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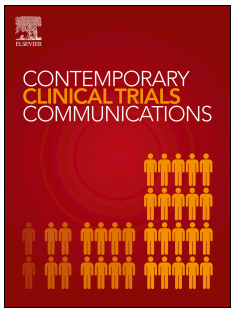

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Telephone delivered Incentives for Encouraging adherence to Supervised methadone consumption (TIES): study protocol for a feasibility study for an RCT of clinical and cost effectiveness

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Abstract

The majority of people receiving treatment for their heroin addiction, are prescribed methadone; for which there is an extensive evidence base. When treatment starts, people take their daily dose of methadone under supervision at a community pharmacy. Supervision guarantees methadone is taken as directed by the individual for whom it has been prescribed, helps to ensure individuals take their correct dose every day, and safeguards against diversion and overdose. However, individuals often fail to attend the pharmacy to take their methadone. Each missed dose is of concern. If a patient misses their daily dose of methadone, they will start to experience opiate withdrawal and cravings and are more likely to use heroin. If they miss three days dose, there are concerns that they may lose tolerance to the drug and may be at risk of overdose when the next dose is taken. Hence there is an urgent need to develop effective interventions for medication adherence. Research suggests that incentive-based medication adherence interventions may be very effective, but there are few controlled trials and the provision of incentives requires time and organisational systems which can be challenging in pharmacies. The investigators have developed the technology to deliver incentives by mobile telephone. This cluster randomised trial will test the feasibility of conducting a

future trial evaluating the clinical and cost effectiveness of using telephone delivered incentives (praise and modest financial rewards via text messaging) to encourage adherence with supervised consumption of methadone in community pharmacies. Three drug services (each with two or three community pharmacies supervising methadone consumption that will enrol 20 individuals, a total of 60 participants) will be recruited and randomly allocated to deliver either i) telephone delivered incentives, ii) telephone delivered reminders or iii) no telephone system. Acceptability, recruitment, follow-up, and suitable measures of clinical and cost effectiveness will be assessed. Findings from this feasibility study will be assessed against stated progression criteria and used to inform a future confirmatory trial of the clinical and cost effectiveness of telephone delivered incentives to encourage medication adherence.

Trial registration: ISRCTN58958179 (retrospectively registered).

Keywords

[opiate substitution treatment, methadone, supervised consumption, pharmacies, contingency management, medication adherence, financial incentives, behavioural reinforcement, heroin use]

1. Introduction

Heroin addiction is a major public health issue. In 2011/12, there were an estimated 256,000 heroin (and other opiates) users in England [1]. Heroin and other opiates are responsible for more than 50% of all drug overdose deaths in England [2]. The costs to society of Class A drug use (including heroin use) were an estimated £15.4 billion in 2003/04[3]. In 2012, there were approximately 155,000 people in treatment for heroin (or opiate) addiction in England. The majority are prescribed opiate substitution treatment (OST) with methadone or buprenorphine [4] for which there is an extensive evidence-base [5,6]. The National Institute for Health and Care Excellence (NICE) recommend substitute prescribing as the most effective treatment, alongside psychological therapies [7]. However, recovery from heroin addiction is a long-term process and many heroin users relapse into heroin use leading to high attrition rates in OST [8]. The Department of Health recommends methadone and buprenorphine consumption is supervised in the early stages of treatment [9,10]. Supervision guarantees methadone is taken as directed by the individual for whom it has been prescribed; and helps to ensure individuals take their correct dose every day to mitigate withdrawal or craving. Moreover, supervision safeguards against diversion onto the illicit market and overdose. Supervision may be relaxed after a few months if stability and clinical progress can be demonstrated. Pharmacists play an important role in dispensing OST medication, with a network of community pharmacists across England providing local availability of medication.

Individuals often fail to attend the pharmacy to take their medication and those who do are very likely to miss multiple doses. In 2005, over a two-week period, 13% of prescriptions for OST had at least one missed pick-up (day when patient had not attended to take their dose) [11,12]. Of these, 73% had one quarter of pickups missed and almost 19% had between one quarter and one half of pickups missed [11,12]. Also, 42% of OST patients at one London drug service had only partial or poor adherence to their medication in the previous 30 days, and more than one third of patients receiving supervised oral methadone had missed pick-ups [13]. For opiate patients it is important to take their medication every day, with each missed dose of concern. If a patient misses their dose it is likely that they will experience withdrawal symptoms and cravings which may lead them to use heroin. If they miss three doses/days, there are concerns that they may lose their tolerance to the drug and be at risk of overdose when the next dose is taken. Clearly the success of any pharmacotherapy depends heavily on medication adherence and as noted, patients in OST are not achieving full patient benefit (abstinence from illicit drugs) due to non-adherence of medication. Furthermore, non-adherence to medication is associated with non-attendance at medical and psychosocial appointments [14,15]. A pharmacist (under local agreement with the drug clinic prescriber) is normally unable to dispense the next day's dose if a patient has failed to pick-up for three consecutive days [9,16,17]. Of concern is the pharmacists lack of consistent reporting to the prescribers about patient's missed doses. Ten per cent of pharmacists stated that they would never or rarely report if a patient misses one or two doses to prescribers but would usually report if three doses were missed [11,12].

Therefore, there is an urgent need to develop effective interventions for medication adherence [18]. A recent Cochrane review of psychological interventions for enhancing medication adherence (medication for substance misuse treatment was not included in this review) concluded that only some improved adherence and none were effective in encouraging long term medication adherence [19].

Contingency management (CM), based on the principles of operant conditioning, involves the systematic application of positive reinforcement to promote positive behaviour consistent with treatment goals and amplify patient benefit. CM in OST is effective at reducing illicit drug use [20,21], adherence to vaccination [22,23,24], HIV anti-retroviral and TB treatment [25,26,27,28]. NICE have recommended that CM be used in UK drug settings to target the reduction of drug use and encourage medication adherence [7, 29]. A recent systematic review of studies using incentives to reinforce medication adherence concluded that incentive-based interventions are promising but understudied (this review did not include OST studies) [30]. Effective methods to improve adherence need to be maintained for as long as the treatment is needed, requiring interventions that can be integrated into the care system in a cost-effective manner [19]. While CM requires time and organisational systems [31] which can be challenging in pharmacies dispensing to a high volume of patients, we believe CM delivered by technology might encourage medication adherence among individuals receiving OST while being resource light and cost-effective. While there is insufficient evidence to conclude that newer interventions such as text messaging reminders can improve adherence, there may be benefit to using text messaging in low-resource settings [19]. In a recent systematic review and meta-analysis of mobile telephone delivered CM interventions to promote behaviour change, CM delivered by mobile telephone was found to be effective at reducing tobacco and alcohol use. Only one study targeted medication adherence and this was to anti-retroviral medications among individuals with HIV and substance misuse [32].

The authors have developed a telephone system for delivering CM via text messages [33]. The study described in this paper aims to assess the feasibility of conducting a future confirmatory randomised controlled trial (RCT) of the clinical and cost-effectiveness of a telephone system for delivering text message incentives to encourage adherence to supervised oral methadone.

2. Material and methods

2.1 Aim

This study aims to assess the feasibility of conducting a future confirmatory RCT of the clinical and cost-effectiveness of i) telephone delivered incentives (positive reinforcement through text messages and financial incentives) to encourage adherence to supervised oral methadone among individuals receiving opiate treatment, compared with ii) text message reminders or iii) no text messages. The intention is that the future confirmatory trial would also use a cluster randomised design. Within each cluster, all participants will receive the same allocated condition. We believe it is necessary that all patients attending the same drug service (and pharmacy) for supervised consumption of methadone receive the same supervised methadone consumption scheme (i.e. telephone delivered incentives, reminders or neither) to ensure there is no risk of contamination by alternative treatments and eliminate possible patient self-selection by choosing pharmacies offering different schemes to receive their medication.

The feasibility study has the following objectives: 1. Assess the willingness of clusters (drug services and allied community pharmacies) to be randomised; 2. Assess numbers of eligible patients relative to those screened, rates of recruitment and suitability of recruitment procedures; 3. Assess rates of follow-up at 12 weeks; 4. Test accuracy of recording/logging of attendance at the pharmacy;5.

Assess the acceptability of the study to patients; 6. Identify different options for quantifying the primary outcome (adherence to medication) for use in a future confirmatory trial and assess the utility and practicality of these options; 7. Characterise aspects of the primary outcome needed for a sample size calculation for a future confirmatory trial (e.g. For a continuous outcome, mean and standard deviation, an estimate of the intraclass correlation to inform a sensible range for the cluster trial design effect); and 8. Assess the most appropriate secondary outcome measures to determine patient benefit and cost-effectiveness, and 9. the availability and usefulness of existing data sets including existing pharmacy dispensing data sets. A process evaluation will be conducted alongside this feasibility trial to assess the acceptability of the intervention and the trial procedures and to determine how contextual factors and treatment process may impact on the primary outcome (attendance). Research ethics approval has been granted by London - South East Research Ethics Committee (18/LO/1722).

2.2 Design and setting

This feasibility study will use a 3-arm cluster randomised controlled design (Figure 1) where drug services and their allied community pharmacists are the cluster. It is intended that this design will give us the feasibility information we need to determine whether it is possible to conduct a future confirmatory trial.

Three sites (two National Health Service (NHS) substance misuse treatment services and one non-NHS) will be recruited from 4 sites approached. All sites will provide OST. This mix of non-NHS and NHS providers reflects current addiction service provision and will enhance the generalisability of the confirmatory study. At each site, two or three community pharmacies dispensing and supervising oral methadone to patients will be recruited. The criteria for enrolling community pharmacies will include: Pharmacists are willing and able to provide six days supervised consumption of oral methadone; Pharmacy has a consultation room on the premises or a separate designated area on the dispensing counter in which participants can consume their oral methadone under supervision; Pharmacy is currently providing supervised consumption of oral methadone to the patients at the drug clinic; Pharmacy is willing and able to provide dispensing records for participants over the 12-week intervention period.

We will enrol eligible and consenting participants at entry to OST at the participating service. They will be provided with OST including daily (6 days a week) supervised oral methadone at their pharmacy for 12 weeks and followed up at 12 weeks after enrolment.

2.3 Characteristics of participants

Participants will be those assessed for a new episode of OST at participating drug services (and will include either those newly presenting to the service or those already attending the service and being re- assessed for OST having not receiving OST for at least 4 weeks). Inclusion criteria for individual participants include: aged 18 years and over at enrolment; presenting to participating drug services for a new episode of OST (this excludes patients receiving a prescription for methadone or other opiate substitution medication within the last 4 weeks as well as those transferred from another service or prison); prescribed oral methadone; receiving supervised consumption of oral methadone from one of the participating pharmacies; receiving their supervised oral methadone six days a

week; owns a mobile phone; and willing and able to provide informed consent. Therefore, they must be able to read English and not require the service of an interpreter.

Patients will be excluded if they cannot read English or would require the service of an interpreter to understand a brief oral description of the study; they have already entered the trial; or they have previously attended the service (drug clinic) and were discharged within the last three weeks.

2.4 Recruitment

Twenty participants will be recruited at each site (drug service) over a three-month recruitment period between mid-December 2018 and mid-March 2019 by drug service staff, giving a total of 60 participants. Each individual presenting to the drug treatment clinic for a new episode of OST will be screened for eligibility.

2.5 Processes/interventions and comparisons

Interventions

Opiate substitution treatment (OST). OST should be delivered in line with existing service protocols at sites. This would include psycho-social interventions usually delivered at the service. Each site will prescribe oral methadone for six days-a-week, with daily supervised consumption provided by a community pharmacy as part of usual treatment.

Telephone system. The telephone scheme will be delivered for 12 weeks in line with current clinical guidelines which recommend that individuals receive their methadone supervised at a community pharmacy in the early stages of their treatment episode [10]. The telephone text message intervention will be discontinued if participants are no longer prescribed oral methadone or supervised consumption or they move to a non-participating drug service or pharmacy .

The technology for telephone delivered incentives has already been developed by the authors, has been adapted and made operational for routine pharmacy use and has been piloted at two pharmacies. The technology uses internet-based software with an intelligent text message alert engine. It is hosted on and accessible through a secure website. The software will monitor all individuals and their supervised methadone appointments through an internet login on tablet computers at the pharmacy. The software is internet-based, thereby accessible from anywhere with an internet connection without the need to install and maintain separate standalone software. The internet-based software can contact individuals via mobile telephone text messages and keeps track of each time a patient logs in to attend a dosing appointment at the pharmacy, each time they do not log in to attend the appointment, and their monetary balance (if appropriate). The telephone system provides either:

i. Telephone delivered incentives: Positive reinforcement through automated text messages of praise and modest financial incentives (CM), sent immediately after an individual logs in at their pharmacy (indicating they have taken their supervised methadone). Each time a participant attends their pharmacy and consumes their supervised oral methadone they will receive a text message giving positive reinforcement (praise) *and* earn a small financial reward of 50p. If they attend for six days consecutively, they will earn a bonus reward of £5. The total possible financial reward is therefore £8/week or £96 over 12 weeks. Participants

will be paid directly through pre-paid debit cards (an automated reward payment platform) issued by the study team. These allow for financial incentives to be electronically loaded onto the participant's card once satisfaction of the target behaviour has been verified. If they do not attend, participants will receive a "shaping message" that evening informing them that they can still earn 50p if they attend the pharmacy (and take their dose) the following day.

ii. Telephone delivered reminders: Text message reminders sent in the morning and afternoon to attend the pharmacy and take their supervised medication that day. Reminders will be sent each day for 12 weeks (comparator group).

with a third group that will not receive any telephone text messages.

Participants in all groups (including those not receiving telephone messages) will use a self-service internet login at their pharmacy to record their attendance and consumption of methadone. Participants will not have access to the tablet to login until they have received their supervised oral methadone. The telephone system also allows for the patients' prescriber to receive weekly reports of their patient's attendance and an early warning if their patient has missed two days. Prescribers for patients not receiving text messages will not receive these.

The pharmacy will be unable to 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 is able to dispense methadone again to the participant (after they have had their dose reassessed by their prescriber).

OST will continue to be delivered to participants after 12 weeks.

2.6 Outcome measures

2.6.1 Feasibility outcomes.

(1) Enrolment rate of patients (Number enrolled per week, relative to those entering OST treatment, over the 12-week period);

(2) Percentage of screened patients who are eligible for participation in the trial;

(3) Percentage of eligible patients who consent to participation in the feasibility trial;

(4) Percentage responding 'yes' to 12 × weekly text message sent by researchers asking if they received all text message incentives or reminders for previous week (this will indicate whether they have mobile telephone and whether they are receiving text messages);

(5) Accuracy of attendance measurement measured by percentage of matches between (a) daily pharmacy dispensing record and (b) record of attendance and medication compliance recorded in self-service internet login at the pharmacy. A 'match' is defined as agreement between (a) and (b) as to whether a participant attended their supervised methadone replacement appointment on a given day;

(6) Number and percentage of participants followed-up for research interview at 12 weeks post enrolment, by arm, relative to those enrolled;

The willingness of (7) drug services and (8) allied community pharmacies to participate - measured as the number and percentage of drug services and pharmacies enrolled relative to those approached;

(9) Acceptability of the study to patients, drug service staff and pharmacists measured by qualitative views and experiences of patients, drug service staff and pharmacist. Focus groups will be held with between 5-8 participants at each service at a minimum of 10 weeks post enrolment. Interviews with drug service staff and pharmacists will be held at the end of the trial;

2.6.2 Primary outcomes for exploration for a future confirmatory trial to look at the best ways to report missing doses/non adherence. Adherence to medication measured by (1) percentage of days during 12 weeks post-enrolment when medication was taken; (2) Median number of days during 12 weeks post-enrolment when medication was not taken; (3) Likert scale categorising participants according to different levels of missed doses (number and percentage in each category), by arm; and (4) Number of days to missed dose analysed using repeated events survival analysis. Adherence to medication will be calculated by (i) enumerating all days during each participant's intervention period, (ii) removing inactive days (those when the participants were paused, off script, or not supervised), and (iii) determining their attendance as indicated in the pharmacy records. Data from daily pharmacy dispensing data sets will be the authoritative source on adherence to medication.

Aspects of the primary outcome measures needed for a sample size calculation for a future confirmatory trial including (5) appropriate summary statistics (for example, mean and standard deviations for continuous outcomes); (6) estimate of the intraclass correlation (ICC) for the clusters. Information from three sites will provide an initial estimate of ICC, which will inform our sample size calculations for a larger trial. However, this estimate will be supplemented by information from previous studies with populations from primary care [34,35] and opiate substitution treatment [20, 21, 36] which suggest values of ICC less than 0.05; and (7) qualitative information on the availability and usefulness of existing pharmacy dispensing data sets.

2.6.3 Secondary outcomes of a future confirmatory trial. (8) Number and percentage retained in treatment over the 12-week intervention period. Illicit drug use measured by Opiate Treatment Index (Section 2 – Drug Use) (Validated)[37] including: (9) Number and percentage using illicit street drugs in past 30 days; (10) Median number of days used illicit street drugs in past 30 days; (11) Median number of days injected illicit street drugs use in past month; (12) Route of use (number/percentage for each); (13) Average cost of each drug used on average day. (14) Alcohol Use Disorders Identification Test (AUDIT) (Validated, mean total score)[38]; (15) Hospital Anxiety and Depression Scale (HADS) (Validated, mean total anxiety and depression subscale scores)[39]; (16) Social functioning measured using the Opiate Treatment Index (Validated, mean social functioning subscale score)[37]; (17) Physical and mental health status (Short form-36 subscale mean scores)[40]; and (18) Missing data by questionnaire and time point.

*2.6.4 Sociodemographic characteristics. Age (*mean and standard deviation); gender (number and percentage in each group); ethnicity (number and percentage in each group); employment status (number and percentage in each group); living situation (number and percentage in each group).

2.6.5 Outcomes for economic evaluation. Economic data collection measured by (1) Resource use schedules AD-SUS [41]; (2) EQ -5D-5L measure of health-related-quality of life [42]; and (3) the ICECAP-A measure of capabilities [43].

2.6.6 Process outcomes. We will conduct focus groups with participants and interviews with participating drug service staff and pharmacists to assess (from each perspective) the acceptability of the intervention and the trial procedures and also to determine how contextual factors and treatment process impact on feasibility criteria (including recruitment, take-up and compliance with assessments) the primary outcome (attendance).

2.7 Participant timeline and study visits

Participants will have a research assessment interview conducted by member of the research team at baseline and again at 12-14 weeks post-enrolment. (Figure 2. Consort). The baseline assessment will be conducted at the earliest opportunity after the participant has consented. In addition to these interviews, towards the end of each participant's intervention period (minimum 10 weeks post-enrolment) the researchers will approach all participants enrolled in the trial (whether or not they continue to receive the trial intervention), drug service keyworkers (whose patients have participated in the study) and pharmacists to ask them if they would be willing to participate in focus groups and interviews to provide information on their experience of taking part in the feasibility trial, using the tablet and receiving the telephone text message incentives or reminders.

2.8 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.

2.9 Randomisation

The three sites will be randomly allocated to one of the following three arms :

A. Supervised Medication + telephone delivered text messages providing positive reinforcement and modest financial incentives;
B. Supervised Medication + telephone delivered text messages providing reminders only; or
C. Supervised Medication with no telephone text messages (Treatment as Usual).

Using simple randomisation in a 1:1:1 allocation ratio, sequences will be generated using a random number generator. Given small the number of sites to be randomised, there will be no blocking, stratification, or minimisation used in the randomisation procedures.

2.10 Blinding

Due to the nature of the intervention being studied, there will be no attempt at blinding either clinicians or participants. The researchers cannot be blinded due to the necessity to monitor the telephone system, with the analysing trial statistician unblinded in order to conduct the randomisation and monitor data. Only the senior trial statistician will be blind to treatment allocation throughout the study.

2.11 Data collection and management

There will be five forms of data collection:

Firstly, researchers will conduct face-to-face interviews with participants at baseline (after consent and immediately preceding enrolment onto the telephone system) and at 12 weeks post-enrolment. Interviews will be sought from all participants including those who discontinue receiving oral methadone treatment and/or discontinue receiving the telephone text message intervention as long as they do not withdraw consent for participation in feasibility trial/continued collection of their data. Participants will receive a £10 reimbursement for their time and travel for the baseline and follow-up interview.

Secondly, the software system will collect information from participants via tablet computers in the pharmacies at each supervised methadone appointment over the 12-week period. This will record a patient nickname and telephone number, the date and time, and whether they attended and consumed their methadone or not. These data will be stored on a secure web site . At the end of the 12-weeks intervention period, these data will be extracted from the software system by a research worker and entered into an SPSS database. This will be stored, along with other trial databases, with password protection on a secure KCL network drive.

Thirdly, dispensing records kept by the allied pharmacies relating to trial participants will be provided to researchers after being pseudo-anonymised by the pharmacist (linked by nickname only). The pharmacist will have participants' names and nickname stored in a password protected file.

Fourth, interviews and focus groups involving patients (including those who have discontinued receiving the telephone system and/or those who have discontinued receiving oral methadone treatment), staff, and pharmacists will be recorded by digital handheld audio recorder (with encryption facilities) and uploaded and stored on a password protected secure KCL network drive. Patient participants will receive a £10 reimbursement for their time and travel for the focus group.

Data from the baseline (0 weeks) and follow-up (12 weeks) interviews will be collected on paper case report forms (CRFs), which will be stored at KCL University. These data will be entered into SPSS databases by researchers at KCL University. 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 per cent of participants to ensure accuracy of data entry, with higher order data queries undertaken by the analysing statistician. SPSS databases will be stored on a KCL secure drive, and will be subject to version control to allow for 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 University.

2.12 Data monitoring

A Data Monitoring and Ethnics Committee (DMEC) will be convened. The DMEC will be responsible for data monitoring throughout this feasibility trial. Monthly recruitment progress will be reported and compared to recruitment targets at each DMEC meeting. Adverse events will also be reported at

DMEC meetings, as detailed below. There are no interim analyses or audits of trial conduct planned. A Trial Steering Committee will be convened to provide independent expert advice on the ongoing conduct of the study.

2.13 Data analysis

A comprehensive statistical analysis plan will be developed and agreed with the trial's oversight committees (DMEC and TSC). All data will be analysed using R 3.5 [44] with the exception of the economic evaluation, focus groups and qualitative interviews.

The feasibility outcomes will be summarised with appropriate summary statistics (generally frequencies and proportions). Differences between arms, where appropriate, will be assessed by examining differences in proportions. Estimates will be provided with 95% confidence intervals to provide an estimate of precision.

The primary and secondary outcomes of a future confirmatory trial will also be summarised using appropriate statistics (e.g. mean and standard deviation/median and interquartile range for normally distributed/non-normally distributed continuous outcomes; counts and proportions for categorical outcomes). The outcome "number of days to missed dose" will likely be analysed using discrete-time survival analysis [45], although we may explore other methods. Differences between arms will be estimated as mean differences, difference in proportions, or by entering dummy variables into a regression model. Differences in survival outcome between arms will be expressed with hazard ratios. Associated confidence intervals will be estimated where appropriate.

The primary purpose of these estimates is to inform sample size calculations of a future confirmatory trial. This analysis is not powered to detect differences between arms in the primary and secondary outcomes of a future confirmatory trial. Therefore, these estimates will be treated as exploratory and not used as the basis for inferential statements. These 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 [46]. Missing scale item data will be handled as per questionnaire specific recommendations or, if no recommendations are available, pro-rating will be used (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.

2.14 Economic data

Data on health and social care service use will be collected using the Adult Service Use Schedule (AD-SUS), modified for use in substance misusing populations (41). The feasibility of the AD-SUS will be explored based on completion rates, missing data (item missing, questionnaire missing), plausible values, and inconsistencies. Service use data will be presented as means with appropriate measures of dispersion together with the proportion of participants reporting each resource use item. We will use the EQ-5D-5L to measure health-related quality of life expressed as mean scores with appropriate measures of dispersion [47]. EQ-5D scores be calculated using 5L tariff and also the 3L tariff using the mapping function recommended by NICE [48]. We will also use the ICECAP-A to

measure changes in participants capability to undertake activities important to them [49]. We will explore the feasibility of the EQ-5D-5L and ICECAP-A measures with sensitivity to changes in comparable clinical outcomes (HADS, SF36 subscales) using appropriate measures of agreement.

2.15 Process evaluation

The qualitative process evaluation will generate evidence that supports refinement of the intervention and the proposed definitive trial. Specifically, we will assess (1) the acceptability of the intervention to participants (service-users) and clinicians; and (2) whether the intervention can be implemented in routine practice and delivered by staff who have the necessary capacity and competencies, and (3) the acceptability of trial procedures. Our qualitative design will involve both interviews and focus groups.

Interviews will be undertaken with pharmacists and prescribers to assess acceptability and satisfaction with telephone delivered incentives and reminders, the impact of monitoring and reporting medication compliance to prescribers, resources required, the organisational impact (both drug service and pharmacy), and factors which help or hinder fidelity. Sampling of pharmacists and prescribers will be purposive, with participants identified based on their relationship to the intervention and propensity to provide an important or distinct perspective (pharmacists n=6; prescribers n=9).

Focus-groups (n=6) will be used to obtain participant perspectives on using self-service internet-login, receiving telephone delivered incentives and reminders, debit card payments and trial procedures (notably randomisation and assessment procedures) We have opted for focus groups (as opposed to 1-2-1 interviews) because they are efficient in reaching numbers of participants and ensuring attendance. They also facilitate participant interaction that supports reflection on the processes under study while (in this context) being low risk in terms of coverage of sensitive subject matter.

All interviews/focus groups will be based on topic guides developed iteratively during the preceding study phases and applied flexibly to ensure coverage of key issues and responsiveness to emergent themes. Participants will be reimbursed £10 for attending a focus group.

Interviews and focus groups will be audio recorded, transcribed verbatim and subject to a thematic analysis supported by NVIVO. The analysis will describe the different stakeholder experiences, and assess whether, how and to what extent, the professional, organisational and social contexts impacts on the delivery of the intervention and the acceptability and feasibility of trial procedures (particularly recruitment, follow-up and outcome assessment).

Data will support refinement of the confirmatory trial intervention, trial design and the scope and focus of the process evaluation which will run concurrently with the planned future confirmatory trial.

2.16 Adverse event monitoring

We will monitor all non-serious adverse events, serious adverse events, and serious adverse reactions to trial interventions, serious deterioration, and active withdrawals from treatment.

Keyworkers and pharmacists will be asked to record events on a CRF and notify us if they are aware of any adverse events or active withdrawals from treatment. We will contact pharmacists and keyworkers once a week to monitor possible adverse reactions. These will be recorded in a specific SPSS database, stored on a secure KCL drive, and reported at each DMEC meeting.

2.17 Progression criteria

To proceed to a future confirmatory trial the following outcomes should be achieved. However, not achieving these criteria does not necessarily indicate unfeasibility of a future trial but underlines changes that need to be made to recruitment procedures, attendance record keeping and resources for follow-up. These include:

- Recruitment of three drug services, two to three pharmacies and 60 participants (20 from each drug service over 12 weeks);
- 50% of target patients (those patients presenting to participating drug services for a new episode of opiate substitution treatment (OST) who have not been receiving a prescription for methadone or other opiate substitution medication for >4 weeks and who have not been transferred in from another service or prison) eligible and consented.
- >95% consistency in recording of pharmacy attendance (comparing daily pharmacy dispensing records vs. self-service internet login).
- Rates of follow-up at 12 weeks (>70%).
- Completion rates of economic data collection (>70%),
- Missing data (item missing/questionnaire missing) (<10% missing data per questionnaire) and inconsistencies.

3. Discussion

The TIES feasibility study seeks to 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 progression criteria to inform a future confirmatory trial.

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Figure 1. Trial design

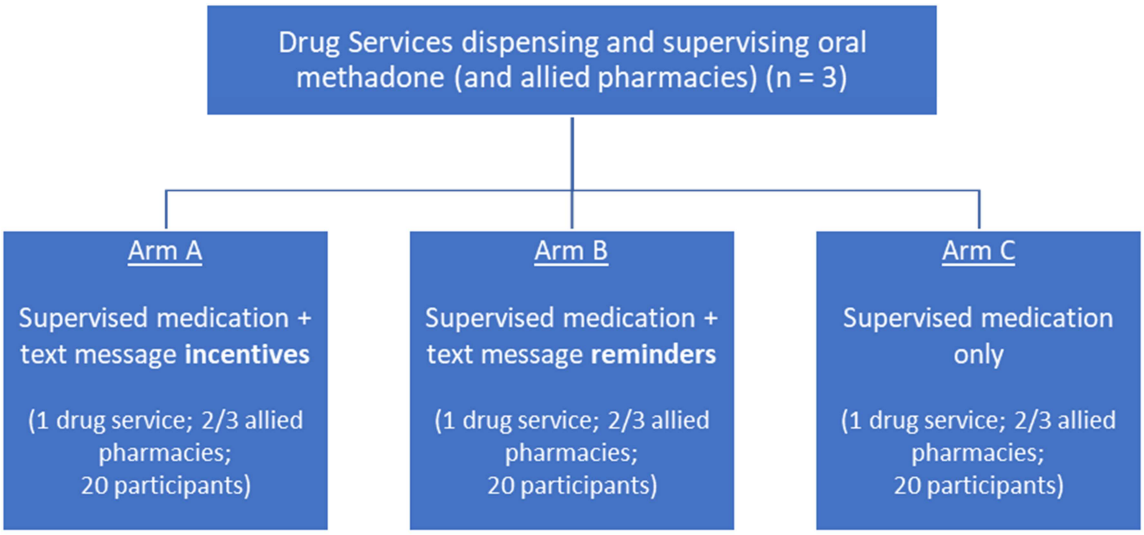

Figure 2. Consort