Positive reinforcement targeting abstinence in substance misuse (PRAISe)

Metrebian, Nicola; Weaver, T.; Pilling, S.; Hellier, Jennifer; Byford, Sarah; Shearer, James Douglas; Mitcheson, L.; Astbury, M.; Bijral, P.; Bogdan, N.; Bowden-Jones, O.; Day, Edward; Dunn, J.; Finch, E.; Forshall, S.; Glasper, A.; Morse, G.; Akhtar, S.; Bajaria, J.; Bennett, C.

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Contemporary Clinical Trials (Study Design, Statistical Design, Study Protocols)

Positive Reinforcement targeting Abstinence In Substance misuse (PRAISe): Study Protocol for a Cluster RCT & Process Evaluation of Contingency Management

Authors

Metrebian N[a]*, Weaver T [b,c]*, Pilling S[d], Hellier J[e], Byford S[e], Shearer J[e], Mitcheson L[f], Astbury M[g], Bijral P[h], Bogdan N[i] , Bowden-Jones O[j], Day E[ak] , Dunn J[l], Finch E[f], Forshall S[m], Glasper A[n] , Morse G[o], Akhtar S[j], Bajaria J[h], Bennett C[j], Bishop E[d], Charles, V[a], Davey C[m], Desai R[a], Goodfellow C[d] , Haque F[a], Little N[d], McKechnie H[b], Morris J[m], Mosler F[a], Mutz Ja, Pauli R[k], Poovendran D[b], Slater E[j], and Strang J [a,f]

**Joint first authors*

[a] *King's College London, Institute of Psychiatry, Psychology & Neuroscience, National Addiction Centre, London UK*

[b] *Imperial College London, London UK*

[c] *Middlesex University, London UK*

[d]*University College London, London UK*

[e]*King's College London, Institute of Psychiatry, Psychology & Neuroscience, London UK*

[f]*South London and Maudsley NHS Foundation Trust, London, UK*

[g] *Dudley & Walsall Mental Health Partnership Trust, Dudley, UK*

[h] *Change, Grow, Live Charity, Management Offices, London, UK*

[i]*South Essex Partnership NHS Foundation Trust, Essex, UK*

[j] *Central and North West London NHS Foundation Trust, London, UK*

[k]*Birmingham & Solihull Mental Health NHS Foundation Trust, Birmingham, UK*

[l]*Camden & Islington NHS Foundation Trust, London UK*

[m] *Avon & Wiltshire Mental Health Partnership NHS Trust , Bristol, UKt*

[n] *Sussex Partnership NHS Foundation Trust, Brighton, UK*

[O] *Turning Point Charity, London, UK*

Corresponding author: Dr Nicola Metrebian, King's College London, Institute of Psychiatry, Psychology and Neuroscience, National Addiction Centre, 4 Windsor Walk, Denmark Hill, London SE5 8AA

Abstract

There are approximately 256,000 heroin and other opiate users in England of whom 155,000 are in treatment for heroin (or opiate) addiction. The majority of people in treatment receive opiate substitution treatment (OST) (methadone and buprenorphine). However, OST suffers from high attrition and persistent heroin use even whilst in treatment. Contingency management (CM) is a psychological intervention based on the principles of operant conditioning. It is delivered as an adjunct to existing evidence based treatments to amplify patient benefit and involves the systematic application of positive reinforcement (financial or material incentives) to promote behaviours consistent with treatment goals. With an international evidence base for CM, NICE recommended that CM be implemented in UK drug treatment settings alongside OST to target attendance and the reduction of illicit drug use. While there was a growing evidence base for CM, there had been no examination of its delivery in UK NHS addiction services. The PRAISe trial evaluates the feasibility, acceptability, clinical and cost effectiveness of CM in UK addiction services. It is a cluster randomised controlled effectiveness trial of CM (praise and financial incentives) targeted at either abstinence from opiates or attendance at treatment sessions versus no CM among individuals receiving OST. The trial includes an economic evaluation which explores the relative costs and cost effectiveness of the two CM intervention strategies compared to TAU and an embedded process evaluation to identify contextual factors and causal mechanisms associated with variations in outcome. This study will inform UK drug treatment policy and practice.

Trial registration ISRCTN 01591254

Key words: Opiate Substitution Treatment; Contingency Management; Financial Incentives; Positive Reinforcement; Opiates; Heroin use; Abstinence; Attendance.

BACKGROUND AND RATIONALE

In England in 2012 there were approximately 256,000 heroin and other opiate users, of whom 155,000 are in treatment for addiction [1]. The majority of people in treatment receive opiate substitution treatment (OST) (methadone and buprenorphine) for their addiction to heroin [1]. There is an extensive evidence-base for OST [2]. It is proven to be cost-effective and estimated to save £9.50 for every £1 spent [3]. The National Institute for Health and Care Excellence (NICE) recommends substitute prescribing as the most effective treatment, alongside psychological therapies to change behaviour. However, recovery from heroin addiction is a long term process and many heroin users relapse and OST suffers from high attrition [4].

Contingency management (CM) is a psychological intervention based on the principles of operant conditioning. It is delivered as an adjunct to existing evidence based treatments to amplify patient benefit and involves the systematic application of positive reinforcement (financial or material incentives) to promote adherence to treatment and/or patient behaviours consistent with treatment goals (e.g. reinforcing medication compliance, or abstinence from street drugs). A number of systematic reviews concluded that, when provided in combination with methadone maintenance treatment, CM can significantly increase attendance, and reduce illicit opiate use during treatment and at follow-up [5,6]. Although this evidence base came primarily from trials conducted in the USA, and has more recently been challenged [7], in 2007 NICE recommended that CM be implemented in UK drug treatment settings to target the reduction of illicit drug use and encourage attendance at treatment appointments [8,9]. However, with no track record of delivering CM in UK addiction services, there were concerns about applying CM in a UK setting [9,10]. USA and UK drug treatment provision differ greatly in treatment philosophy and service configuration. Thus it was thought that careful assessment was needed of the application, implementation, treatment process and clinical outcome of CM in the UK NHS drug treatment settings [9].

A cluster randomised trial with different CM reinforcement schedules to evaluate whether CM encouraged completion of hepatitis B vaccination scheme among opiate dependent drug users was recently undertaken by the authors [11]. Findings showed modest financial incentives (both fixed and escalating schedules) significantly increased the proportion completing hepatitis B vaccinations compared to those not receiving financial incentives. This suggests that CM can effectively promote attendance at appointments and short term behaviour change. For CM to be effective at targeting important clinical outcomes such as abstinence from non prescribed opiates research needs to demonstrate that CM can also effectively promote longer term behaviour change.

The trial described in this paper evaluates the clinical and cost effectiveness of CM (positive reinforcement through praise and financial incentives) targeted at attendance at keywork appointments and abstinence from heroin. The feasibility of conducting such a trial has been proved in the authors' previous CM cluster trial [11] which provided information on the feasibility and effectiveness of different reinforcement schedules and helped to develop and refine practice guidance and protocols for the implementation of CM. It also informed the intervention strategies and staff training delivered and evaluated in this trial. A process evaluation being conducted

alongside this trial will investigate how and why CM works (or not) by examining contextual factors and causal mechanisms associated with variation in outcome.

METHODS

Objective

The 3 arm trial will test whether the use of positive reinforcement (praise and financial incentives) targeted at (a) the provision of urine samples negative for opiates AND on-time attendance at treatment sessions will increase abstinence from street heroin when compared to a control condition (Treatment As Usual [TAU]) in which no positive reinforcement is offered among individuals receiving OST. It will also test (b) whether the use of positive reinforcement targeted at on-time attendance at treatment sessions only will increase abstinence from street heroin when compared to TAU in which no positive reinforcement is offered. What has been unclear is whether any benefit derived from CM comes from a direct effect of CM aimed at the selected target behaviour or is a benefit from CM- improved attendance at treatment sessions (and possibly consequently improved retention in treatment). The trial includes an economic evaluation which will explore the relative costs and cost effectiveness of the two CM intervention strategies compared to TAU.

Alongside the trial a process evaluation will be undertaken to identify contextual factors and causal mechanisms associated with variation in outcome to better understand how and why the intervention does or does not work and the process and impact of delivering CM on services, clinicians and service users. In addition fidelity will be assessed to established whether the intervention was delivered as intended. Process evaluations incorporating qualitative components have been advocated in the MRC framework for the evaluation of complex interventions to understand the implementation, delivery and fidelity of randomised controlled trials in health services [12, 13], and are recommended for use pre, during and post trial [,14,15,16]. The process evaluation aims to (a) identify the factors that are present in UK drug services that would facilitate or hinder the implementatin of CM; (b) describe the contingency management (CM) intervention delivered during the CM urinalysis and keywork sessions and assess whether it is delivered as intended; (c) investigate whether (and how) organisational, professional and contextual factors present within the experimental study setting influences the implementation, delivery and outcome of CM in urinalysis/keyworker sessions and identify factors which might promote or impede recruitment (of sites, clinical staff and participants) to the trial.

Trial Design

The trial uses a cluster randomised controlled design as individual randomisation is not feasible. Each of the drug treatment clinics will be their own cluster. Within each cluster, all participants will receive the same allocated condition, thus minimising the risk of contamination. The most common configuration of services providing OST is for one or more clinics to provide coverage to a large geographical area. There is a high probability of contamination if staff were delivering, and service users receiving, different interventions within the same clinic. Also service-users themselves constitute a local social network and individual randomisation (with CM incentives for some service-users while not for others at the same clinic) would be highly likely to encounter inter-service-user as

well as inter-staff contamination. For these reasons it is not feasible for clinicians to provide, simultaneously, both the experimental and control intervention with fidelity within a single clinical setting. Also, because subjects in treatment as usual (TAU) would be denied an incentive offered to others in the same clinic, there would be a high probability of trial-induced low recruitment, poor compliance and high drop-out within the control arm. Sites (clusters) were recruited in stages and then randomised. We recruited participants at entry to treatment. They were provided with 12 weekly keywork sessions and followed up at 12 and 24 weeks after trial entry.

Study setting

The research was originally intended to be conducted at only NHS drug treatment clinics providing OST. However, with major changes to the NHS organisation of the whole addiction provider network, non-NHS treatment agencies providing OST have been additionally recruited. This reflects current addiction service provision and thus enhances the generalisability of participating sites. Thirty-three clinics (i.e. clusters) providing OST will be recruited across NHS Trusts and non NHS organisations in England. Sites will be recruited in London, Sussex, Hertfordshire, South Essex, Avon and Wiltshire, Birmingham and Dudley and Walsall.

Eligibility criteria

Each individual presenting to the drug treatment clinic for a new treatment episode of OST (not transferring from prison or another drug service) will be screened by the assessment nurse/drugs worker for eligibility

Inclusion Criteria

Participants aged above 18 years and reporting regular use of street heroin in the preceding one month as evidenced by self-report 15/30 days in preceding month and at least 3 days use each week. Must have a minimum of one urine drug screen (UDS) in the last month positive for opiates. Opiate dependent, meeting ICD-10 criteria for opiate dependence, and at liberty to participate in the study for 24 weeks. Willing to receive a 12 week CM intervention reinforcing abstinence and willing and able to provide informed consent.

Exclusion Criteria

Cannot read English and require the service of an interpreter to understand a brief oral description of the study – these participants cannot be considered to have given informed consent and will NOT be entered into the trial. Pregnant or breast feeding women. Those referred through the criminal justice pathway. Clients with an ongoing or recent (< 1 month) drug treatment episode.

We will record the reasons for non-participation of all screened subjects.

Interventions

Opiate Substitution Treatment

OST should be delivered in line with existing service protocols at all sites. This would include usual methadone or buprenorphine medication and psycho-social interventions usually delivered at the drug treatment clinic.

Keyworking

Each site will offer weekly keyworking sessions with a named keyworker of up to 50 minutes. The keyworker session should take place in a private consultation room and include assessment, review and core psychosocial interventions and include harm reduction, regular care plan review and reviews of progress, identification and assessment of risk to children, brief interventions and other psychosocial interventions according to competence, and help to address social problems. The act of merely attending the service or obtaining a script does not constitute attendance at a trial keywork session on the part of the client. The keyworker session offered in each site will be identical across treatment arms, and the treatment offered will differ only in terms of the absence / presence (and type) of adjunctive positive reinforcement schedule.

Contingency management

Contingency management will be delivered at the 12 x weekly keywork sessions, and will consist of verbal praise and a small financial incentive (£10 shop voucher). Findings from a previous cluster randomised trial with different CM reinforcement schedules showed no difference between fixed and escalating incentive monetary schedules in encouraging the completion of vaccinations among individuals receiving opiate substitution treatment [11]. Therefore, as escalating was considered the more challenging to implement, a fixed schedule was used in both trials arms.

CM will be targeted at behaviours described in detail below but which (in the interests of brevity) we refer to as either 'abstinence' or 'attendance'. With the CM targeted at 'abstinence', to receive the incentive the patient must attend their weekly keyworker session on time (within 15 minutes of scheduled time) <u>and</u> provide a UDS negative for opiates. The first four weeks will reinforce the provision of the urine sample (priming weeks) where the patient will receive reinforcement for providing a UDS sample irrespective of result. Priming is recognised to be a potentially useful component of CM protocols in circumstances where subjects may need to learn that desirable benefits can accrue from participating in treatment (17). We employ priming in recognition that achieving abstinence from heroin while undergoing titration may have been too challenging a target for many. We wanted to ensure that subjects accepted the testing regime, gained direct exposure to the reinforcer and understand its value before the requirement to provide an opiate free UDS.

With CM targeted at 'attendance', to receive the incentive the patient must attend the weekly keywork session on time (within 15 minutes of scheduled time).

Training and supervision

Clinic staff already providing keywork sessions as part of usual care will receive training on trial procedures and, if working in an intervention site providing CM , will receive a bespoke one day training course in the principles and practice of CM including simulation and role play from psychologists on the research team. A CM Training Handbook written by the research team will be provided to all keyworkers. CM will be delivered in the first part (5-10 minutes) of all keywork sessions before the core part of the session. Only this part will be audio recorded. All trial keywork sessions will be audio recorded and uploaded onto a secure audio recording web site held by the King's College London Clinical Trials Unit (KCL CTU).

Supervision will be provided to keyworkers working in sites allocated to CM throughout the trial by a psychologist or senior clinical member of the drug clinic staff team (local supervisors). These supervision sessions will be conducted in a group at each drug treatment clinic and audio recorded and uploaded onto a secure audio recording web site held by the KCL CTU. These recordings will be available to supervisors who will provide feedback to clinicians in the experimental groups as part of their supervision. The local supervisors will be provided with supervision themselves (either face-to-face or telephone) by the psychologists on the research team.

Outcome measures

Primary outcome

The primary outcome will be abstinence from heroin determined by the number of urine drug screen (UDS) results negative for opiates/heroin during weeks 9-12 after randomisation.

We have selected negative UDS results as the appropriate measure for the primary outcome of this trial, as this is the widely accepted measure of outcome in the vast majority of similar trials undertaken in the United States of America, where proportion of negative UDS results is one of the main measures, with the other main measure being attendance rates/retention in treatment. In the UK context, we are also interested in measuring reductions in the extent of drug use (i.e. not just measuring absolute abstinence), and so UDS results will be considered as a continuous variable (the proportion of UDS results negative for heroin during the last month (i.e. a score between 0 to 4 based on weekly tests)) rather than using a categorical assignment to achievement of complete abstinence throughout this period.

Non-compliance with provision of a urine sample will result in the UDS being recorded as positive for opiates/heroin. We consider it appropriate to follow the usual clinical practice of presumption of positive UDS results if the urine specimen is refused or not provided through non-attendance. We have used this assumption in our previous trial [18,19].

Secondary Outcomes

Secondary outcome measures will include UDS results for opiates/heroin at weeks 21-24 (as above); retention in treatment; and patient's attendance at keywork sessions. The following patient personal characteristics and measures of health status will be assessed at baseline, 12 and 24 weeks: Socio-demographic schedule (non-validated)including -age, gender, ethnicity, employment status, living situation; drug use history (non-validated) and illicit drug use (Opiate Treatment Index (Section 2 – Drug Use) (Validated)[20]including number of days used illicit street drugs in past 30 days; number of days injecting drug use in past 30 days ; frequency of illicit drug use in past month; route of use; average cost of each drug used on average day; Alcohol Use Disorders Identification Test (AUDIT) (Validated) [21]; general health status measured using the SF-36 (Validated)[22]; EQ-5D-3Lmeasure of health-related-quality of life (Validated)[23] and Hospital Anxiety and Depression Scale (HADS) (Validated)[24] ; social functioning measured using the Opiate Treatment Index (Validated)[25]; single item measure of delay discounting (validated in other areas of addiction)[26]; and motivation measured by the Treatment Self-Regulation Questionnaire for Drug Abstinence [27]. Therapeutic

alliance (ARM-5 Client's Scale (Validated)[28]) will be measured by participants' self-report at 4,8 and 12 weeks .

For the economic evaluation, intervention resource use will be collected from questionnaires of keyworkers records of session attendance, voucher rewards and urine drug screens. Data on use of hospital, community health and social care services, and crimes committed by and against (victims of crime) study participants, will be collected using the Adult Service Use Schedule (AD-SUS) adapted for drug users [29]. Information about time off work (absenteeism) will be collected using the WHO Work Performance Questionnaire [30].

In order to investigate and explain the implementation, conduct and outcome generation of the trial the process evaluation will address the following key research questions:

a. What were the facilitators and barriers that influenced the integration, implementation and delivery of contingency management (Contextual/organisational factors/situational issues/cultural; Training; Competence and confidence; Barriers to recruitment/retention; Staff and service user appraisal; Staff engagement; Congruency and Resources Relationships (service user and staff, staff and management)and Allocation of work);

b. How did staff and service users experience and appraise the CM?

c. What impact did CM have on the relationship between staff and service users and how did this influence engagement, therapeutic alliance and outcome?

Participant timeline & study visits

Participants will have a research assessment interview conducted by independent researchers at baseline and again at 12 and 24 weeks. The baseline research assessment will be completed at the earliest opportunity after the participant has consented and will precede the first appointment with the key worker (week 1) by at least 24 hours.

Attendance at the 12 potential keyworker sessions and compliance with specified clinic dates and times will be recorded. Also provision of 12 UDS results (either positive or negative for opiates) will be recorded. Adherence to appointments and provision of urine sample will be recorded as part of the outcome assessment

All participants will be asked to provide a weekly urine sample during weeks 9-12 and 21-24. UDS will be tested for opiate/heroin use for the primary outcome measure (9-12) and secondary outcome measures (21-24) and not for the purposes of the CM intervention. All participants will receive a research interview at weeks 12 and 24. Attendance at the 12 potential keyworker sessions and compliance with specified clinic dates and times will be recorded.

We will collect observational data from researcher field notes across the sample of clusters in all study arms. However, only a sub-set of the CM sites will be selected for the process evaluation focus groups which will be held with (a) keyworkers who have participated in the trial (to understand the CM intervention and trial procedures) and (b) service users (to explore their experience of CM and

trial procedures). We will separately interview the managers (and consultants depending upon involvement).

[INSERT FIGURE 1] Trial flowchart

OST (opiate substitution therapy); TAU (treatment as usual); CM (contingency management).

Sample size

The primary outcomes will be analysed as the proportion of heroin/opiate free UDS results during weeks 9-12. A recruitment of 20 participants per cluster in 33 clusters will yield over 80% power with a type 1 error rate of 5% to detect an effect size of 0.39.

Lussier's meta-analysis reported three studies with opiate use as an outcome measure (CM vs control) with a mean weighted effect size of 0.39 [5]. Prendergast et al [6] reported a meta-analysis on CM for treatment of substance use disorder which revealed a larger effect size of 0.65 in treating opiate use. However the majority of studies in the meta-analysis used methadone as the CM incentive, whereas we focus on vouchers. Thus we have used the more conservative effect size of 0.39 to calculate the sample size.

Applying these results to a simple randomised control trial requires 111 participants per arm providing 80% power for a 2-sided test at 5% significance (assuming 5% loss to trial through non-availability e.g. prison). To account for possible cluster effects the sample size will be increased by an inflation factor of 1.95, assuming an intra-class correlation (ICC) of 0.05 on the basis of previous studies [5, 6] with 20 participants per cluster and 11 clusters per intervention - 220 (~111X1.95) participants per arm. We have taken a conservative approach to power calculation considering one of the CM conditions vs TAU. Thus each intervention will be trialled in 11 sites, recruiting 20 or more per site (n=660 in total, 220 per trial intervention, 33 clusters in total).

We were given the opportunity by the sponsor to recalculate the sample size needed at each cluster when we had recruited 13 cluster's due to the attrition rate being 10%; larger than we expected. We increased to number needed to recruit from 20 to 22 per site.

Process evaluation: We will purposively select 5 out of the 11 sites in the abstinence arm and 5 out of the 11 sites in the attendance arm. The sampling process will reflect the variation in structure (locality/provider) treatment process (usual urinalysis and keyworker arrangements) and progress with trial (good or poor recruitment and retention during intervention phases.)

Randomisation

Randomisation units are clusters (clinics). The randomisation is undertaken independently by the Kings Clinical Trials Unit (Institute of Psychiatry, Psychology and Neuroscience).

Clinics are stratified by type of service provider (NHS or non-NHS). This stratification factor was chosen as we believed that this was the most politically sensitive and it was therefore important that the type of service provider be equally distributed between treatment interventions arms.

Clusters are assigned to treatments using random permuted blocks within strata using a block length of 3 in a 1:1:1 allocation ratio. Eleven clusters are randomly allocated to each trial arm:

1. TAU, control condition: OST with 12 weekly keywork sessions with no positive reinforcement;

2. CM condition 'attendance': OST with12 weekly keywork sessions with positive reinforcement for on-time attendance at keywork sessions, 12 week programme

3. CM condition 'abstinence': OST with 12 weekly keywork sessions with positive reinforcement for on-time attendance at keywork sessions and the provision of UDS (weeks 1-4) negative for opiates (weeks 5-12), 12 week programme

Blinding

Due to the nature of the intervention being studied and the necessity for both clinician and patient to be aware of the treatment protocol, there will be no attempt at blinding either the subject or the clinicians at the clinics. The researchers also cannot be blinded to treatment allocation due to the necessity for them to monitor the trial at the clinics. The trial statistician will remain blinded throughout the study until the database is locked, analysis complete and study unblinded.

Data collection, management and analysis

Data collection

Each assessment nurse/drugs worker will inform new participants entering the drug treatment clinic and receiving opiate drug treatment of the trial by giving them a Participant Information Sheet, screen them for eligibility and take informed written consent. If eligible (and providing informed consent) participants will be referred to see the researcher either the same day or the next day. The researcher will meet with them to conduct a baseline interview, check they have provided informed consent and reveal which trial treatment they have been allocated to. Participants will then be provided with more detailed information about the treatment they will receive.

Researchers will ask participants for their consent to retain contact and tracking information (postal addresses and telephone numbers) in order to recruit subjects to follow-up interviews and qualitative interviews or focus groups as part of the process evaluation.

Participants will be asked to provide UDS samples at weeks 9-12 and weeks 21-24. These anonymised samples will be sent through the post to Kings College Hospital Pathology Laboratory for analysis. Anonymised results will be entered onto an electronic database at the laboratory and sent directly to the Trial Data Manager at KCL CTU. The Data Manager will check these results against hard copy reports from the laboratory and will check participants' initials, trial ID and date that the urine was provided against data obtained and entered into MACRO; InferMed Ltd (Good Clinical Practice (GCP) compliant electronic data collection system for clinical research) by the research team. Services will not receive individual results. Participants will be told that these results will not be disclosed to their treatment services and they are for research purposes only.

Data management

Quantitative data will be recorded coded and entered into MACRO which is hosted on a dedicated server at King's College London. The King's College London Clinical Trials Unit will design, set up and host the database and maintain it throughout the trial. At the end of data entry the database will be locked. A Data Monitoring and Ethics Committee (DMEC) has been established. DMEC members are independent from the sponsor and have no conflict of interest; and include experts in biostatistics and addiction science. The DMEC will make recommendations to the Trial Steering Committee (TSC) in relation to conduct of the trial. In addition, a research management group consisting of principal investigators, co-investigators, researchers and team members has been formed and will meet monthly to monitor progress of the trial

Statistical methods

Quantitative data analysis will be performed in STATA V14.0. A statistical analysis plan will be prepared and discussed with the Data Monitoring Committee and Trial Steering Committee before data collection is complete. Analyses will be carried out by the trial statistician and trial health economist. There are no planned interim analyses. The analysis of the data will be conducted once the trial database has closed. The significance level will be 5% (2-sided) for all specified main and secondary analyses with estimates and confidence intervals presented for all effects.

The primary analyses of efficacy will be based on the intention-to-treat sample, utilising all available follow-up data from all randomised participants. All randomised participants will be analysed in the groups to which they were originally allocated to, regardless of whether they actually retained that specific treatment over the course of the trail or not. Participants who withdraw consent for use of their data will not be included in any analyses.

All descriptive analyses, recruitment rate, consent rate, loss to follow-up, departures from randomised treatment and the prevalence of serious adverse events will be reported post-randomisation and summarised by treatment arm over the course of the study. All causes of withdrawal from randomised treatment will be reported. Summaries will be presented as means and standard deviation of those variables that are approximately normally distributed, or medians and IQRs for skewed variables. Categorical variables will be summarised as frequencies and percentages. Transformations will be used when distributional assumptions are not fulfilled for inferential tests on a continuous measure.

We will examine and account for the influence of clustering at the site level on the outcomes. All models will adjust for stratification factor (NHS or non NHS) and randomised treatment.

The main objective of the statistical analyses is to assess the effect of the two active CM arms on the primary outcome, opioid tested urines, at the primary assessment time points weeks 9 to 12 compared to the control arm. A total score for this period will be calculated for each participant. This summary score will be analysed within a generalised linear model (GLM) framework, specifying an ordinal outcome. In Stata GLLAMM or a mixed effects GLM will allow for the clustering effects. This framework can be repeated for urine results 21 to 24.

The clinical assessments over the study period will also be evaluated within a Linear Mixed Model (LMM) framework. To allow for correlation between outcomes on the same individual participants, subject wise random intercepts will be used. Including a treatment × time interaction term in the model will allow treatment differences to be estimated for each time point separately. Between treatment retention and adherence will be evaluated with logistic regression.

Particularly given the nature and circumstances of the study population and the observed attrition in trials of OST, there is expected to be some missing data in the post-treatment outcomes variables. The analyses are based on maximum likelihood and will provide valid inferences under a missing at random (MAR) missingness mechanism. We will explore predictors of missingness, if deemed suitable for adjustment we will include these as explanatory variables in the analyses [31]. If post randomisation or unsuitable baseline variables are identified a Multiple Imputation model will be considered (32).

Reporting of results will be in accordance with the principles of Consolidated Standards of Reporting Trials(-CONSORT) statements extended for cluster randomised controlled trial (RCT)[33].

Economic evaluation

Economic evaluation will explore relative costs and cost-effectiveness of CM intervention strategies compared to TAU at 24 weeks follow-up. A societal perspective will be taken including all NHS and personal social services (PSS) used, as well as criminal justice sector resources and lost productivity. The primary economic outcome will be based on the results of the urinalysis of four weekly samples collected before the final follow-up interview (week 24). The 24-week follow up was chosen because it is the most relevant time horizon for policy makers as it provides information on the longer term impact of CM on costs and outcomes. A secondary analysis will explore cost-utility in terms of quality-adjusted life years (QALYs) calculated using the EQ-5D-3L previously used in economic evaluations of treatments for heroin dependence. Whilst the National Institute for Health and Clinical Care Excellence (NICE) has a preference for an NHS/PSS personal social services (PSS) perspective [34], this perspective is considered too narrow for economic evaluations within the complex mental health field. Addictions have a significant impact on many aspects of an individual's life, including their physical and mental health status, their social and family functioning and their ability to work. Thus, in the recent NICE examinations of drug misuse treatment, NICE took the unusual step of considering wider societal costs as well as the more restricted NHS/PSS perspective [34]. From the perspective of the wider community, addictions have a substantial impact on the criminal justice sector, as well as the productive economy. From a welfare economics standpoint, it would be inappropriate to exclude these additional costs (or benefits) from the proposed analysis. However, results will be reported by sector and separate analyses will explore the narrower NHS/PSS perspective, to help inform comparative resource allocation decisions from a policy perspective.

For the economic evaluation, complete case data on the mean resources used, costs and outcomes will be presented. All analyses will be carried out with missing cost and outcome data imputed using multiple imputation by chained equations (MICE) [35]. All analyses will be adjusted for the baseline costs and/or outcome variables of interest, stratification variables (NHS, non-NHS) and clustering (site). Cost-effectiveness will be assessed by estimating incremental cost-effectiveness ratios (ICERs), both for the primary clinical outcome and QALYs calculated using the EQ–5D measure of health-related quality of life [36]. A joint distribution of incremental mean costs and effects for the

two groups will be generated using non-parametric bootstrapping to explore the probability that one of the treatments is the better choice, subject to the NICE 'willingness-to-pay' threshold of £20,000 to £30,000 per QALY [36] or for the clinical outcome a review of the cost-effectiveness literature [37]. Uncertainty around the cost and effectiveness estimates will be represented by cost-effectiveness acceptability curves[38]. Sensitivity analysis will be used to explore uncertainty around 1) the impact of missing data using complete case analysis; and 2) the perspective (varied from societal in the base case to NHS/PSS).

Process evaluation

In order to explore intervention process and outcome generation within the trial we will implement a process evaluation. This will seek to identify contextual factors and causal mechanisms associated with variation in outcome, to better understand how and why the intervention(s) do or do not work, and the process and impact of delivering CM on services, clinicians and service users.

To address these issues and the research questions described above, mixed methods will be used comprising direct observation, quantitative service activity data, and interviews and focus groups with staff and clients and an attitudinal survey conducted with staff.

Direct observation within the services where CM is delivered allows us to observe the actions of service users and staff in situ and talk to people about any issues as they arise. In this way we record what people actually do as opposed to what they say they do [39]. For this purpose the researchers in each clinic will be perceived as the research instrument. Observation will take place opportunistically but longitudinally and recorded in chronological field notes. The recordings will gather information about the context, interactions, delivery and implementation of the interventions as they occur fulfilling a number of functions: They can be used to record what actually happens in the service; relay information enabling team members to keep abreast of developments impacting on the trial; the practice of writing the field notes enables clarity of thought about issues that have arisen and require action. All trial researchers will complete structured field notes recording the conduct of the trial at each site throughout the recruitment and intervention phases. Specific details reported by staff or participants about session may also be recorded. These observations will help to describe and understand the context within which any variation in practice are generated, and the circumstances in which breaches of protocol or failures to maintain fidelity may occur. The field notes will be written up at the end of the session by the researcher, fully anonymised and entered into Nvivo for thematic analysis.

Quantitative service activity data are being collected through a structured instrument which records the keyworkers work with each client. This will measure attendance, compliance with intervention procedures, engagement and the content of keywork sessions. Service users will be asked to complete a measure of therapeutic alliance at baseline, weeks 4, 8 and 12.

The process evaluation includes in-depth ***qualitative interviews and focus-groups*** with team managers, staff and service-users. Areas of investigation will include (a) factors that promote and hinder the acceptability, delivery and take-up of CM and (b) assessment of the relationships between treatment process, contextual factors and outcomes, and (for staff) impact of CM on

service culture. Recorded consultations will be used to assess fidelity with CM. This will occur in both CM arms. The information and themes arising from data gathered will be fed back to the research team.

Interviews and focus groups with staff and service users are taking place in the clinic once at least half of the participants have completed their intervention phase and will explore the experiences and perspectives of the CM intervention amongst subjects exhibiting different levels of adherence to keywork appointments . The topic guide will be informed by CM literature, previous research conducted by the authors in CM [11] and the field notes recorded prior to and during the intervention as well as feedback and suggestions from the user group and advisory committee. It will be refined during the research process by incorporating emergent themes. Trial recruitment will be a key theme within the topic guides for each. The manager and key workers providing the keywork sessions will be approached and asked to participate in an interview as key informants. Purposive sampling will be used to decide exactly who should be asked to participate in the two sets of focus groups consisting of other staff members and services users [40] Service users will be approached through their key worker. Focus groups will be used for this part of the process evaluation to encouraging discussion about topics related to the CM intervention through interaction from clients who have all participated in the trial [41].

A ***survey of staff attitudes*** towards the CM intervention is also being conducted. This involves surveys at pre- and post-intervention time points. (i.e. Pre-intervention: before CM training and intervention delivery; Post-intervention: when all participants in the cluster have completed the intervention.) These data will be compared to assess attitudes towards CM and measure whether attitudes change after involvement in delivery of the intervention.

Assessment of treatment adherence*.* The first part of all trial keywork sessions (i.e. only the part of the session during which CM is delivered) are being audio recorded and uploaded onto a secure audio recording web site held by the KCL CTU. A random sample of 40 recordings will be analysed. These will be stratified by CM treatment allocation and keywork sessions type and outcome. Specifically we will sample sessions at which participants are (a) compliant with clinic times, and provide urine sample negative for opiates and receive the incentive; (b) compliant with clinic times, and receive the incentive; (c) compliant with clinic times but fail to provide a urine sample negative for opiates and do not receive the incentive; and (d) non-compliant with clinic times and do not receive the incentive).

These recordings will be independently rated by two reviewers for adherence to the intervention protocol to assess fidelity using a bespoke measurement scale. Recordings from supervision sessions will be reviewed by researchers to assess fidelity to CM.

Serious Adverse Events

Occurrences of serious adverse events are monitored. Information about the occurrence of any adverse events is sought at all scheduled assessments. All serious adverse events reported in the study will be notified to the overviewing ethics committees.

Discussion

The PRAISe trial is a large cluster randomised controlled trial comparing CM targeted at 'abstinence' or 'attendance' versus no CM and delivered at 12 weekly keywork sessions as part of OST. There has been good evidence from international research for the effectiveness of CM but CM has not been used in a consistent way in UK NHS drug treatment settings. The authors seek to replicate the findings from international research while also ensuing that the design and implementation of the CM intervention is appropriate to a UK NHS setting. This is to ensure that if found to be effective CM could be rolled out into routine setting. Some aspects of the research design were modified for a UK setting these including training existing staff rather than inserting CM counsellors and delivering CM once a week (asking for a UDS once a week) rather than multiple times a week. The decision to have just one UDS per week was a pragmatic one influenced by the finite resources available to UK treatment services. We were advised that multiple tests per week would have been beyond the resources of treatment services and thus impossible to implement (even if evidence-based). We therefore evaluated a model of CM which had a testing regime that was more likely to be feasible to implement under real-world conditions.

Previous research by the authors has demonstrated that CM (using praise and modest financial incentives) significantly increases the proportion completing hepatitis B vaccinations compared to those not receiving financial incentives [11]. This suggests that CM can effectively promote attendance and short term behaviour change. For CM to be effective in targeting clinical outcomes such as abstinence, research needs to demonstrate that CM can promote long term behaviour change too. What has been unclear is whether any benefit derived from CM comes from a direct effect of CM aimed at the selected target behaviour or is a benefit from CM- improved attendance at treatment sessions (and possibly consequently improved retention in treatment). By assessing both CM targeted at 'abstinence' and CM targeted at 'attendance', the trial aims to answer this question. Hence, the trial aims to assess whether these differing CM schedules are effective in promoting abstinence between weeks 9 and 12 of a 12 -week intervention and subsequent follow-up at 24 weeks to assess whether any behaviour change has been sustained after discontinuation of CM.

There have been major disruptions to the whole of the NHS addiction provider network during the period of site recruitment. A large number of NHS services managed by our collaborating Trusts have been retendered and some are now run by independent providers. In response to this non NHS drug treatment providers providing OST have been additionally recruited. This reflects current addiction service provision and thus enhances the generalisability of participating sites. Findings from this trial will be used to inform policy and future clinical practice in UK addiction services and internationally.

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Figure 1. Consort

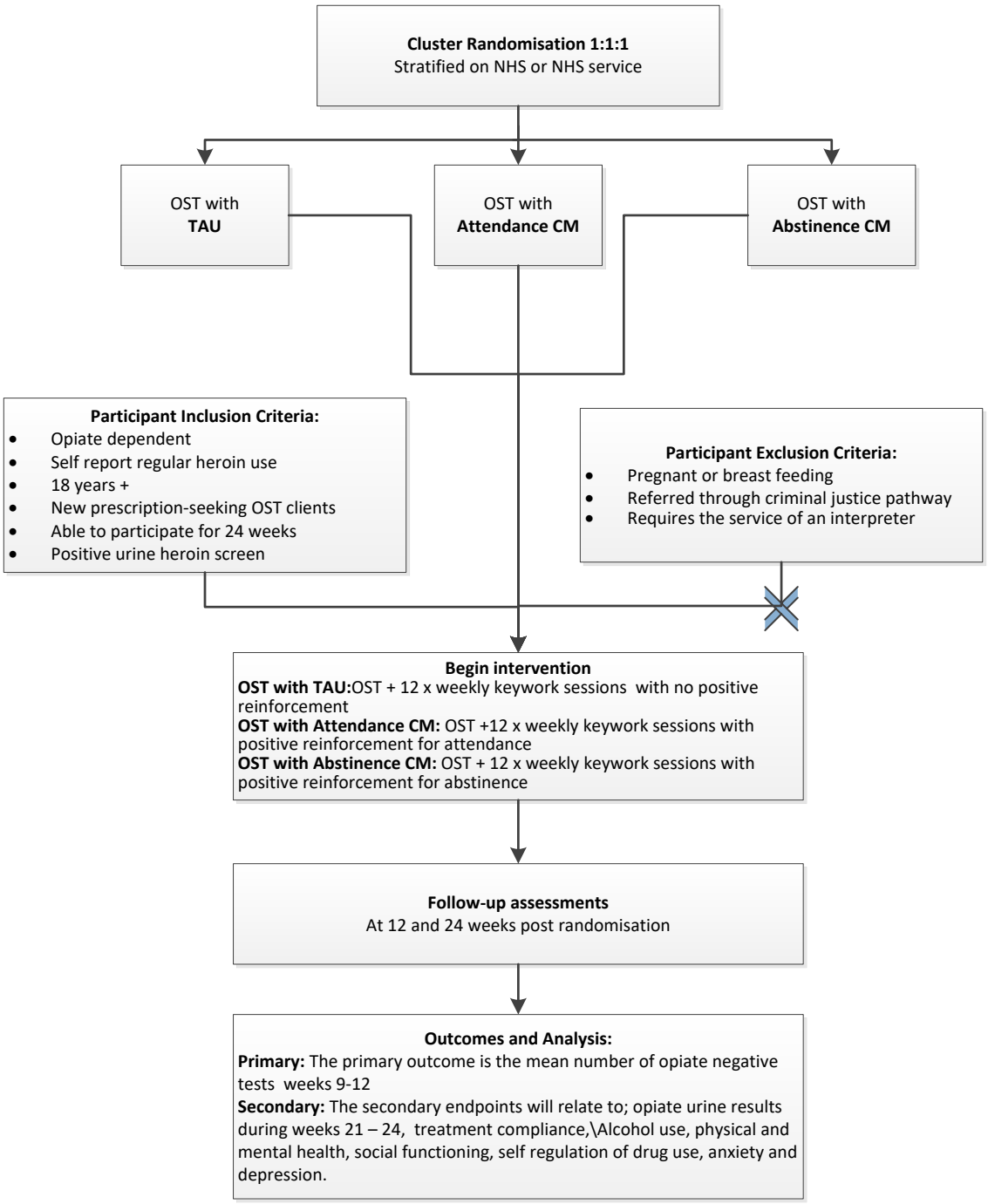

Table 1. Trial procedures & interventions by week and trial arm

Week	**ARM** CONTROL Treatment As Usual Keywork only	**ARM** INTERVENTION CM Attendance Keywork + Positive Reinforcement of attendance	**ARM** INTERVENTION CM Abstinence Keywork + Positive Reinforcement of attendance & abstinence	**TRIAL PROCEDURES**
0		**Baseline assessment**		
1	K	K(PR)	K + U (PRp)	
2	K	K(PR)	K + U(PRp)	
3	K	K(PR)	K + U (PRp)	
4	K	K(PR)	K + U (PRp)	
5	K	K(PR)	K + U(PR)	
6	K	K(PR)	K + U(PR)	
7	K	K(PR)	K + U(PR	
8	K	K(PR)	K + U(PR)	
9	K	K(PR)	K + U(PR)	Research Urine
10	K	K(PR)	K + U(PR)	Research Urine
11	K	K(PR)	K + U(PR)	Research Urine
12	K	K(PR)	K + U(PR)	Research Urine & **12 week Assessment**
13 - 24	Treatment as usual	Treatment as usual	Treatment as usual	Research Urine 21-24 weeks & **24 week Assessment**

Key:
K Keywork sessions without reinforcement of attendance.
K(PR) Keywork sessions with Positive Reinforcement of attendance. Point at which Positive Reinforcement (voucher) (PR) would be given if the target behaviour (attendance at keywork session) attained.
U(PR) Urine testing with Positive Reinforcement. Point at which Positive Reinforcement (PR) (voucher) would be given if the target behaviour (abstinence, defined as provision of a urine sample free of street heroin) is attained (together with attendance at Keywork session)
U(PR*p*) First weeks 1-4 Positive Reinforcement of provision of urine sample (priming weeks) where client will receive reinforcement for providing UDS irrespective of result