Pilot and Feasibility Studies

STUDY PROTOCOL

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Mobile telephone contingency management to encourage adherence to supervised medication among individuals most at risk of non-adherence to opioid agonist treatment: a study protocol for a feasibility study (TIES2)

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Abstract

Background Supervision of opioid agonist treatment (OAT) ensures that individuals take their correct daily dose to minimise withdrawal and craving, safeguard against diversion and overdose, and receive optimal benefit from OAT. There is an urgent need to develop effective interventions to increase medication adherence and technological solutions to streamline communication between pharmacies and prescribers. The authors have developed technology to deliver contingency management (CM) remotely by mobile telephone (mCM) and alert prescribers of missed doses. In a previous feasibility study, the authors found mCM was feasible to deliver and acceptable to patients, prescribers, and pharmacists but encountered difficulty recruiting patients starting methadone treatment. Since COVID-19, supervision guidelines have changed to focus on patients at risk of/not adhering to their medication. This study aims to assess the feasibility of conducting a future confirmatory trial to assess the clinical and cost-effectiveness of mCM to encourage adherence with supervised methadone or buprenorphine. It will use broader eligibility criteria, including patients receiving buprenorphine, and target a revised group of serial re-starters.

Methods Using a cluster randomised design, three drug services will be randomised 1:1:1 and 20 patients, attending seven pharmacies linked to each service, will be recruited (i.e. a total of $N=60$). Each drug service providing supervised medication will be randomly allocated to deliver: (i) telephone-delivered text-message reinforcement with modest financial incentives; (ii) telephone-delivered text-message reminders; or (iii) no telephone text-messages. Prescribers will receive reports of patient attendance. Feasibility will be determined based on four progression criteria: the number of patients enrolled, the percentage of screened patients who are eligible, adherence to the telephone system, based on matches between sign-in at the pharmacy and pharmacy dispensing records and follow-up rates. We will also undertake qualitative assessments of clinicians' perspectives on the revised eligibility criteria undertaken.

Discussion This study will assess the feasibility of using mCM to target a clinically important group of patients non-adhering to their supervised medication. In the future, and if effective, mCM will encourage medication adherence among patients, enabling them to achieve an optimum dose and full benefit from OAT.

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Trial registration ISRCTN33965312 (26/06/2023). This manuscript was submitted on February 27th, 2024. While recruitment was due to end on February 29th, we recruited our last patient on February 12th. The last patient/last visit took place on May 2nd, 2024.

Keywords Opiate substitution treatment, Methadone, Buprenorphine, Supervised consumption, Pharmacies, Contingency management, Medication adherence, Financial incentives, Behavioural reinforcement, Heroin use

Background

Heroin addiction is a major public health issue. In 2020/2021, there were an estimated 314,000 opioid users in England and Wales [1]. In 2021, there were approximately 141,000 people in opiate agonist treatment (OAT) for heroin (or opiate) use disorder in England [1]. Most people are prescribed methadone or buprenorphine, which prevent opioid withdrawal and reduce opioid cravings [2] for which there is an extensive evidence base [3, 4]. The National Institute for Health and Care Excellence (NICE) recommends substitute prescribing as the most effective treatment, alongside psychological therapies [5]. However, recovery from heroin use disorder can take a long time, and many people receiving OAT relapse into heroin use leading to high attrition rates in OAT [1].

Following concerns that rates of methadone-related fatal overdose were higher in England than in other countries with supervision of OAT [6, 7], in 1999, the Department of Health recommended that consumption of OAT be supervised by a pharmacist until a patient is stable before permitting takeaway dosing [8, 9]. Methadone-related overdose deaths rapidly reduced after the introduction of supervision [10–12] and have remained low [13]. Unsupervised consumption is considered unsafe if there is evidence of continued medication non-adherence and illicit drug use [8]. Supervision ensures that individuals take their prescribed dose every day to minimise the experience of withdrawal or craving, safeguard against diversion and overdose, receive optimum dose, and achieve full benefit from OAT [8].

The COVID-19 pandemic forced changes to the supervision of methadone and buprenorphine within community pharmacies. In April 2020, interim guidance permitted patients to take home a 2-week supply of OAT medication and consume it without supervision to protect patients and pharmacy staff and safeguard against potential closure due to illness [13]. Following concerns over increased methadone-related deaths between April and September 2020 [14, 15], supervision was reinstated in 2021 and has become targeted at groups most at-risk of non-adherence [16]. This includes patients who regularly miss three or more supervised doses and must re-present at the clinic to restart their prescription ('re-starters'). These patients are usually hardest to contact and potentially have the highest risk of overdose.

It is important for OAT patients to take their medication every day; each missed dose is a cause for concern. When patients miss three doses, the pharmacist should cease dispensing their medication and speak to the patient's prescriber. The patient may have to return to the drug treatment service to have their dose re-titrated and receive a new prescription [8]. This costs pharmacies and drug services time and resources. There is a lack of consistent reporting by pharmacists of missed doses [17]. This is a concern, particularly due to the increased use of pharmacy locums. There is an urgent need to develop effective interventions to increase medication adherence and to develop technological solutions to streamline working practices and communication between community pharmacies and prescribers.

Contingency management (CM), based on the principles of operant conditioning [18], involves the systematic application of positive reinforcement (e.g. through financial incentives) to promote behaviour change consistent with treatment goals and amplify patient benefit. CM has an established evidence base, demonstrating its efficacy in promoting positive behaviour changes across various substance use related health behaviours, such as abstinence from opiates, cocaine, cannabis, tobacco, and alcohol [18–24], improves treatment attendance [21, 25–28] and increases medication adherence [29], including physical health interventions [30–32]. In opiate treatment, CM notably enhances appointment attendance [28] and encourages abstinence [20]. Research in UK drug treatment services indicates CM significantly boosts adherence to hepatitis B vaccinations [32], treatment attendance, and opiate abstinence [33], with potential cost-effectiveness [34, 35]. CM is recommended by the National Institute for Health and Care Excellence (NICE) for use in UK drug treatment services to improve treatment engagement and reduce illicit drug use [36].

However, despite the evidence for CM interventions in the treatment of substance use, there are barriers to implementation. CM requires frequent monitoring of behaviour change and differential delivery of reinforcement, making implementation resource-intensive and burdensome for patients and clinical staff. Remote delivery has enabled greater accessibility of CM interventions, allowing them to be delivered without the need for recurrent attendance at clinical services [37]. Technology

enables CM to target substance use and other health behaviours in individuals who might not normally access treatment services. It also enables services to maintain contact with patients longer to support recovery and provides an early warning of relapse [37]. Recent studies have shown the effectiveness of remotely delivered CM via mobile telephones (mCM) [38–41]. Remote behavioural monitoring through mCM has seen satisfactory engagement and compliance, with many patients finding the technology user-friendly [37, 42, 43]. Mobile telephone-delivered CM (mCM), specifically, is effective in reducing substance use [37], acceptable [37] and well received among patients in treatment for substance use disorder in UK treatment services [44]. With 96% of individuals receiving drug and alcohol treatment reporting mobile phone ownership in a recent survey conducted by the authors [45], this may also be a feasible approach.

The authors have developed a CM intervention which can be delivered by mobile telephone (mCM) to encourage adherence to supervised consumption of opiate agonist medication (e.g. methadone) [46]. The application monitors patients' attendance at supervised dosing through a self-service internet login at the pharmacy. Prescribers receive weekly reports of attendance and early warnings of missed doses.

In 2017, the authors undertook a trial to assess the feasibility of a future confirmatory trial into the clinical and cost-effectiveness of mCM to encourage medication adherence among individuals with opioid use disorder [17, 47]. The trial focused on patients starting a new episode of OAT and receiving supervised methadone, following clinical guidance that new patients should have their methadone consumption supervised in the first 3 months of treatment [8]. The study used a cluster randomised controlled design where drug services and their allied community pharmacies formed the clusters. Three drug services were randomised to one of three arms: text message praise and financial incentives (mCM), text message reminders (mR), or no text messages (treatment as usual (TAU)) [47]. The mCM was found to be feasible and well-received by patients, staff, and pharmacists. Participants appreciated the supportive praise messages, while prescribers valued the email alerts for efficient patient monitoring and time-saving. Pharmacists reported ease of use with the tablet system [44]. Follow-up rates, data completion, and consistency between self-reported attendance and pharmacy records were excellent [48, 49].

However, not all feasibility criteria were met. It was feasible to recruit drug services and pharmacies, but recruitment of patients to the study was not feasible using the applied eligibility criteria. Ten out of the target of 60 participants, representing just 9% of screened patients, were found to be eligible. Most exclusions were due to patients being existing clinic patients receiving a dose re-assessment after missed doses, rather than a new presentation, not receiving methadone (these patients were receiving buprenorphine), and not attending a participating community pharmacy. Due to low recruitment, we could not assess whether the 'text message reminders' arm (mR) could be delivered successfully or assess the accuracy of pharmacy self-login in this group.

For the current study, we have refocused our research question and design to reflect practice changes in supervision following the COVID-19 pandemic and answer new feasibility questions. These changes are detailed below.

Methods

Aim

This study aims to assess the feasibility of conducting a future confirmatory randomised controlled trial to assess the clinical and cost-effectiveness of mCM to encourage adherence with supervised methadone/buprenorphine in community pharmacies among individuals receiving opioid agonist treatment, most at risk of non-adherence. This includes:

(1) Whether revised recruitment procedures (including revised eligibility criteria and an increased number of pharmacies) will allow us to recruit to target.
(2) Whether we can recruit the revised target patient group and whether this group participates in the study.
(3) Important feasibility information on the number of patients receiving and remaining on supervision and the number of patients restarting their prescription.
(4) The acceptability of the intervention for patients in the reminders arm (mR).
(5) The feasibility of an adapted mCM intervention.

The feasibility study has the following objectives:

a) To assess the number of eligible patients, rates of recruitment and recruitment procedures.
b) To assess the acceptability of the study to patients not receiving incentives (mR and TAU arms).
c) To test the accuracy of recording attendance at the pharmacy via self-login among participants not receiving incentives (mR and TAU).
d) To assess the utility and practicality of different options for quantifying the primary outcome measure (medication adherence).
e) To characterise aspects of the primary outcome needed for a sample size calculation for a larger trial (including an estimate of the intra-class correlation).

f) To assess participant and clinician perspectives on the operation of our modified eligibility criteria.

Design and setting

This feasibility study will use a three-arm cluster randomised controlled design (Fig. 1) (Protocol V1.1 24.11.2023) where drug services and their allied community pharmacists form the clusters. Within each cluster, participants will receive the same allocated condition, minimising the risk of contamination between arms. Drug services (each with up to seven allied community pharmacies) will be randomly allocated (1:1:1) to deliver either:

A. Supervised medication + telephone-delivered text messages providing positive reinforcement and modest financial incentives (mCM)
B. Supervised medication + telephone-delivered text messages providing reminders (mR)
C. Supervised medication with no telephone text messages (TAU)

We will recruit three drug services, one or two from South London and the Maudsley NHS Foundation Trust (SLaM) and one or two from a large non-NHS service provider (Turning Point).

Pharmacies allied to each drug service will be chosen for recruitment based on the number of patients attending the pharmacy to receive their methadone/buprenorphine. To minimise the number of patients excluded for not attending a participating pharmacy, at each drug service we will rank local pharmacies based on the number of patients that they dispense methadone/buprenorphine to. We will seek to recruit the top 7 pharmacies, compared to three in our previous study [44, 47, 48]. None of the 7 pharmacies affiliated with a drug service will be included in the lists of top local community pharmacies affiliated with the other participating drug services. If any refuse, we will approach pharmacies lower down the list until 7 have been recruited for each drug service.

We will survey community pharmacists approached to take part to investigate their willingness to participate, their views on the acceptability and feasibility of the mobile telephone intervention, and the feasibility of recruiting pharmacies for a future confirmatory trial.

We aim to recruit 20 participants in each cluster over 6 months, giving a total of 60 participants.

Eligibility of drug services and allied pharmacies

Drug services will be eligible if they are providing OAT (methadone or buprenorphine).

The criteria for enrolling community pharmacies will include:

- Pharmacists are willing and able to provide 6 days supervised consumption of oral methadone or buprenorphine.
- Pharmacy has a consultation room on the premises or a designated area on the dispensing counter in which participants can consume their oral methadone or buprenorphine under supervision.
- Pharmacy provides supervised consumption of oral methadone or buprenorphine to the patients at the drug clinic.
- Pharmacy is willing and able to provide dispensing records for participants over the 12-week intervention period.

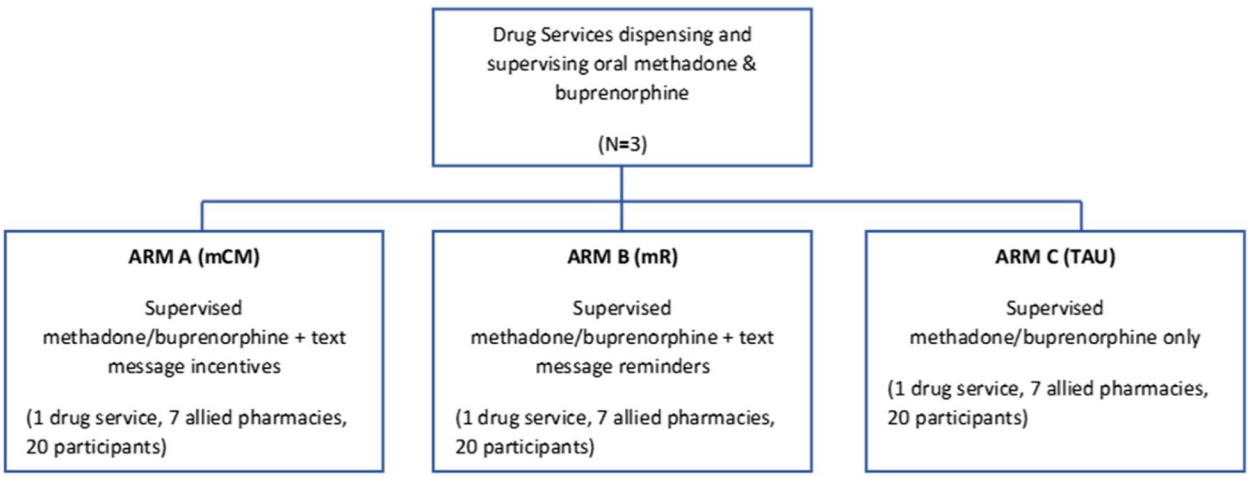

Fig. 1 Trial design

Eligibility of participants

We aim to enrol the clinically significant group of existing patients receiving supervised opioid agonist treatment who are most at risk of non-adherence. This includes patients who regularly miss doses and must re-present at the clinic for a dose assessment.

Inclusion criteria for individual participants include:

- Aged ≥ 18 years at the time of enrolment.
- Receiving OAT.
- Missed three doses of OAT and re-presenting at the clinic for dose assessment/re-start.
- Receiving supervised methadone or buprenorphine prescription for 6 days a week.
- Attending a participating pharmacy.
- Owns a mobile telephone.

Exclusion criteria for individual participants include:

Unable to read English or would require the service of an interpreter to understand a brief oral description of the study.

Recruitment

We will enrol 20 participants at each cluster (drug service) over a 6-month recruitment period between 23rd August 2023 and 29th February 2024, giving a total of 60 participants. We will aim to screen all patients undergoing a medication restart assessment during the recruitment period, ensuring all patients in the target patient group have the opportunity to participate. Eligible patients will be provided with information about the study and asked to provide written informed consent. Screening and consent will be undertaken by drug service clinical staff.

Processes/interventions and comparisons

OAT will be delivered in line with existing service protocols at sites. All participants will receive supervised methadone or buprenorphine 6 days a week at a participating community pharmacy.

The applicants have developed a mCM intervention to encourage adherence to supervised consumption of methadone and buprenorphine [44, 46, 47]. It provides positive reinforcement through automated text messages of praise and modest financial incentives (CM) to encourage individuals receiving OAT to regularly take their medication under supervision at their pharmacy. In addition, a linked system for monitoring and reporting medication non-compliance to the patients' prescriber has been developed.

The telephone system uses an intelligent text-message-alert engine and is aware of and tracks all individuals and their supervised dosing (methadone/buprenorphine) appointments at their pharmacy through the computer tablet internet login at the pharmacy. The system contacts individuals through text messages sent to their mobile telephone. The system keeps track of each time a patient attends a dosing appointment at the pharmacy, each time they do not attend the appointment and their monetary balance. The system either reminds patients of their appointments or rewards them when they attend. The system stores patients' mobile phone number, which is needed for the SMS messages to be sent and a memorable nickname. It also stores patients' attendance (and taking medication) at the pharmacy. For further information see Metrebian et al. [47]. Participants are enrolled onto the system (with nickname and mobile telephone number) when they are enrolled into the trial. The system is hosted on and accessible through a secure web-site.

Participants receive financial incentives through pre-paid debit cards. Money earned is uploaded onto the cards.

Participants will record their attendance at their pharmacy via a tablet computer to indicate they have taken their supervised medication. The tablet computer will be kept in the dispensing/consultation room or on or behind the dispensing counter in the pharmacy, where the participant consumes their medication, to ensure participants record their attendance only after consuming their medication. Participants will receive the telephone system for 12 weeks. This time period is informed by previous mCM research and clinical stakeholders who identified 12 weeks as an appropriate time for establishing adherence to medication in this patient group [32].

Clusters will be randomly allocated (1:1:1) to one of three treatment allocations:

A Supervised medication + telephone-delivered text messages providing positive reinforcement and modest financial incentives (mCM).

Each time a participant attends their pharmacy and consumes their supervised medication, they will be sent a text message confirming they have achieved the target behaviour and earned a small financial reward of £1. If they attend for 6 days consecutively, they will earn a bonus reward of £5. The total possible financial reward is £11/week. Earnings will be delivered remotely to participants through pre-paid debit cards. If they do not attend, participants will be sent a message confirming they did not achieve the target behaviour but that they can attend the pharmacy the following day.

The intervention is informed by a logic model (see supplementary materials) that provides a contextualised 'theory of change' showing how mCM operates adjunctively to supervised prescribing. It describes the intended relationships between the inputs, resources, activities and outputs and sets out our assumptions about how these interact to generate the intended outcomes.

B Supervised medication + telephone-delivered text messages providing reminders (mR).
Participants will be sent text message reminders at 9 am to attend the pharmacy and take their supervised medication. If they do not attend, another reminder will be sent at 1 pm.

C Supervised medication with no telephone text messages (TAU).
Participants will not be sent any text messages and will continue to receive treatment as usual.

In mCM and mR, weekly reports of adherence and alerts of missed doses will be sent to prescribers. All communications via the phone system will be encrypted using the Secure Sockets Layer (SSL) protocol.

The pharmacy cannot dispense the next day's dose if a patient has failed to pick up for three consecutive days. Therefore, the telephone system will be paused if a participant fails to attend their pharmacy and take their dose for three consecutive days. The telephone system will be re-instated when the pharmacy can dispense methadone or buprenorphine again to the participant (after their dose is reassessed by their prescriber).

Participants resume their usual treatment after the 12-week treatment period.

Qualitative interviews

Our previous feasibility study included a qualitative process evaluation which examined the participants' experiences of the intervention and its acceptability to all key stakeholders [48, 50]. Given the unchanged intervention and our previous finding that the 'activities' described in the logic model were feasible, acceptable, and functioned as intended (notably the automated feedback to prescribers regarding compliance with all supervision appointments), we do not propose replicating work that has already generated positive findings. However, as outlined previously, we have revised our eligibility criteria to acknowledge changes in policy and practice due to the COVID-19 pandemic. We will conduct semi-structured interviews with nine drug service staff (3 at each service) involved in the recruitment of study participants at each site to ascertain their perspectives on the revised eligibility criteria. Interviews will be recorded and transcribed and subject to a thematic analysis.

Outcome measures

The primary feasibility outcome is the number of eligible patients enrolled per week over the 12-week recruitment period.

Secondary feasibility outcomes include:

1. Number and percentage of screened patients eligible for inclusion and reasons for ineligibility.
2. Number and percentage of eligible patients who consent to participate and reasons for refused consent.
3. Adherence to the phone system based on matches between self-login at the pharmacy and pharmacy dispensing records (*N* days where these match/*N* days total).
4. Number/percentage attending follow-up interview, of those enrolled.
5. Number/percentage of weeks spent on supervised consumption during the 12-week intervention.
6. Number/percentage on supervised consumption at the end of the intervention period, of those enrolled.
7. Number of restarts during the intervention period (where a participant misses three or more appointments and needs to re-present at the clinic).
8. Number of days from last dose (i.e. last attendance at supervised consumption appointment) until prescription restart.
9. Qualitative assessment of clinician perspectives on the revised eligibility criteria.

Primary outcomes for exploration for a future confirmatory trial:

The primary clinical outcome for a future confirmatory trial is medication adherence. Three options for measuring this outcome will be evaluated:

1. Number/percentage of days (when on supervised consumption) patient presents at the pharmacy and takes supervised medication.
2. Number of days (when on supervised consumption) that medication not taken.
3. Likert-like scale categorising patients according to different missed dose patterns aspects of the primary outcome measure needed for a sample size calculation for a future confirmatory trial.

We will also collect information needed to inform sample size calculations of the future confirmatory trial:

4. Appropriate summary statistics of the primary clinical outcomes (1, 2, 3).
5. An estimate of the intra-class correlation (ICC) for the clusters (drug services). As Eldridge et al. [51] note, pilot studies for cluster randomised trials are

generally too small to provide precise estimates of key parameters such as the ICC. ICC estimates from a feasibility study will always be uncertain, but they can still offer useful preliminary insights into clustering effects and help inform future trial design.

Secondary outcomes of the future confirmatory trial include:

6. Number/percentage retained in treatment over the 12-week intervention period.
7. Opiate Treatment Index (Sect. 2—Drug Use) [50, 52].
8. Alcohol Use Disorders Identification Test (AUDIT) [53].
9. Hospital Anxiety and Depression Scale (HADS) [54].
10. Social functioning, measured using the Opiate Treatment Index [55].

Participant timeline and study visits

Participants will have a research assessment interview conducted by a research team member at baseline (0 weeks post-enrolment) and follow-up (12 weeks; last patient followed up on or before 23rd May 2024; see Fig. 2 CONSORT and Fig. 3 SPIRIT; and SPIRIT Checklist in supplementary material).

Attendance and medication adherence will be recorded via patient self-login using tablet computers at the pharmacy. The software system will record attendance and (for the mCM arm only) their monetary balance.

The implementation of our revised eligibility criteria will be assessed qualitatively through semi-structured interviews with a sample of clinicians (three per site) involved in screening/recruitment.

Sample size

One of the aims of this feasibility trial is to estimate parameters needed for a sample size calculation for a larger confirmatory trial. Therefore, at this stage, no formal sample size/power calculation was undertaken. However, we can describe how the chosen sample size (60 participants, 20 per arm) will influence the precision of estimated feasibility outcomes. For the primary feasibility outcome ('Number of eligible patients enrolled per week'), we will be able to estimate the expected enrolment rate of 10 patients/month (a total of 60 during the 6-month enrolment period) to within a 95% exact confidence interval of ± 2.7 (95% confidence interval of 7.6 to 12.9 patients enrolled per month). For the second feasibility outcome ('Percentage of screened patients eligible for inclusion and reasons for ineligibility'), we can estimate the expected percentage of 40% to within a 95% confidence interval of 34 to 46%. This is based on screening 300 patients, of whom we expect 40% to be eligible, and half are expected to consent to participate.

Randomisation

The three sites will be randomly allocated using simple randomisation in a 1:1:1 allocation ratio to one of the following three arms (Fig. 1):

A. Supervised medication + telephone-delivered text messages providing positive reinforcement and modest financial incentives (mCM).
B. Supervised medication + telephone-delivered text messages providing reminders (mR).
C. Supervised medication with no telephone text messages (Treatment as Usual) (TAU).

The trial statistician (EC) will conduct the randomisation using a script written in R. After generating the random sequence, cluster allocations will be securely shared with the study team via email before the start of recruitment.

Blinding

Due to the nature of the intervention being studied, and the aims of this feasibility trial, neither clinicians nor participants will be blinded to treatment allocation. The researchers cannot be blinded due to the need to monitor the telephone system. Therefore, the participants, key workers, pharmacists, chief investigator, co-investigators, researcher, and trial statistician will be unblinded to treatment allocation.

Data collection and management

There will be five forms of data collection.

First, researchers will administer questionnaires during face-to-face interviews with participants at baseline (at enrolment) and follow-up (12 weeks post-enrolment). Interviews will be sought from all participants, including those who discontinue treatment or stop receiving the telephone text message intervention. Participants will receive a £10 reimbursement for attending the baseline and follow-up interviews.

Second, the software system will collect information on whether participants attended the pharmacy and consumed their medication or not at each supervised methadone or buprenorphine appointment over the 12-week period. Information is captured via participants self-login to tablet computers in the pharmacies. The software will capture a patient nickname and telephone number, and the date and time of any login. These data will be stored on a secure server hosted by the company

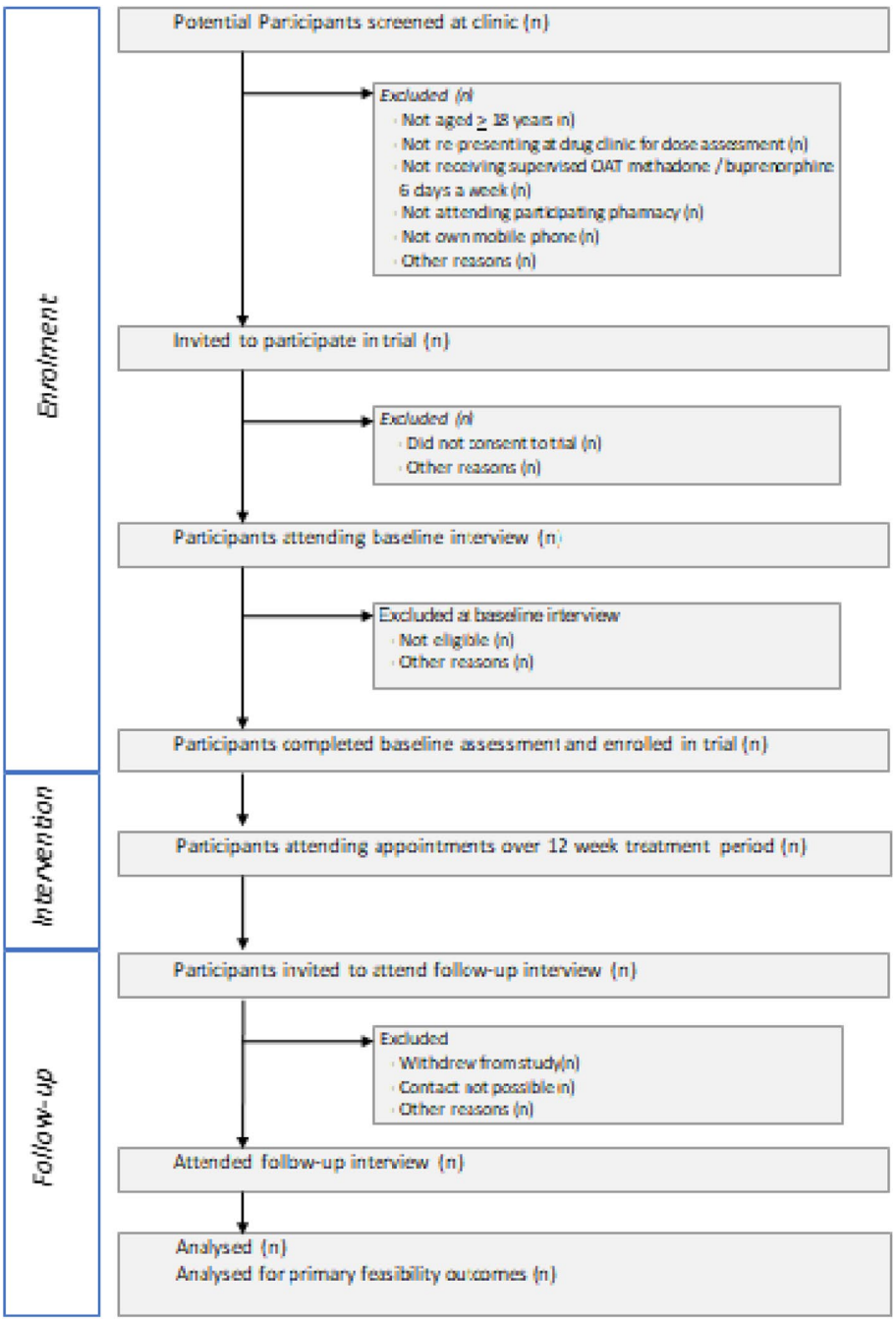

Fig. 2 CONSORT diagram

Mindwaves Ventures Limited who developed the system with South London and Maudsley NHS Foundation Trust (SLaM). All text message communication will be over Secure Sockets Layer (SSL). Tablets used in pharmacies for patient self-reporting will all use Mobile Iron for security. At the end of the 12-week intervention period, these data will be extracted from the software system by a researcher and entered into an SPSS database. All trial databases will be password-protected and stored on a secure KCL network drive.

Third, PharmOutcome data relating to trial participants will be pseudonymised (using nickname only) by the pharmacist and provided to researchers at the end of the study. PharmOutcomes is a secure clinical service

	Enrolment	Post Enrolment			
TIMEPOINT**	***-t_1***	***1-12 weeks***		***12 weeks***	
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
INTERVENTIONS:					
mCM		x			
mR		X			
TAU		x			
ASSESSMENTS:					
Sociodemographic	x				
OTI Drug use	x			x	
OTI Social functioning	x			X	
AUDIT	x			x	
HAD	x			x	
Attendance at pharmacy & supervised OAT consumption		x			

Fig. 3 SPIRIT

platform for community pharmacies and commissioners to capture data on dispensing and supervision of medication.

Fourth, interviews with staff will be recorded using digital handheld audio recorders (with encryption facilities) and stored on a password-protected secure KCL network drive.

Fifth, we will conduct a survey of the community pharmacists we approach to take part in the study, to investigate their willingness to participate in the study and assess the feasibility of recruiting pharmacies for a future confirmatory trial (and potential roll-out). The survey will assess pharmacists' views on the acceptability and feasibility of delivering the mobile telephone intervention. The researcher will survey the top 7 pharmacies (dispensing methadone/buprenorphine to the most patients) identified by each drug service. The researcher will administer the questionnaire to the senior pharmacist at each pharmacy either in person or over the telephone.

Data from the baseline (0 weeks post-enrolment) and follow-up (12 weeks) interviews will be collected on paper case report forms (CRFs), which will be stored at

King's College London (KCL). These data will be entered into Statistical Package for Social Sciences (SPSS) databases by researchers at KCL. Data from the telephone system will also be exported into an SPSS database. The SPSS databases will be developed by KCL researchers and statisticians. Data entry will be undertaken by KCL researchers. Range checks will be used. Data entry will be checked against paper case report forms in 10% of participants to ensure the accuracy of data entry. SPSS databases will be stored on a KCL secure drive. Version control will be used to provide an audit trail of database changes. Only members of the KCL research team will have access. Data extracts will be provided to the trial statistician upon request. Copies of the pharmacy dispensing records will be stored at KCL.

Data monitoring

A Trial Steering Committee (TSC) will be convened to provide independent expert advice on the ongoing conduct of the study. The TSC will meet every 6–8 months during the study. To monitor safety during the trial, an independent Executive Committee will be formed comprised of a statistician and clinician. The Executive Committee will review the numbers of adverse events and serious adverse events by arm, before each TSC, and make recommendations to the TSC chair.

Data analysis

A statistical analysis plan (SAP) will be developed and agreed upon by the TSC. All quantitative data will be analysed using SPSS or R.

Feasibility outcomes will be summarised with appropriate summary statistics (e.g. mean and standard deviation/median and interquartile range for normally distributed/non-normally distributed continuous outcomes; frequency and percentage for categorical outcomes). Differences between arms, where appropriate, will be assessed by examining differences in the relevant summary statistic. Estimates will be provided with 95% confidence intervals.

Clinical outcomes for the future confirmatory trial will also be summarised using appropriate statistics (as above). Differences between arms will be summarised (e.g. differences in means or percentages) but not used as the basis for inferential statements. The primary purpose of these estimates is to inform sample size calculations for a future confirmatory trial. This analysis is not powered to detect differences between arms. Estimates of treatment efficacy will be treated as exploratory and not used as the basis for inferential statements. Analyses will be done under the intention-to-treat principle; there will be no per-protocol or subgroup analyses.

All efforts will be made to avoid missing baseline data (i.e. requiring completion of baseline data before randomisation), but if this occurs, missing values will be imputed according to current recommendations. Missing scale item data will be handled using recommendations for each questionnaire or pro-rating if no guidance is available (if less than 20% of items are missing, the missing items will be replaced by the mean of the complete items). Given this is a feasibility study and the focus is not on between-arm comparisons, multiple imputation for missing data will not be used.

Interviews will be transcribed verbatim and subject to a thematic analysis. After familiarisation with the data (reading transcripts), an initial coding frame will be developed based on the a priori topic guide and themes developed in the data. This coding frame will be developed and refined as data collection and analysis progress. The framework will be applied to the data (indexing) with the aim of allocating all data to a theme (either already defined or emergent at this point). The analytical stage will seek to discern patterns, consistencies, and divergences in the data and to support the identification of themes that enable a comprehensive and detailed response to the research questions.

Adverse event monitoring

We will monitor all adverse events (AE), serious adverse events (SAE), serious adverse reactions to trial interventions (SAR), serious deterioration, and active withdrawals from treatment. We will contact pharmacists and keyworkers once a week to monitor possible adverse events and reactions. These will be recorded in a specific SPSS database, stored on a secure KCL drive, and reported at each TSC meeting.

Progression criteria

Criteria for proceeding from the feasibility study to a larger confirmatory trial include:

	Green	Amber	Red
1. Number of eligible patients enrolled over the 6 months recruitment period	≥ 40, at least 10/per arm	≥ 25, at least 7/arm	< 25
2. Percentage of screened patients who are eligible for inclusion in the feasibility trial	≥ 30%	≥ 20%	< 20%

	Green	Amber	Red
3. Adherence to phone system based on percentage of matches between sign-in at pharmacy and pharmacy dispensing records, by arm	≥ 70% in all arms	≥ 50% in all arms	< 50% in all arms
4. Number and percentage attending follow-up interview at end of 12-week intervention period (compared to number enrolled)	≥ 70%, at least 14/per arm	≥ 50%, at least 10/per arm	< 50% in all arms

While not achieving these criteria does not necessarily indicate the unfeasibility of a future trial, it does underline changes that may need to be made to the trial design and resources needed. As our primary feasibility outcome measure is the number of eligible patients enrolled per week over the 12-week recruitment period, we would expect to achieve at least amber for these criteria to consider the trial feasible.

Confidentiality

Participants will be recruited and consented by clinical staff at the drug and alcohol service they are receiving treatment from. Participants are known to the community pharmacies as they are already receiving their methadone/buprenorphine treatment from them. As part of the study, each patient creates a nickname that they will use to log in to the computer tablet. The software does not store personally identifying patient information, other the patients' mobile phone number, which is needed for the SMS messages to be sent. The telephone system will also store patients' attendance at the pharmacy when they log in.

Each patient will be given a unique ID, and only this will be recorded on research questionnaires. These forms will be stored at KCL and entered into an SPSS database. The telephone system will provide weekly reports of attendance to participants' prescribers at the drug clinic via NHS emails. Participants have provided their consent for this.

Access to data

The trial database will only be accessible to the principal investigator (NM), researcher (CAG), and trial statistician (EC).

Dissemination

We plan to share findings to our service user research group. We plan to disseminate to research participants through handouts and participating clinics through meetings and NHS trust newsletters. We will disseminate to pharmacists through proposed publications in *Pharmaceutical Journal* (which has a wide readership among community pharmacists). We plan to disseminate to academic, clinician and service user advocacy groups through addiction conference oral and poster presentations at both a national and international conferences.

Discussion

TIES2 will assess the feasibility of conducting a future trial of delivering a behavioural intervention by telephone to improve medication adherence. There is little work in this area. Findings from this study will be assessed against pre-specified progression criteria to inform a future confirmatory trial.

The mCM will target a clinically important group of patients non-adhering to their supervised medication (serial re-starters). If effective, mCM will encourage medication adherence, enabling patients to achieve an optimum dose and full benefit from OAT leading to increased potential to maximise treatment benefit. Further benefits include reducing the resources needed for re-presentations for dose assessments and benefits for clinicians and the wider NHS through automated reports of patients' attendance and early warning alerts of missed doses, enabling prescribers to make informed decisions. A reliable mechanism for pharmacists to report missed doses will free up prescribers' time spent checking attendance through telephone calls and pharmacist difficulties getting through to drug services by phone. Moreover, these reports will allow patients to provide evidence of medication adherence, helping them to demonstrate their readiness to move away from supervision.

Abbreviations

AE	Adverse events
AUDIT	Alcohol Use Disorders Identification Test
CM	Contingency management
COVID-19	Coronavirus disease pandemic 2019
CRFs	Case report forms
HADS	Hospital Anxiety and Depression Scale
ICC	Intra-class correlation
KCL	King's College London
mCM	Contingency management delivered remotely by mobile telephone
mR	Reminders delivered remotely by mobile text message
NICE	National Institute for Health and Care Excellence
OAT	Opioid agonist treatment
OTI	Opiate Treatment Index
SAP	Statistical analysis plan
SAE	Serious adverse events
SAR	Serious adverse reactions
SLaM	South London and Maudsley NHS Foundation Trust

SPSS	Statistical Package for Social Sciences
TAU	Treatment as usual
TSC	Trial Steering Committee

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-025-01614-8.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
NM originally conceived the study design. CAG, EC, TW, SP, MK, JSc, JS and NM substantially contributed to the study design and protocol development. NM drafted the manuscript and all authors contributed to and approved the final manuscript.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
UK NHS Research ethics approval was granted by West Midlands—Black Country Research Ethics Committee (23/WM/0098) on 23rd May 2023.

Consent for publication
Not applicable.

Competing interests
NM has received, through her university, King's College London, research funding from Mundipharma Research Ltd (pharmaceutical company that produces a naloxone nasal spray). CAG has no competing interests. EC has no competing interests. TW has no competing interests. MK has taken part in industry sponsored research for Camurus, Indivior and Mundipharma. JSc has received payment from the College of Mental Health pharmacy for delivering training on their short course programme and for delivering a keynote talk at their 2023 conference. JS and SP have contributed to UK guidelines on the potential role of contingency management in the management of opioid addiction (NICE, 2007; convened by SP, chaired by JS), SP receives funding from NICE for the production of clinical guidelines. JS has chaired the broader-scope pan-UK working group preparing the 2017 and 2007 Orange Guidelines for the UK Departments of Health and Social Care, providing guidance on management and treatment of drug dependence and misuse, including guidance on possible inclusion of contingency management. JS is a researcher and clinician who, through his university, has worked/is working with pharma and tech industries to identify new or improved interventions and his employer (King's College London) has received grants, travel costs and/or consultancy payments; this includes discussion and investigation of new naloxone formulations with, past 3 years, Mundipharma, Accord and dne pharma (all of whom have naloxone products). His employer (King's College London) also earlier registered intellectual property on a buccal naloxone formulation, naming JS and colleagues, and he was previously named in a patent registration by a pharmaceutical company regarding concentrated nasal naloxone spray. JS does not receive any personal payment from these arrangements. JS has also worked with various drug policy organisations and advisory bodies including the Society for the Study of Addiction (SSA) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). JS was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. For a fuller account, see JS's web-page at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx.

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