraindication for baclofen
- History of allergic or adverse reactions to baclofen, placebo, or their excipients
- Where there are “Special warnings and precautions for use” according to the Reference Safety Information (Summary of medicinal product characteristics, SmPC) and where the risk vs benefit ratio for prescribing is not in favour of prescribing medication.
- Current and ongoing substance dependence (including alcohol), except for opiates and nicotine, with no desire to stop at this time
- Clinician does not deem that the individual is suitable to undergo dose reduction or detoxification from methadone at this time
- Use of regular prescription or illicit medications or drugs which in the opinion of the investigators will interfere with subject safety or study integrity
- Severe chronic obstructive pulmonary disease or Type 2 respiratory failure
- Unable to follow study protocol due to serious mental health disorder e.g. enduring psychotic illness, suicidal intent
- Any woman who is pregnant, of child-bearing potential refusing a pregnancy test or unwilling to use adequate contraception for the duration of the trial

Informed consent

Written informed consent to enter the study will be sought from each participant by a trained member of the research team only after a full explanation of the study has been provided, a Participant Information Sheet (PIS) given and time allowed for consideration. Consent will be obtained at the participant’s addiction service (approved trial site) before any screening procedures are carried out. The PIS will be read through carefully with the participant by a trained member of the research team. If they wish to participate, they will be informed that participation is entirely voluntary and that they can leave the study at any time without their decision affecting the treatment they will receive. Consent forms will be signed by the participant and researcher in paper format and filed in the trial source

documents, with a copy uploaded to the participant's medical record and a copy given to the participant to keep.

Explicit consent will be sought for audio recording of entry, exit interviews and AWARD study interviews, for future contact to take part in other research studies, and for data to be shared with other institutions (participants can opt out of each of these). There are no special consent provisions for biological specimens as none are collected.

Recruitment

Strategy

We plan to open 10 sites within the initial internal 6-month feasibility phase, and to add further sites during the subsequent proof-of-concept phase (up to a maximum of 30), depending on initial recruitment and retention rates. A 12-month recruitment period is planned for the study in total. To randomise 112 participants, a target recruitment rate of 0.62 participants per site per month across 15 sites will be required assuming a 50% retention rate. Alternatively, a total of 4 or 5 randomisations per site provides $n=68$ participants, which will be sufficient if $>80\%$ retention rate.

This trial will take advantage of the organisational structure of UK addiction services, whereby a single NHS or non-NHS organisation provides drug and alcohol services at multiple sites. For example, Change Grow Live (a single non-NHS organisation with one regulatory/governance procedure) operates >40 drug and alcohol services in the London and Manchester areas, many offering methadone prescribing. CNWL (an NHS organisation), operates 4 addiction services in North West London.

This trial is a National Institute for Health and Care Research (NIHR) 'adopted' study, so will benefit from support from relevant Research Delivery Networks for recruitment support and trial delivery.

Site identification

In collaboration with Change Grow Live (CGL) and NHS services we will identify suitable

research sites. Capacity and suitability of a site will depend on several factors: 1) numbers of patients receiving methadone who may wish to reduce or detoxify, 2) proximity to other sites where trial-specific Research Nurses are operating (i.e. near London or Manchester), 3) availability of Clinical Research Practitioner (CRP) staff (now called Research Delivery staff) to support the study, 4) service infrastructure and adaptability and 5) receipt of satisfactory outcomes on a Site Feasibility Questionnaire.

The trial will be promoted on the website, and via approved posters and flyers that will be displayed at trial sites.

Referrals

Referrals can come from any staff within services, or individuals can self-refer to the trial via advertising material. They will be referred to the trial team (usually the research nurse) who will explain the study and provide the PIS. For those with a language barrier, we will seek support from local translation services to facilitate participation, where possible.

Committing to methadone dose reduction or detoxification is an important decision and can take time. Potential participants can defer participation to a later point if now is not the 'right time' to start a detoxification/tapering. In this case, they will be re-contacted, according to their wishes. Participants who decline to take part will be asked the reason(s) and this will be recorded, where possible.

Promotion of retention and completion of follow-up

The trial team and clinical service will endeavour to schedule trial visits to coincide with 'usual care' visits to reduce burden, reduce travel costs and increase retention.

Wherever possible, the same research nurse and/or delivery support staff will conduct all participant visits and will be the point of contact for the participant throughout their trial journey, to build rapport and trust, and to promote retention.

Participants will receive telephone reminders in advance of scheduled in-person appointments, and automated reminders to complete their ePRO questionnaires. For the 3-

month out-of-trial follow-up, the team will continue to try and contact participants until the trial closure date, to reduce data loss at this distal timepoint.

All participants with primary outcome data will be included in the primary analyses.

Participants who discontinue trial medication will remain in the trial, and will be encouraged to continue to provide follow-up data. Some outcome data can be collected via access to clinical notes (e.g. methadone dose, concomitant medications). See Statistical Methods section for handling of missing data.

Participant compensation

Travel costs for trial visits are reimbursed, and participants will receive compensation for their time at the longer trial visits, as follows (see Figure 1): For each in-person research visit (baseline, initiation, 0-, 3-, 6-, 9-, 12-week, tapering/exit), participants will be compensated for travel expenses. Additionally, as the baseline and 12-week visits are longer than the regular in-person research visits, participants will be offered £25 compensation for their time taken attending each of these visits. This would be a maximum of £50 compensation for both visits. In addition, for each weekly follow-up questionnaire set completed, participants will be compensated £5 for their time, if completed within 3 days of distribution.

Payments are made in the form of gift vouchers that can be topped up throughout the trial at regular intervals, as needed, and the amounts are in line with NIHR guidelines.

Interventions

Treatment Arms

Participants will be randomised to receive oral baclofen, or placebo in a 1:1 ratio, stratified by sex as there is evidence that sex is a moderator of baclofen tolerability (41). The medication will be supplied in tablet form, and taken daily at home for the duration of the trial. Tablets will be supplied in foil blister packs designed for each of the three stages of the medication dosing regimen as follows:

- 1) titration phase (gradual increase in dose until maintenance dose is reached),

- 2) maintenance phase (continued daily dosing at chosen maintenance dose until the 12-week visit, or until methadone abstinence is reached, whichever occurs sooner)
- 3) tapering phase (gradual reduction in baclofen/placebo dose to zero).

Trial medication phases and dosing

The titration phase (duration; ~7 days) begins at the initiation visit, at which participants will receive a titration medication pack. During titration, baclofen/placebo will be titrated up to a minimum dose of 30mg/d, administered as 10mg tds; 30mg/d is the target maintenance dose.

The maintenance phase begins at Week 0 (duration; up to 12 weeks), at which participants will be provided with maintenance medication packs (usually 3 weeks' supply at a time). During the trial maintenance phase, the baclofen/placebo dose can be increased up to a maximum of 60 mg daily (20mg tds), as tolerated, or can be reduced, according to clinical need.

At the 12-week visit, or earlier if the participant reaches early abstinence from methadone, participants enter the tapering phase (duration; ~7-14 days, depending on maintenance dose), and are provided with a tapering medication pack. During the tapering phase, the baclofen/placebo will be tapered to zero.

A schematic showing the possible treatment trajectories for trial medication and methadone dose is provided in Figure 2, and an example treatment regimen is provided in Table 2. Participants will return periodically throughout the trial for follow-up visits, to collect trial medication and to return used medication packs.

[insert Figure 2 near here]

[insert Table 2 near here]

Figure 2: Example study treatment trajectory

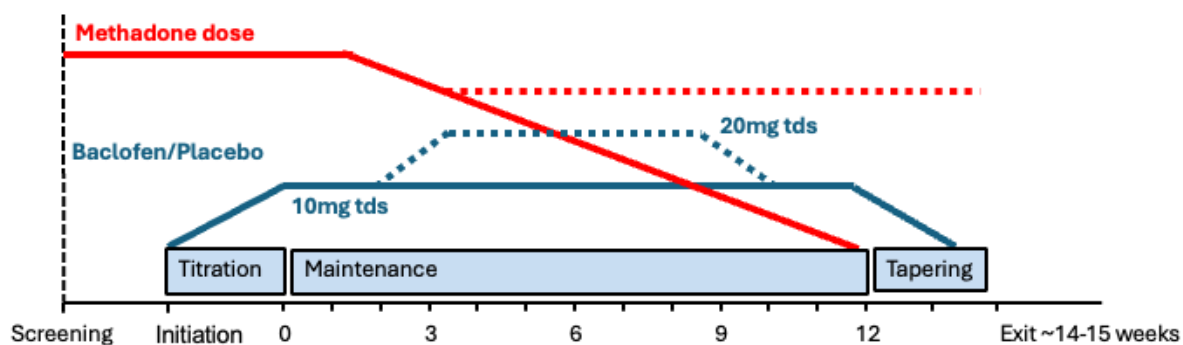


Figure 2; examples of how a participant's dose of methadone and trial medication may change over the course of the trial. **Titration phase:** Starting dose of baclofen/placebo is incrementally increased over ~7 days (see table 2). **Maintenance phase:** Target dose of 10mg tds (30mg) maintained for 12 weeks (or until participant reaches early abstinence). Dose can vary according to clinical need (max 20mg tds). **Tapering phase:** Dose incrementally reduced as needed, at 12-weeks or point of abstinence (see table 2). **Methadone dosing examples:** The solid red line indicates methadone dose for a participant who regularly and consistently reduces their methadone dose between weeks 1 and 12 of the trial, reaching abstinence at week-12. The dotted red line indicates a participant who begins reducing their methadone at week 1 but does not reduce further from week 3 onwards. **Trial medication examples:** The solid blue line indicates a participant whose baclofen/placebo dose was titrated up to the target dose (10mg tds) and remained at that same dose throughout the trial until they were tapered following the 12-week visit. The dotted blue line represents a participant whose dose was increased at week 2 to the maximum 20mg tds, until week 9 at which point they reduced back to 10mg tds until the week 12 visit.

Table 2: Example schedule of titration, maintenance and tapering

Table for titration/tapering/dosing	Day	Titration	Number of tablets	Maintenance Dose
1. Titration up phase (~7 to 12 days)				
For a target dose of 30mg	1-3	5mg tds	4.5	
	4-6	10mg tds	9	
	7+	10mg tds	3	30mg
For a target dose of 60mg	1-3	5mg tds	4.5	
	4-6	10mg tds	9	
	7-9	15mg tds	13.5	
	10-12	20mg tds	18	60mg
2. Maintenance phase- continue dosing up to 20mg tds for up to 12 weeks (Week 0 to Week 12)				
3. Tapering down phase (started at week-12 visit, ending by week 14)				
Tapering down from 30mg	1	5,10,10mg	3	30mg
	2	5,5,10mg	2	
	3	5,5,5mg	1.5	
	4	5,0,5mg	1	
	5	0,0,5mg	0.5	
	6	end		
Tapering down from 60mg	1	10,20,20mg	5	60mg
	2	10,10,20mg	4	
	3	10,10,10mg	3	
	4	5,10,10mg	2.5	
	5	5,5,10mg	2	
	6	5,5,5mg	1.5	
	7	5,0,5mg	1	
	8	0,0,5mg	0.5	
	9	end		

Suggested dose schedule for titration and tapering to/from 30mg or 60mg dose

Receipt of medication

Trial medication will be supplied to the participant at in-person visits, according to the prescription and will be provided at initiation (titration pack), at Weeks 0, 3, 6 and 9 (maintenance packs) and at Week 12 (tapering pack), or earlier if participant reaches abstinence before 12 weeks. It is intended that prescribers provide up to 3-weeks' supply of trial medication at each visit, but this can be flexible, according to clinical need and/or site

operational requirements. In these cases, participants may attend more or less regularly, as applicable (see Table 1, schedule of events).

If a participant temporarily stops taking the trial medication during the trial, e.g. misses doses or misses an appointment to pick up medication, and wishes to continue taking the trial medication, they can be re-titrated back up to their maintenance dose. There are no restrictions on the number of times that the trial clinician may decide to increase or decrease the baclofen/placebo dose, up to a maximum of 60mg/d. The speed of escalation or de-escalation can be modified according to patient need, experience of side-effects or clinical assessment. Any changes to dose will be recorded.

Stopping or discontinuing medication

If a participant decides to discontinue trial medication, they should be tapered off the medication according to the example treatment regimen. These participants will be encouraged to remain in the study to provide follow-up data at each visit including exit questionnaire. The trial team will continue to record any changes in methadone dose, and the dose at 12-weeks, alongside other measures from clinical records unless the participant withdraws consent.

Monitoring medication compliance and adherence

Participants will be asked to return used and/or empty trial medication blister packs for a 'verified' pill count to check compliance. In the absence of returned packs, estimated compliance will be assessed using self-report. Participants will also be asked at each in-person visit, and in the weekly ePRO how many tablets they are taking daily. Follow-up visits will include checks on medication tolerability and compliance.

Concomitant care and changes to methadone dose

The clinical team will administer and oversee changes to the adjunctive baclofen/placebo trial medication, while participants continue to receive the standard 'usual care' treatment that is offered by their treating service, including prescribing of methadone. Other concomitant medications can be prescribed, according to clinical need, and will be

recorded.

It is anticipated that different addiction services will offer different 'usual care' for those who wish to undergo methadone tapering and/or detoxification. Participants will be asked to take their methadone according to their usual schedule (usually daily but may also be twice daily in divided doses). Any adjustments to the methadone dosage during the trial will be determined by the clinical team in consultation with the participant. Any changes in methadone dose will be recorded (derived from self-report at in person and ePRO questionnaires and verified from clinical notes).

After enrolment in the trial, clinicians are allowed to provide alternative treatment to that specified in the protocol in the participant's best interest, but the reasons for doing so will be recorded. In this case the participant will remain in the trial for the purposes of follow-up and data analysis.

Trial medication will not be available after the trial, and participants will return to usual care.

IMP management; appearance, manufacturing, packaging, labelling and supply

Appearance and manufacturing

Baclofen tablets will be supplied in 10mg tablets (white, round, scored) and can be split in half for 5mg doses. Placebo tablets will be manufactured to create an identical visual match to placebo and will be supplied in identical blister packs. Each pack will have a unique identifying kit number that will relate to the randomisation code.

Sharp Clinical will be responsible for the procurement of baclofen, manufacture of matched placebo and packaging, preparation and labelling of treatment packs in accordance with the randomisation list, with Good Manufacturing Practice (GMP) and Annex 13 (MHRA) requirements. They will also be responsible for QP release. Titration, maintenance and tapering packs will be prepared to create a participant 'kit', containing the requisite number of tablets assuming a 30mg maintenance dose is prescribed throughout the trial, with

additional packs supplied to allow the maximum of 60mg to be prescribed. Participant 'kits' will be stored at Sharp Clinical in a central site, for distribution to receiving sites at the point of randomisation.

Randomisation and blinding

A randomisation list (1:1), stratified by sex, using random block sizes was generated by Imperial Clinical Trials Unit's clinical data system (CDS) team using Sealed Envelope within OpenClinica to maintain blinding of investigators. Separately, CDS also send the kit list and associated allocation to the manufacturing pharmacy (Sharp Clinical) and to ESMS Global; the 24/7 emergency unblinding service. To ensure full concealment of allocation sequence, Sharp Clinical will use this list to pre-label the IMP kit boxes before any randomisations take place.

Eligible participants who are ready to be randomised and to initiate treatment will be randomised to baclofen or placebo using the randomisation tool, available in the custom-built OpenClinica Clinical Data Management and Electronic Data Capture software database, and the online software application, Sealed EnvelopeTM.

After consent, screening and baseline procedures have been completed and the participant is confirmed as eligible by the Principal Investigator, a member of the trial team with 'randomisation' permissions (either the participant's clinician or the research nurse) will input the relevant details into the OpenClinica database to trigger randomisation. The participant will be randomised to either baclofen or placebo, and be allocated a randomisation kit number by OpenClinica. The OpenClinica database will store the output of the randomisation, and send an automated email to Sharp Clinical detailing the kit code to be provided. Sharp Clinical will ship the associated allocation (containing the entire treatment pack for that participant) to the trial site at the participant's addiction service. Kits will be stored securely locally until participants attend for visits to collect their medication.

Blinding and unblinding

Participants, clinicians and study investigators are blinded. Trial statisticians are initially

blinded and will write the Statistical Analysis Plan (SAP) during this blinded period, but will be unblinded after the first data extraction from the database has occurred for Data Monitoring Committee (DMC) reporting.

Upon randomisation of each new participant, the automated email generated by OpenClinica will also be sent to ESMS Global, the 24/7 emergency telephone unblinding service, informing them of the participant ID number and kit number. ESMS are providing 24/7 emergency cover with clinician advice available to both participants and staff. Participants are provided with ESMS's emergency contact details in case of out-of-hours medical queries. ESMS also provide the emergency unblinding service for trial staff. ESMS will have access to the unblinding manual and can use this to unblind in case of medical emergency, at the request of a medical professional.

Reference Safety Information

Baclofen is a licensed product in the UK. The Reference Safety Information (RSI) is therefore a Summary of Product Characteristics (SmPC), and the chosen brand was Accord. Updates to the SmPC, including changes to the Reference Safety Information (RSI), will be submitted to the MHRA for approval and incorporated into the trial, as appropriate.

Outcomes

In the following sections we describe the studies primary, feasibility, secondary and safety outcomes. The main feasibility outcomes will be assessed at the end of the internal feasibility phase (first 6 months) to inform the feasibility of this study and at the end of study to inform feasibility of a future sufficiently-powered study. All other outcomes will be assessed at the end of the study.

Primary Outcome (Efficacy) Variable

Change in methadone dose (in mg) from baseline at 12 weeks, or time of abstinence if sooner (termed 'early abstinence').

Feasibility Outcomes

Main feasibility outcomes

- The percentage of the proposed recruitment rate achieved: defined as the number of participants randomised per site per month/planned recruitment rate x 100. The planned recruitment rate per protocol is 0.62 participants per site per month.
- Number of participants randomised.
- Study retention rate at time of the primary endpoint measurement (at Week 12 or at time of abstinence if earlier): defined as the number of participants that initiate treatment (any duration and are still alive, not formally withdrawn or lost to follow up from the study) before 12 weeks/number randomised x100.

Other feasibility measures: compliance, acceptability and tolerability

- Measures of trial compliance: pill count, % completed questionnaires, success of blinding measures, time (days) in active detoxification/tapering treatment
- Measure of attrition between consent and randomisation, between randomisation and initiation of medication, during titration, and between initiation and completion, time between these timepoints, tapering window length.
- Medication compliance (self-reported adherence), visit attendance and time in active methadone detoxification, concomitant (rescue) medications
- Tolerability, assessed using a modified version of the SMARTS checklist (42) for a range of 12 symptoms experienced over the last 7 days, each scored 0 (not at all) to 4 (always).

Secondary outcomes

Methadone abstinence

- Incidence of successful abstinence from methadone at 12 weeks (or at point of abstinence for those achieving it earlier), defined as the first instance of a reduction in methadone dose to 0mg for 3 or more days between initiation of trial medication and the end of the 12-week maintenance period.
- Time (days) to successful abstinence from methadone, measured between initiation of trial medication and the first instance of a reduction in methadone dose to 0mg

for 3 or more days up to the end of the 12-week maintenance period.

- Days of abstinence from methadone between initiation of trial medication and the end of the 12-week maintenance phase or until time of successful abstinence if earlier, measured using total number of days 0mg methadone taken as reported by participants using electronic data capture form (ePRO).

Methadone dose

- Methadone dose regardless of any period of abstinence measured using prescribed methadone dose extracted from clinical records (and where data permits, self-reported dose) at Week 12.
- Number of methadone dose changes from initiation of trial medication up to end of the 12-week maintenance period or until time of successful abstinence if earlier, as measured by (i) participant report (at in-person visit), participant report (on ePRO) and (iii) prescribed dose.

Trial medication dose

- Maximum baclofen/placebo dose administered during maintenance phase as reported by participant (on ePRO) and as reported by prescribing service
- Proportion of time during maintenance phase at minimum target dose (10mg tds) and maximum target dose (20mg tds) as reported by participant (on ePRO) and prescribing service
- Number of baclofen/placebo dose changes during maintenance phase as reported by participant (on ePRO) and prescribing service

Patient Reported Outcome Measures

The following are collected both at in-person visits (retrospectively for the previous 3 weeks) and weekly through electronic questionnaires:

- PROMs from the modified Treatment Outcomes Profile Scale (TOPS) (43):
 - Total days using heroin
 - Total days using other drugs (alcohol, cocaine)
 - Total days smoking cigarettes/e-cigarettes
 - Total days using heroin during the maintenance phase and in the previous 4 weeks at week 12 (or time of abstinence if earlier)

- Total days using other substances including alcohol, nicotine, cocaine during maintenance phase and in the previous 4 weeks at Week 12 (or time of abstinence if earlier)
- Total days abstinent from all illicit substances during maintenance phase
- Total days abstinent from all substances (incl. nicotine and alcohol) during maintenance phase.
- Rating of psychological health, physical health and overall quality of life
- Visual analogue (VAS) and numerical rating scales:
 - Rating of need (VAS-N) and want (VAS-W) for heroin and cocaine (Visual Analogue Scale; VAS, 100mm) (44)
 - Rating of craving for heroin and methadone, anxiety, withdrawal, sleep, mood and restless legs symptoms (numeric rating scale; 0 to 10) (45)
 - Rating of drug effect 'liking' and 'want more' from Drug Effects Questionnaire (DEQ) (46)
 - Opiate use disorder improvement (PRO-S/I) score at Week 0 and Weeks 3, 6, 9 and 12 of maintenance period (numeric rating scale from 0 to 7) (47)
- Additional Outcome Variables At Week 12 or Time of Successful Abstinence: Anxiety Spielberger Trait Anxiety Index (STAI) total score (48), Beck Depression Index (BDI) total score (49), Pittsburgh Sleep Quality Index (PSQI) score (50), Restless legs syndrome (RLS) rating scale total score (51), Assessment of Recovery Capital (ARC) total score (52), Substance Use Sleep Scale (SUSS) total score (53), Clinical Opiate Withdrawal Scale (COWS) total score (54).

Safety outcomes

- Number of adverse events
- Number of participants with at least one adverse event
- Mean (IQR) number of adverse events per participant
- Number of adverse events by body system, Medical Dictionary for Regulatory Activities (MedDRA) preferred term
- Number of adverse events by severity

- Number of serious adverse events (SAEs)
- Number of adverse reactions (ARs), unexpected adverse reactions (UARs), serious adverse reactions (SARs) and unexpected serious adverse reactions (USARs)

Data collection and management

Data collection instruments

FORWARDS-2 will collect the measures outlined in the 'Outcomes' section, according to the Schedule of Events (Table 1). The measures collected in the initial 6-month feasibility phase will be identical to those collected in the subsequent proof-of-concept phase. The vast majority are validated questionnaires (see citations in Table 1), though some have been modified to better suit the timescale of collection or the participant group. Source data will be captured in paper case report forms (with the exception of the ePRO measures), and transferred to online databases.

A custom-built OpenClinica Clinical Data Management and Electronic Data Capture software database will be used as the trial database for primary and secondary outcome measures. Exploratory outcomes will be captured using REDCap (Research Electronic Data Capture) tools hosted at Imperial College London. REDCap is a secure, web-based software platform designed to support online or offline data capture for clinical research studies (55, 56). Electronic patient reported outcomes (ePRO) questionnaires will be sent out to participants via automated notifications from the OpenClinica ePRO module. Participants with access to digital tech (e.g. smart phones) will complete these ePRO measures directly on their devices. Those without access to a smart device, computer or internet can complete them on paper instead.

Confidentiality

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

Participants will be assigned a unique study ID number. All participant data will be pseudonymized according to this allocated ID. All data will be stored and processed according to the UK Data Protection Act (2018), and the Medicines for Human Use (Clinical Trials) Amended Regulations (2006). Identifiable and personal data will not be disclosed to anyone outside the trial team except in accordance with the protocol, or as required by law e.g. regulatory purposes for safety monitoring. Data will be archived according to the Sponsor policy, in line with those of the MHRA and REC.

Adverse event reporting

All adverse events will be collected and reported. For each adverse event the following information will be collected in the participants medical notes in addition to the trial database: date of onset, frequency of event, severity of event, causality (if know), outcomes and action(s) taken. Adverse events will be coded as per the MedDRA dictionary

Solicited tolerability data will be acquired separately, according to the schedule of events (Table 1, see 'secondary outcomes').

Statistical methods

Sample size

This study was not designed to provide a definitive assessment of effectiveness for the primary outcome, however the following power calculations were conducted to characterise the effect size that could be detected with the potential available sample size for this feasibility and proof-of-concept study.

To detect a 10mg absolute difference between treatment arms, with 90% power, one-sided 5% significance, standard deviation=12.5 (57), n=28 subjects per arm are required. This is equivalent to detecting a standardised effect of 0.8 ($=10/12.5$). An absolute difference of $\geq 10\text{mg/d}$ methadone dose reduction would represent a 2-4 week reduction in treatment engagement, therefore a clinically meaningful difference (8). The cohort studied are anticipated to be taking an average of 25mg methadone at the study start, so a 10mg/d reduction represents an average 40% reduction in dose.

Dropout from detoxification was estimated to be up to 50% (27, 58), so up to 112 patients were planned to be recruited to obtain data on 56 individuals for analysis. This sample size would also provide a good estimate for feasibility information on recruitment and study retention, which will inform a larger future sufficiently-powered trial on abstinence. With $n=112$ we will be able to estimate an overall proportion with a binomial exact 95% CI to within at most $\pm 9.6\%$ (calculation based on proportion requiring the largest sample size i.e., 50%).

In the event of lower realised loss to follow-up (0%), to allow for 5% loss to follow-up 60 patients will be required to be recruited to obtain $n=56$ for analysis. With $n=56$, for the main feasibility outcomes, we will be able to estimate an overall proportion with a binomial exact 95% CI to within at most $\pm 13.6\%$ (calculation based on 50% proportion).

With a reduced sample size of <56 available for analysis, this feasibility and proof-of-concept study would still obtain a valuable proof-of-concept signal on the primary efficacy outcome. With data on 25-56 participants recruited and followed up no formal statistical hypothesis testing will be conducted and the precision for the between arm difference in the primary outcome is ± 10.4 mg to ± 7.1 mg assuming a SD of 12.5mg. With $n=25$, for the main feasibility outcomes, we will be able to estimate an overall proportion with a Binomial exact 95% CI to within at most $\pm 20.2\%$ (calculation based on 50% proportion).

General analysis principles

Analysis and reporting will be in line with Consolidated Standards of Reporting Trials (CONSORT) guidelines (59, 60). Participant flow through the trial will be reported in a CONSORT flow diagram and baseline characteristics and outcome will be summarised descriptively by treatment arm and overall using suitable measures of central tendencies. For continuous data, means/medians and SD/interquartile range, and frequencies/proportions for categorical data will be reported. The main analysis will use the modified intention-to-treat population which will include all patients who initiate randomised treatment with a non-missing outcome, according to the group to which they

are randomised, regardless of subsequent treatment actually received. All treatment effect estimates will be accompanied by 95% confidence intervals. A detailed statistical analysis plan was written and agreed before the first extraction from the database and is available in Additional File 2. Analysis will be performed using Stata/IC (StataCorp, College Station, TX, USA).

Interim analyses and stopping guidelines

Internal feasibility phase

The internal 'Feasibility Phase' of the trial will closely monitor recruitment and retention rates for 6 months, to ensure adequate rates are achieved for this study. The main feasibility outcomes (recruitment rate, number randomised and study retention rate at Week 12) after six months of recruitment will be tabulated and assessed by the study team. A progression dashboard with red/amber/green thresholds will determine whether the internal feasibility phase should proceed to the full 12 month recruitment period, as follows. Green: >85% of proposed rate, >32 patients randomized, >80% retention at 12 weeks; trial to continue as planned. Amber: 66-85% of proposed rate, 26-32 patients randomized, 50-80% retention at 12 weeks; acceptable rates but may need changes to strategy. Red: <66% proposed rate, <26 patients randomized, ≤50% retention rate at 12 weeks; consider all options including discontinuation. A mixture of thresholds will result in re-strategising for continuity of the trial (e.g. opening more sites, further training and support). A report to the funder will be prepared, with input from the TSC and DMC to decide any changes to be implemented. The trial will not be paused to recruitment during this time.

Stopping criteria

The DMC will review unblinded safety data throughout the trial, prepared by the trial statistician. All SAEs and AEs will be tabulated by treatment group and sex. We will also provide the DMC with non-binding statistical boundaries for safety monitoring to help guide the DMC on SAEs. These will be constructed using a Bayesian Beta-Binomial model and the criteria for stopping will be based on the probability of the risk difference between the two

arms on the SAEs being greater than 0.1 by a predetermined upper threshold probability of 0.9 (61). The prior for this model will be the beta prior = zero events for both treatment arms (informed from FORWARDS 1 where no SAEs occurred). This will be presented for the total number of SAEs in the first instance. This may be repeated for individual SAEs at the request of the DMC.

Primary estimands

The primary efficacy outcome to assess proof of concept will be analysed using a) prescribed methadone dose from clinical records and b) participant's self-reported methadone dose at the Week 12 in-person visit. The two primary estimands are therefore the mean difference in the reduction from baseline in a) prescribed and b) participant-reported methadone dose at 12 weeks (or time of abstinence if sooner) in people with opioid use disorder or opioid dependence, treated with methadone substitution therapy, who would like to undergo dose reduction or detoxification (fulfilling the defined trial eligibility criteria) and initiate treatment with baclofen compared to placebo regardless of: stopping randomised trial medication (baclofen or placebo) early, stopping the detoxification pathway early prior to completion, using other medications or relapsing prior to 12 weeks, whilst participants are alive. The estimands are described by the attributes in table 3.

[insert Table 3 near here]

Table 3 – Primary estimands

Attribute	Description
Population (who the treatment effect is being estimated for)	People with a history of severe opioid use disorder or opioid dependence, treated with methadone substitution therapy, who would like to undergo dose reduction or detoxification (fulfilling the trial eligibility criteria) <i>and</i> initiate trial medication treatment
Treatment conditions (what is being compared)	Initiating trial medication treatment with baclofen or placebo (at any dose), regardless of adherence
Outcome (measurement being compared)	Reduction from baseline in a) prescribed and b) participant-reported methadone dose at Week 12, or at time of abstinence if sooner (evaluated separately)
Handling of intercurrent events (how post randomisation events are dealt with)	- Failing to initiate randomised trial medication (with baclofen/placebo) - Principal stratum¹ - Stopping randomised trial medication early - Treatment policy² - Changing dose of trial medication (baclofen/placebo) - Treatment policy² - Use of other medications e.g. anxiety/depression medication – Treatment policy² - Relapse/use on top – Treatment policy² - Death – while-alive³
Summary measure	Mean difference

¹A principal stratum strategy targets the population of participants who would not experience the intercurrent event

²A treatment policy strategy considers the occurrence of the associated intercurrent event as part of the treatment condition, and interest lies in the effect of the intervention given it leads to the occurrence of the intercurrent event; thus participant data are analysed regardless.

³A while-alive strategy evaluates the effect of the intervention prior to the intercurrent event; only outcomes up to the time of the intercurrent event will be included in the analysis.

Note: Relapse/use on top known to investigators is expected to be minimal hence a treatment policy strategy has been selected. A supplementary estimand will alternatively consider treating these events as a poor outcome.

Supportive Estimands

We will also assess supportive estimands for the primary outcome in this proof-of-concept study to understand the effect of initiating and remaining on detoxification treatment with baclofen or placebo (at any dose) for up to 12 weeks (Table 4). The analysis population and model will be the same as for the primary estimand, however for each participant we will use the methadone dose outcome at 12 weeks, or the last known time point when they remained on randomised study treatment (trial medication) if earlier, or the time of successful abstinence if earlier. This will be done separately for a) prescribed and b) participant reported methadone dose. We will also explore two other pre-planned supplementary estimands for the primary outcome if adequate data is obtained. These are

set out in the full Statistical Analysis Plan (SAP) which is available in Additional file 2.

[insert Table 4 near here].

Table 4 – Supportive estimand

Attribute	Description
Population (who the treatment effect is being estimated for)	People with a history of severe opioid use disorder or opioid dependence, treated with methadone substitution therapy, who would like to undergo dose reduction or detoxification (fulfilling the defined trial eligibility criteria) and initiate trial medication treatment
Treatment conditions (what is being compared)	Initiating trial medication with baclofen or placebo (at any dose) and remaining on treatment for up to 12 weeks
Outcome (measurement being compared)	Reduction from baseline in a) prescribed and b) participant-reported methadone dose at week 12 or last known time point on trial medication if earlier or time of abstinence if earlier (evaluated separately)
Handling of intercurrent events (how post randomisation events are dealt with)	• Failing to initiate randomised trial medication - Principal stratum¹ • Stopping randomised trial medication early – While-on-treatment³ • Changing dose of baclofen/placebo - Treatment policy² • Use of other medications e.g. anxiety/depression medication – Treatment policy² • Relapse/use of top – Treatment policy² • Death – While-alive³
Summary measure	Mean difference

¹A principal stratum strategy targets the population of participants who would not experience the intercurrent event

²A treatment policy strategy considers the occurrence of the associated intercurrent event as part of the treatment condition, and interest lies in the effect of the intervention given it leads to the occurrence of the intercurrent event; thus participant data are analysed regardless.

³A while-alive or while-on-treatment strategy evaluates the effect of the intervention prior to the intercurrent event (of death or stopping randomized trial medication early respectively); only outcomes up to the time of the intercurrent event will be included in the analysis.

Statistical methods for primary, secondary and feasibility outcomes

The analysis population for the primary estimands will use the modified intention-to-treat population which will include all randomised patients who initiated detoxification with baclofen/placebo with a non-missing methadone dose at 12 weeks (or at time of abstinence if achieved earlier) according to the group to which they are randomised, regardless of detoxification retention and treatment actually received. Excluding patients who do not initiate randomised treatment (baclofen/placebo) will not introduce bias as this is a double-blinded trial, thus reasons to not initiate will be considered independent of treatment (62). The primary estimands will be estimated using two separate linear regression models using

a) prescribed and b) participant-reported methadone dose. Each model will include fixed effects for treatment, baseline methadone dose and sex (randomisation stratification factor). Data transformations will be reviewed if model assumptions are invalid, with alternative models applied where appropriate.

Multiple imputation using data retrieved from treatment dropouts will be used to handle missing data (63). The imputation model will be run separately for each primary outcome analysis to impute missing values for a) prescribed and b) participant-reported methadone dose, respectively. Non-missing values for prescribed dose will not be used to impute missing values for participant-reported dose and vice-versa. The imputation model will be run for each treatment arm separately, and will include the following variables: baseline prescribed methadone dose, sex and separate variables to indicate whether participants were on or off treatment at Weeks 3, 6, 9 and 12, as well as the methadone dose at Weeks 3, 6, 9 and 12. This does not include the tapering period.

Secondary and feasibility outcomes will be analysed using the same analysis population as for the primary analysis. Secondary continuous outcomes will be analysed using the same modelling approach as the primary outcome. A complete case approach will be used. Analysis of secondary binary outcomes will be conducted using logistic regression with adjustment for sex. For the time-to-event outcomes Kaplan-Meier curves will be produced and Cox regression used to calculate hazard ratios including adjustment for sex. For count outcomes analysis will be conducted using Poisson regression, negative binomial regression or zero-inflated Poisson regression models, after checking the distribution of the dependent variable using the Pearson chi-square goodness-of-fit tests to ensure the selection of the most appropriate statistical model (including adjustment for sex). Feasibility outcomes will be summarized descriptively.

Every effort will be made to reduce missing data. Patterns of missingness will be explored and its relationship to the outcome described. The primary analysis will assume data is missing-at-random. Sensitivity analysis will explore the robustness of results to alternative missing data assumptions using multiple imputation and a pattern-mixture modelling approach (64). A complete case analysis will also be conducted as a sensitivity analysis.

Analysis methods for qualitative sub-study

Interviews will be audio recorded on MacWhisper software and transcribed automatically. Transcripts will be reviewed against the audio recordings to ensure accuracy and anonymity, edited, and uploaded to Atlas.Ti for inductive semantic thematic analysis (65). The identification and coding will be an iterative process, with data collection and analysis conducted simultaneously in line with established procedures for qualitative research (66). The process involves the repeated reading of the transcripts, development of a code list, and coding of the data to identify emerging patterns relevant to study objectives. This allows for the emergence of new themes, pivotal for exploratory research, which will be divided into categories affecting initiation only, completion only, or initiation and completion. Quantitative data for context, implementation and mechanisms of impact domains of the process evaluation will be reported for randomised participants, with exploratory analysis where prompted by findings.

Safety reporting

Adverse events will be tabulated and described for all subjects who received at least one dose of trial medication. Adverse events will be tabulated by type (e.g. adverse event, adverse reaction, unexpected adverse reaction, serious adverse event, serious adverse reaction, unexpected serious adverse reaction) and by treatment arm. Adverse events coded as per the MedDRA dictionary will be summarised at the preferred term level and body system class. Events will be tabulated by treatment arm including information on the number with at least one event and the number of events to account for recurrent events.

In addition, risk differences between those experiencing at least one event for each event at preferred term between treatment arms with corresponding 95% confidence intervals (CIs) will be calculated and incident rate ratios to account for recurrent events with 95% CIs using a suitable model e.g. a negative binomial or zero inflated Poisson model as appropriate. These results will be presented in both a table and graphically using a dot plot.

Oversight and monitoring

Trial management group, Trial Steering Committee and Data Monitoring Committee

The Trial Management Group (TMG) will be convened at the co-ordinating centre, including the Chief Investigator, Co-Investigators, trial manager, researchers, statisticians and key collaborators. The TMG will be responsible for day-to-day conduct of the trial, providing organisational support and operational issues, meeting regularly.

The Trial Steering Committee (TSC) includes an independent Chair, independent clinician, independent statistician, the Chief Investigator, Project Manager, Trial Manager, trial statisticians and two members with lived experience. The role of the TSC is to provide overall supervision of trial conduct and progress.

A Data Monitoring Committee (DMC) meets regularly to discuss study progress, recruitment targets, safety data and future planning. The committee includes an independent Chair, independent clinician and independent statistician. The DMC met on initiation of the project and agreed the type, frequency and format of data reports to be prepared by the trial statistician.

Details of membership, responsibilities and frequency of meetings for the TSC and DMC are defined in a separate Charter/Terms of Reference. The Chief Investigator (ALH), Co-Investigator/Project Manager (LP) and Trial manager (GL) will sit on both TSC and TMG committees providing continuity and cross-communication.

This trial is an Imperial Clinical Trials Unit (ICTU) adopted study. ICTU is a UK Clinical Research Collaboration (UKCRC) registered clinical trials unit. The FORWARDS-2 trial will adhere to ICTU Standard Operating Procedures (SOPs), as applicable, and ICTU provides additional trial oversight with an Operations Manager (CS), QA/QC services, and Clinical Data Systems (CDS) services.

Trial Monitoring

All trial sites will be monitored by the Clinical Trial Manager at least twice; once after the

first randomisation, and at least one other time during the course of recruitment. The monitoring visits assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data, including source data verification. A risk-based monitoring approach will be taken and monitoring will be done according to the monitoring plan, taking account of the trial risk assessment.

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU Head of QA in collaboration with the Trial Manager. The result will be used to guide the risk-based monitoring plan. The plan will be updated as required during the trial.

Communication and dissemination plans

Approval of protocol amendments will follow Sponsor, ICTU, MHRA and REC procedures.

Implementation will follow HRA and local site (NHS and non-NHS) procedures.

Dissemination of important trial-related changes (e.g. protocol amendments, updated SOPs) will be circulated to all sites by the trial manager, and implanted by the local PIs, research nurses and site staff, as applicable. The trial team will organise monthly meetings with all local investigators and their teams to update everyone on the trial progress; these meetings will be minuted and these minutes shared with all involved.

The study will be reported in accordance with CONSORT guidelines. Results will be published on the ISRCTN website. We plan to disseminate findings via local, national and international conference presentations such as at meetings of Society for Study of Addiction, British Association for Psychopharmacology, Royal College of Psychiatrists to reach academic, clinical, service user and public audiences. We will also disseminate results in peer-reviewed journals and during training events for addiction services. The results of the study will be reported and disseminated in peer-reviewed scientific journals, and internal reports commensurate with their author eligibility guidelines. Every attempt will be made to provide written feedback to study participants, as well as to referring services, and presentation of findings at the recruiting sites and at service user groups.

Access to data can be obtained via reasonable request to the chief investigator.

Participant and Public Involvement (PPI)

Verbal feedback was provided by three individuals with lived experience on the Participant Information Sheet and on relevant aspects of the protocol during trial design, including matters of compensation, burden and follow-up. There are two members of the public with lived experience on our TSC, to help monitor the progress of the research. We will continue to ask those with lived experience to provide feedback on any significant changes to our protocol and study materials before they are submitted to REC for approval, as appropriate.

Findings will be made available to the public via the FORWARDS study website <https://www.imperial.ac.uk/brain-sciences/research/psychiatry/forwards/> in addition to reporting results at educational/training events, relevant conferences and public events as appropriate. This will include the results of the AWARD study, which will additionally report on the process evaluation, and the barriers and facilitators to detoxification from participant, service user, staff and commissioner perspectives.

All publications will seek to adhere to the GRIPP2 reporting checklist which provides guidelines for the use and reporting of PPI in trials (67).

Trial status

Protocol version number and date: 2.0, dated 27th June 2024

Date recruitment began: 11 March 2024

Anticipated date for end of recruitment: 31 Oct 2025

At the time of writing, the trial had passed the internal feasibility phase and proceeded to proof-of-concept after re-strategising with extended timelines for trial delivery and a revisiting of statistical analyses for assessing precision for the primary endpoint.

Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ARC	Assessment of Recovery Capital
AWARD	Attitudes to Withdrawal and Abstinence thRough Detoxification
BDI	Beck depression inventory
CDS	Clinical Data Systems
CONSORT	Consolidated Standards of Reporting Trials guidelines
COWS	Clinical Opiate Withdrawal Scale
CSQ-8	Client Satisfaction Questionnaire
CTIMP	Clinical Trial of an Investigational Medicinal Product
DEQ	Drug Effects Questionnaire
DMC	Data Monitoring Committee
DSM	Diagnostic and Statistical Manual of Mental Disorders
eCRF	Electronic Case Report Form
ePRO	Electronic patient reported outcome
FORWARDS	Facilitating Opiate Recovery: Withdrawal and Abstinence thRough Detoxification Support
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GDPR	Good Data Protection Regulation
GMP	Good Manufacturing Practice
GRIPP	Guidance for Involving Patients and the Public
HRA	Health Research Authority
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health and Care Research
NHS	National Health Service
OST	Opioid substitution therapy
ODU	Opioid Use Disorder

PPI	Patient and Public Involvement
PROM	Patient Reported Outcome Measure
PRO-S/PRO-I	Patient reported outcome for the Opioid Use Disorder severity scale
PSQI	Pittsburgh Sleep Quality Index
REC	Research Ethics Committee
RLS	Restless Legs Syndrome
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SMARTS	Systematic Monitoring of Adverse events Related to TreatmentS
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STAI	Spielberger Trait Anxiety Index
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUSS	Substance Use Sleep Scale
TMG	Trial Management Group
TOPS	Treatment Outcomes Profile Scale
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

Discussion

This pragmatic trial will represent the first UK opioid detoxification trial of an ‘investigational medicinal product’ (CTIMP) in community settings in decades. Many individuals who present to addiction services in the UK for help with their heroin dependence seek to be drug-free. Whilst treatment OST is readily offered alongside psychosocial approaches to improve outcomes (8), few who seek abstinence are able to achieve this through a supported detoxification pathway. Indeed, the number in England who leave treatment ‘drug-free’ is declining (19).

There are several reasons that have contributed to this decline, including the focus on maintenance treatment to reduce transmission of infection (e.g. HIV, hepatitis) and

overdose deaths. In 2018 the loss of lofexidine, the only licensed non-opioid adjunctive medication to attenuate opioid withdrawal symptoms, resulted in community based opioid detoxification programmes being adversely impacted and fewer individuals completing them successfully. During the COVID-19 pandemic, addiction services were advised not to offer opioid detoxification. These latter two events happened after the current trial was initially designed. The trial is therefore expected to stimulate establishment or re-establishment of opioid detoxification pathways in services. This is likely to benefit staff who may be inexperienced supporting opioid detoxification due to the extra support from the trial. In addition, it will give individuals who would like to be drug-free a supported detoxification pathway.

The trial has been designed pragmatically, with built-in flexibility wherever possible, to cater to the differing needs and treatment goals of participants, and also to facilitate implementation in diverse treatment settings with differing needs and resources. The addition of the AWARD sub-study will provide crucial information about such a provision.

It is anticipated that one outcome of this CTIMP is that opioid detoxification will be discussed more often as a treatment option than currently happens. Further, if the proof-of-concept phase demonstrates that baclofen provides clinically meaningful benefits over placebo, this could offer a new pharmacological tool to support opioid detoxification, marking a significant step forward for OUD treatment.

Another key outcome of this trial is expected to be the training of a range of staff working in addiction services in the NHS and in non-NHS settings (third/voluntary sector) to successfully deliver a CTIMP. For the majority of staff and services, this will be the first CTIMP they have been involved with. In England, CTIMP regulatory and governance procedures are largely written for NHS services and will require adaptation where an addiction service site is led by the 3rd sector. Further research delivery networks may not have worked with 3rd sector, addiction or community settings. All of these factors are key elements of our feasibility study and an important aspect to inform further such studies. Therefore the trial will establish new infrastructure for OUD research in UK addiction services, supporting future studies on detoxification pathways, withdrawal management,

and relapse prevention.

Supporting Information

Trial registration (ISRCTN): ISRCTN98180939, registered: 31/01/2024

Protocol version: 2.0, 27 June 2024

Declarations

This study has been approved by the West of Scotland REC 1 committee (REC reference: 23/WS/0064), and has Clinical Trials Authorisation from the UK Competent Authority; MHRA/IRAS Reference: 1007293. Any important protocol modifications will be disseminated to the relevant parties by the research team and/or by regulatory bodies. Written, informed consent to participate will be obtained from all participants.

All authors of the manuscript have read, contributed to, and agreed its content and consent to its publication.

Availability of data and materials

The FORWARDS trial website is available at <https://www.imperial.ac.uk/brain-sciences/research/psychiatry/forwards/>

Publications will be made available in the public domain i.e. open access. The study team will retain the exclusive use of data until publication of major outputs has been completed. After this, data access including the full protocol, statistical analysis plan, statistical codes and participant-level data will be made available upon reasonable request to the CI, in accordance with the Data Protection Act. The statistical analysis plan (SAP) is available (see Additional File 2).

Competing interests

ALH has funding from Indivior for a research study, is a member of Steering group for a trial led by Astra Zeneca, and advisor (unpaid) for Eli Lilly, Libero, Camurus, Opiant. She is Chair

of Addiction Healthcare Goals, Office for Life Sciences, UK Government.

LP has provided consultancy services to Indivior.

All other authors declare that they have no competing interests.

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The sponsor is the Research Governance and Integrity Team, Imperial College of Science Technology and Medicine, Exhibition Rd, South Kensington, London SW7 2BX.

The funders and sponsor had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Authors' contributions

ALH and LP developed the idea and wrote the protocol with GL. SC and LH provided statistical design and input and CS advised on clinical trial design and operational management. ALH is the CI, LP and SC are co-investigators. GL is Clinical Trial Manager, and was involved in protocol development and led the regulatory submissions. AB developed the qualitative aspects of the trial and led the design and protocol development of the AWARD sub-project with LP and ALH, and assisted with regulatory amendments. LP wrote the manuscript. All authors contributed to, reviewed then approved the final manuscript.

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Weaver (Associate Professor of Mental Health Research), Dr Louise Choo (Independent statistician), Dr Kirstie Soar (Clinical Trial Manager), Mr Richard Coyle (lay member) and Mr Jim Pope (lay member). We also thank our Data Monitoring Committee (Prof Alex Baldacchino (chair), Prof Eilish Gilvarry (Professor of Addiction Psychiatry) and Prof Hakim-Moulay Dehbi (Independent statistician).

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At time of writing, the following 15 NHS and non-NHS (third sector) community drug and alcohol services had approved the FORWARDS-2 trial and agreed to act as trial sites:

- Central and North West London NHS Foundation Trust (CNWL); 3 sites at Brent, Hillingdon and Hounslow, with an additional shared site at Ealing which is shared with non-NHS partner Change Grow Live (CGL)
- Change Grow Live (CGL); 6 sites at Ealing, Bradnor Point, Carnarvon Street, Tameside (Ashton), Accrington, Waltham Forest.
- Via (non-NHS partners at CNWL Brent and Hillingdon sites).
- Barnet, Enfield and Haringey (BEH) Mental Health NHS Trust; 2 sites at The Claverings and Vincent House
- Essex Partnerships NHS Foundation Trust; 2 sites at Chelmsford STARS and Colchester STARS
- Greater Manchester Mental Health NHS Foundation Trust; 2 sites at Salford and Bolton

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