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Effectiveness and cost-effectiveness of adjunctive personalised psychosocial intervention in treatment-resistant maintenance opioid agonist therapy: a pragmatic, open-label, randomised controlled trial

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SUMMARY

BACKGROUND: Opioid use disorder (OUD) is a chronic, debilitating and costly disorder with an unprecedented increase in prevalence in many countries. Maintenance opioid agonist therapy (OAT) with oral methadone or sublingual buprenorphine is the first-line, empirically-supported treatment. However, many patients do not stop using illicit or non-prescribed drugs while enrolled in OAT. To address this, we developed a personalised psychosocial intervention (PSI) as an adjunct to continued OAT implemented with a toolkit of behaviour change techniques. The aim was to estimate if the PSI was effective and cost-effective.

METHODS: This was a pragmatic, open-label, randomised controlled trial at a specialist NHS community addictions clinic in England. We recruited adults enrolled in OAT for a median of 26 weeks (IQR 10-88), voluntarily seeking continued OAT, who were treatment-resistant (defined as using illicit or non-prescribed opioids and/or cocaine on one or more days in the past 28 days at study screening and verified by positive urine drug screen).

Participants were allocated (1:1) by a web-accessed randomisation sequence (stratified by OAT medication, current cocaine use, and current injecting) to receive continued standard OAT (treatment-as-usual, TAU) or standard OAT and personalised PSI. Outcome data were collected by independent research assistants. The primary outcome was treatment response at 18 weeks, defined as abstinence from illicit and non-prescribed opioids and cocaine in the past 28 days recorded by the Treatment Outcomes Profile and negative urine drug screen.

Taking a societal cost perspective, an evaluation of cost-effectiveness was done by taking a wide range of values of willingness-to-pay (WTP) for a unit improvement in the probability of treatment response, and EQ-5D-3L derived quality adjusted life years (QALYs). The planned analysis was intention-to-treat (ITT), including all those who were randomly allocated. This trial is registered with the ISRCTN registry, number ISRCTN69313751.

FINDINGS: Between June 7, 2013 and December 21, 2015, we randomly allocated 136 participants (50%) to the PSI group and 137 participants (50%) to the TAU group. The trial database was locked for analysis on April 19, 2017. In error, we re-randomised three participants. These cases were excluded from all analysis. Due to this error, the analysis is classified as a modified ITT (mITT). All other randomised participants were included.

In the mITT analysis, treatment response was greater in the PSI group (22 [16·3%] of 135) compared to the TAU group (9 [6·7%] of 135; adjusted log odds 1·20, 95% CI 0·01 to 2·37, p-value=0·048). The PSI had a higher probability of being cost-effective than TAU. There was a

probability range of 47% to 87% for WTP thresholds of £0 to £1,000 for a unit Improvement in the probability of treatment response. QALYs were higher in the PSI group than the TAU (mean difference 0·048, 95% CI 0·016 to 0·080, p-value=0·004), with a 60% and 67% probability of cost-effectiveness at the NICE willingness to pay thresholds of £20,000 and £30,000 per QALY, respectively.

There was no statistically significant difference in the number of adverse events. One participant in the TAU group was hospitalised with acute sepsis and died, another was hospitalised with head injury. One participant in the PSI group was hospitalised with a panic attack. None of these severe adverse events was judged to be trial-related.

INTERPRETATION: In maintenance opioid agonist therapy, an adjunctive personalised psychosocial intervention was effective and cost-effective at helping treatment-resistant patients abstain from using illicit and non-prescribed opioids and cocaine. During on-going opioid agonist therapy, a personalised psychosocial intervention can enable treatment to be effectively tailored to individual need.

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RESEARCH IN CONTEXT

Evidence before this study

Including all randomised controlled trials published to November 2006, the UK National Institute of Health and Care Excellence (NICE; Clinical Guideline 51) on psychosocial interventions (PSI) for drug misuse (no amendments or additions since) endorsed only behavioural reinforcement ('contingency management' [CM]), behavioural couple and family interventions, and 12-Step-based groups for opioid use disorder (OUD).

We conducted searches of Cochrane Library, Scopus, Psychinfo and PubMed for relevant systemic reviews, reports of meta-analysis, and individual trial reports of PSI adjunctive to maintenance opioid agonist treatment (OAT) between November 2006 to May 2018. Search terms included, "heroin* (OR cocaine* OR crack OR opiate* OR opioid* OR methadone OR buprenorphine) AND adjunctive OR psychosocial OR psychotherapy", and article types were clinical trials or randomised controlled trials. We identified 191 relevant studies with no study including non-response to OAT as an inclusion criterion.

Added value of this study

This is the first study, to our knowledge, examining the effectiveness of an adjunctive, personalised PSI for patients who are retained in ongoing OAT and are using illicit and non-prescribed opioids and/or cocaine. The results indicated that a personalised PSI is an effective means of helping patients abstain from these drugs (or use them less often) and achieve better social functioning. The economic evaluation indicated that the additional costs of the PSI were more than offset by the significantly greater reductions in crime related costs among intervention participants compared to TAU.

Implication of all the available evidence

Appropriately trained and supervised assistant psychologists can deliver an effective and cost-effective personalised PSI to OAT-resistant patients. This clinical population should be offered a personalised PSI.

INTRODUCTION

Opioid use disorder (OUD) is a chronic and debilitating psychiatric condition associated with a high global burden of disease [1] and substantial social costs (£13·9 billion in England and Wales in 2014) [2]. Internationally in recent years, there has been an unprecedented increase in the prevalence of OUD and opioid poisoning mortality [3].

The first-line intervention for OUD is maintenance opioid agonist treatment (OAT) with oral methadone (a full *mu*-opioid receptor agonist; usual dose: 60-120 mg/day) or sublingual buprenorphine (a partial *mu*-agonist [also available in a 4:1 formulation with naloxone]; usual dose 12-24 mg/day). In the United Kingdom (UK), patients are enrolled in community treatment services providing OAT, receive medical management and are assigned a clinical key worker (often a nurse) for general drug counselling and support [4].

Systematic review evidence from trials of OAT for illicit OUD [5] suggests that flexible dose methadone maintenance is more effective than flexible dose buprenorphine maintenance at retaining patients (six trials with 837 participants; relative risk [RR] 0·82, 95% confidence interval [CI] 0·69 to 0·96), but with no statistical difference for the suppression of heroin use (mean difference -0·12 days, 95% CI -0·32 to 0·12). For pharmaceutical OUD [6], there is no statistically significant difference between methadone and buprenorphine for retention (three studies, 360 participants, RR 0·69, 95% CI 0·39 to 1·22) or suppression of non-prescribed opioid use (mean difference -1·41 days, 95% CI -3·37 to 0·55).

There are three issues of concern about OAT in routine practice. Despite efforts to select the best medication and dose for each patient, many discontinue treatment [7]. Other patients are retained but may not take their prescription as directed or continue to use illicit or non-prescribed pharmaceutical opioids (herein 'opioids'), or relapse to pre-treatment levels. For example, in an English study of 12,745 patients enrolled for 12-26 weeks, 63·5% were using opioids on 10 or more of the past 28 days at clinical review [8]. Cocaine use disorder (particularly with the base form *crack*) [9], and co-occurring anxiety and mood disorders are prevalent in the clinical OUD population and can moderate OAT engagement and response [10,11]. Family relationships and social networks can either support or hinder recovery [12].

Adjunctive psychosocial intervention (PSI) in the form of a stand-alone, manual-driven therapy has been extensively trialled as a strategy to improve treatment efficacy. However, the UK National Institute for Health and Care Excellence (NICE) endorses only behavioural reinforcement ('contingency management' [CM]), behavioural couple and family interventions, and 12-Step-based groups [13]. A subsequent Cochrane review of 13 different interventions was pessimistic, concluding that OAT effectiveness is not enhanced by the addition of any PSI support [14]. Our focus has been on OAT-resistant patients — a prevalent but understudied

clinical population. The standard design for efficacy studies in the substance use disorders field has been for practitioners to follow a therapist manual, so that patients are offered a set progression of interventions. This has advantages for fidelity and internal validity of inferences about efficacy; however, it offers little flexibility to tailor treatment and adapt it to the patient's personal preference, subsequent response and evaluation.

As an alternative, we developed a case formulation-driven approach to tailor behaviour change components for each patient [15]. Common in mental health treatment, a case formulation is a collaborative discussion to develop a working hypothesis of how a disorder is being maintained, focusing on cognitive, affective and interpersonal factors. This assessment (usually supplemented with information gathered from rating scales and clinical case conference) informs the selection of interventions. As treatment proceeds, the patient and therapist monitor review progress, adapt therapeutic components as required and update the formulation. This approach has not been used before in studies of adjunctive PSI during OAT.

We report the results of a randomised controlled trial of the effectiveness and cost-effectiveness of an adjunctive, case-formulation driven, PSI for treatment-resistant patients in on-going OAT.

METHODS

Study design, setting and participants

In this pragmatic, parallel-group, open-label, randomised controlled trial (the Addiction Recovery Clinic [ARC] study), our aim was to determine the effectiveness of a personalised PSI adjunctive to on-going OAT, compared to OAT treatment-as-usual (TAU). The study was done at a specialist NHS community addictions service, operated by South London and Maudsley NHS Trust. ARC also included a subsidiary biomarker study of treatment response (results reported elsewhere).

Eligible patients were adults aged ≥18 years, meeting criteria for opioid and/or cocaine dependence in the past 12 months (MINI international neuropsychiatric interview [16] for Diagnostic and Statistical Manual of Mental Disorders-IV [DSM-IV] [17]; opioid use disorder (OUD) and cocaine use disorder for consistency with contemporary DSM-5 terminology), voluntarily seeking continued oral maintenance OAT with oral methadone, sublingual buprenorphine, or sublingual buprenorphine-naloxone.

At study enrolment, we set six weeks as the minimum duration of OAT in the current episode, with no upper limit. All participants were classified as non-responders by structured interview (Treatment Outcome Profile [TOP] [18]) on the basis of the patient’s report of opioid and/or

cocaine use on one or more day in the past 28 days (verified by positive urine drug screen [UDS]). Otherwise eligible patients were excluded if they had a suicide plan in the past month or an attempt in the past six months; medically uncontrolled health conditions; current legal proceedings risking incarceration; or if they had participated in a substance use disorder treatment intervention study in the past six months.

Potential participants were identified via the service's electronic patient case record. They were told the purpose of the study was to determine the effectiveness of a PSI for people in OAT who wanted help to abstain from opioids and/or cocaine. Patients interested in the study attended the service to receive written information, complete screening and give their written informed consent.

Ethical approval for the study was granted by the UK Health Research Authority (London-Bromley Research Ethics Committee: 13/LO/0640). Details of the study protocol and PSI have been published [19]. In this article, the research procedures, clinical interventions and results are reported following the CONSORT extension for pragmatic trials [20]; the TIDieR guideline for complex interventions [21]; and the CHEERS guideline for cost-effectiveness evaluations [22].

Randomisation and masking

Following baseline data collection, participants were randomly allocated (1:1) to the PSI or TAU group, with stratification by OAT medication (methadone or buprenorphine), and any use of cocaine, or illicit drug injecting in the past 28 days. The King's College London Clinical Trials Unit developed and managed a web-accessed, password-protected randomisation sequence, with random permuted blocks of size two or four. After each participant-to-group allocation, the randomisation system issued a confirmatory email and the participant was immediately informed. Due to the open-label nature of OAT and PSI in this pragmatic trial, it was not feasible to mask participants, clinicians or the independent research assistants to group allocation.

Procedures

After consent, all participants attended a research assistant-administered, face-to-face, 60-minute baseline interview. This included a calendar-prompt ('time-line follow-back') procedure in the TOP to record opioid and cocaine use in the past 28 days, and completion of the following instruments and procedures:

(1) Montreal Cognitive Assessment (MoCA, version 7.1; score range: 0-30; ≥26 is the cut-off for current normal functioning [23]);

(2) the 9-item depression version of the Patient Health Questionnaire (PHQ-9; score range: 0-27; ≥10 is the cut-off for moderate level symptoms during the past two weeks [24]);

(3) the 7-item Generalized Anxiety Disorder Scale (GAD-7; score range: 0-21; ≥10 is the cut-off for moderate level symptoms during the past two weeks [25]);

(4) the Work and Social Adjustment Scale (WSAS; impairment attributed to opioid and/or cocaine use disorder; score range: 0-40; ≥10 is the cut-off for social functioning impairment during the past two weeks [26]);

(5) the three-level version of the EuroQol measure of health-related quality of life (EQ-5D-3L) for the calculation of quality adjusted life years (QALYs) [27]; and

(6) A tamper-proof, instant result UDS device with temperature sensor (Integrated E-Z Split Key Cup; www.concateno.com) to detect for morphine (opioids) and benzoylecgonine (cocaine's primary metabolite) with 300ng/ml detection sensitivity.

Prior to treatment in the PSI group, a 90-minute assessment and case formulation were done by a senior psychologist (accredited by the British Association of Behavioural and Cognitive Psychotherapy [BABCP]) and an assistant psychologist. Shorter assessment appointments at the clinic were arranged for a minority of participants (e.g. those with depression). We used a patient-centred communication style and charts of relationships and supports [28]. All case formulation and clinical team discussions were completed in a maximum of six weeks. Treatment plans were reviewed weekly in a case conference attended by all therapists and the senior clinicians in the study.

We assembled a toolbox of psychological change methods including: CBT for craving skills and behavioural experiments to modify disorder maintaining beliefs [29]; CM to reinforce abstinence, recovery activities and clinic attendance using retail store vouchers as the reinforcer [13]; 12-step group facilitation [30]; Behavioural Activation for depression [31]; and techniques to engage partners and family members in the participant's treatment [32]. The case formulation, MoCA total score and the PHQ-9, GAD-7 and WSAS items and total score were used to inform the content of the PSI and all participants were encouraged to select one of the three CM behavioural targets.

The PSI was designed for completion in 12 weeks to coincide with most discrete psychotherapies recommended by NICE. However, we decided to optionally allow two additional weeks to replace any treatment sessions missed due to hospital attendance, police

custody, or therapist absence. Each session was weekly, face-to-face, for 60 minutes; with an option for 30-minute sessions twice-weekly to help attention for participants with depression.

The PSI assistant psychologists were graduates or had a master's degree. They received fortnightly individual supervision and weekly group supervision with senior psychologists. PSI sessions were audio-recorded with consent. An independent BABCP-accredited consultant psychologist rated a random five percent of these recordings for therapist competence on the 12-item Cognitive Therapy Scale-Revised (CTS-R) [33]. On each item, a score of ≥3 indicated competent practice.

All participants had scheduled fortnightly individual appointments (~30 minutes) at the service with their keyworker for drug counselling. Adjustments to medication dose were made during periodic medical review. Participants in the TAU group were not offered any additional intervention.

Research assistant-administered interviews to record drug use and UDS data were scheduled at 6, 10, 14 and 18-weeks post-randomisation. For each visit, participants received public transport travel support and £20 in retail store vouchers for completing research measures. In our clinical experience, some patients in OAT leave for many weeks but then re-present requesting that their medication is re-started. Rather than accept low attrition, we anticipated a long duration of follow-up for some participants.

Outcomes

The primary outcome was treatment response status at 18 weeks post-randomisation after the 12 to 14-week PSI. Treatment responders were defined as those who: (1) reported no use of opioids or cocaine during the 28 days prior to the final follow-up interview and (2) provided one or more negative UDS tests for heroin and cocaine in the 28 days prior to final follow-up and no positive tests. We judged that this biochemically-verified measure of abstinence was an appropriate and clinically meaningful indicator for patients who were retained, but not responding to OAT.

At 18 weeks post-randomisation, participants defined as non-responders reported opioid and/or cocaine use on one or more days in the past 28 days or had incongruent self-report and UDS data (i.e. they reported total abstinence, but their UDS result indicated use of opioids, cocaine or both). Conservatively, all missing clinical visits for a scheduled UDS procedure were imputed positive for opioid and cocaine use.

Secondary outcomes (recorded at baseline and 18-week follow-up) were: the number of abstinent days for opioids and cocaine in the past 28 days recorded by TOP; retention in treatment (defined as the number of days from randomisation to the endpoint or exit); treatment adherence (operationalised as attendance at one-third or more scheduled sessions); mean scores on the MoCa (alternate version at follow-up), PHQ-9, GAD-7, WSAS and EQ-5D-3L; and mean costs of service use measured using a version of the Adult Service Use Schedule (AD-SUS) developed for drug and alcohol use disorder populations, described below.

All adverse events — recorded by seriousness and likely relationship to the study — were reviewed by the senior investigators and the DMC.

Statistical Analysis

Our sample size calculation was based on the NICE Clinical Guideline 51 meta-analysis of adjunctive PSI during OAT with opioid abstinence as the outcome [13]. Taking an 18% difference in abstinence for the PSI (an RR of 1·75), and with 16% inflation for attrition (a rate of drop-out after six months of OAT in English specialist clinics [8]), we estimated that 368 participants recruited would give 90% power to detect a group difference, with a two-sided, five percent alpha. The statistical analysis plan was agreed with the Trial Management Group, the Data Monitoring Committee (DMC), and the Trial Steering Committee and summarised in the published protocol [19]. All reported analyses were conducted in accordance with the published protocol, with no changes made except that log time was used in the model (see section on ‘analysis of the primary outcome’). The analysis of effectiveness was by intention-to-treat (ITT).

Stata (version 14·1) was used for all clinical and economic analyses. For the primary outcome, we estimated the group difference in binary responder status at each assessment point using a mixed-effects, maximum likelihood logistic regression model (command: *meqrlogit*). This included randomisation group, the study stratification factors and time of the assessments (days post-randomisation, both linear and quadratic log time) as covariates. We fitted a group x time interaction term to estimate treatment effects 18 weeks post-randomisation, with a participant-varying random intercept to account for correlation between repeated measures on the same participant.

Time-specific estimates of treatment effect (expressed as log-odds) were obtained as functions of model coefficients (command: *lincom*) with 95% CI based on the parameter covariance matrix. The delta method was used to calculate CI for absolute proportions. Differences in log-odds were displayed by post-estimation, with time and group covariates

fixed (command: *margins*). A sensitivity analysis was done to determine the robustness of outlying assessments included in the effectiveness model by removing endpoint assessment data collected 24 weeks post-randomisation.

The analysis of the secondary outcome measures was done using a generalised, repeated measures, linear mixed-model framework with the following covariates: randomisation group, baseline score of the outcome measure, stratification factors, time of the assessment, and a group x time interaction term. For an adjusted treatment effect, we calculated Cohen's *d* effect size (ES) using the within-group pooled standard deviation (SD). Between treatment retention was evaluated using an unadjusted and adjusted Kaplan-Meier survival estimate and a log-rank test of equality between groups. Personal social services included services provided by local authorities including accommodation, day care and drop in centres.

Costs and cost-effectiveness

We took a broad societal perspective, including NHS and personal social services (NHS/PSS), productivity losses (time off work due to illness), and criminal activity — the latter important for treatment research on substance use disorder [34]. The impact of treatments on crime is recognised by NICE as an appropriate extension to the NHS/PSS perspective for drug treatment evaluation [35]. Personal social services included services provided by local authorities including accommodation, day care and drop-in centres.

Our pre-specified primary economic evaluation assessed cost-effectiveness in terms of the primary clinical outcome at 18-weeks converted to an average marginal effect. This expressed the probability of a positive treatment response. With a broad societal perspective, we did a secondary evaluation of cost-effectiveness in terms of QALYs, derived from the EQ-5D-3L. Sensitivity analyses explored cost-effectiveness based on the NICE reference case, with QALYs and the narrower NHS/PSS perspective [35]. The health states described in the EQ-5D-3L were assigned a utility weight or score using responses from a representative sample of adults in the UK [36]. These weights were applied to the time between interviews and QALYs calculated by area-under-the-curve.

The version of the AD-SUS in the current study (available from the authors on request) included a section with questions about crimes committed by, and against, participants. We also collected data on the use of the PSI intervention, keyworker sessions and collated methadone and buprenorphine prescriptions from the electronic patient record.

We applied unit costs (see **Tables S1-S3** in the Appendix), for the 2015/16 financial year, uprated where necessary using the Hospital and Community Health Services Index [37]. Discounting was unnecessary because the follow-up period was less than 12 months.

We costed the PSI using a standard micro-costing approach [38]. Therapist salary costs included employer costs (national insurance and superannuation) and overheads (buildings, management, administration and utilities). We adjusted for indirect time using questionnaires completed by therapists and keyworkers on the ratio of direct to indirect time (i.e. face-to face contact, and therapy preparation, notes, supervision, and training). National unit costs were applied to all other health and social care services [39], OAT medication [40], and criminal activity. We took a human capital approach to value productivity losses [41].

All economic analyses included adjustment for study stratification factors and baseline values. Mean cost differences were analysed by *t*-test, with bias-corrected non-parametric bootstrapping. We imputed missing cost and outcome data with multiple imputation using chained equations, under the assumption that these data were missing-at-random. Variables used in the multiple imputation model included the stratification factors, duration of follow up, baseline outcome score and baseline costs.

Cost-effectiveness was explored in two steps. First, we calculated incremental cost-effectiveness ratios by dividing the difference in mean costs between the two groups by the difference in mean outcomes. Then we explored uncertainty around these point estimates using scatterplots of bootstrapped incremental mean cost and group outcome differences and cost-effectiveness acceptability curves. This indicated the probability that each treatment is the optimal choice for different values of willingness-to-pay (WTP) for a unit improvement in the probability of treatment response (a nominal £0 to £1,000 per one percentage point increase), and £0 to £30,000 per QALY, as preferred by NICE [35].

This trial is registered with the ISRCTN registry, number ISRCTN69313751.

Role of the funding source

The funder for the ARC trial had no role in the study design, data collection, analysis and interpretation, or report writing. The corresponding author had full access to all study data and took final responsibility for the decision to submit for publication.

RESULTS

Participants were recruited between June 7, 2013 and December 21, 2015. The trial database was locked for analysis on April 19, 2017 ending the study. 348 patients were assessed for

eligibility (15 [4%] ineligible and 60 [17%] declining to participate). 273 participants gave their signed consent and were randomised: 137 (50%) to the TAU group and 136 (50%) to the PSI group. The trial profile is shown in **Figure 1**.

Three patients who were allocated to the TAU group and completed the study, re-presented to take part again at a screening session administered by a different worker. All three patients did not declare that they had been in the study before. In error, the worker did not properly check the participant list and these patients were randomised again: one allocated to the PSI group and two allocated to the TAU group. The patient allocated to the PSI group was detected before the start of their case formulation. The three patients were informed of the error and continued in their original allocation of TAU. We consulted the DMC and published guidance [42]. These cases are included in the trial flow and tabulated sample characteristics, but they were removed from all subsequent analysis. The remaining 270 participants formed a modified ITT population (mITT).

Between group allocation and the start of the PSI, 12 participants withdrew from the PSI group and 13 participants withdrew from the TAU group. After the intervention began three participants withdrew from the PSI group, and five withdrew from the TAU group. All of these participants gave their consent for all data collected to be used in the analysis.

Participant and clinical characteristics were well balanced between groups (**Table 1**). All participants met diagnostic criteria for OUD or cocaine use disorder. Overall, in the 28 days before study enrolment (n=273), 250 (92%) used opioids; 228 (84%) used crack cocaine (a minority used powder cocaine: 26 [9·5%]), and 89 (33%) injected drugs. The sample had been enrolled in a current OAT episode for a median of 25·50 weeks (IQR 10-88).

Treatment exposure and fidelity

At the endpoint, 125 (93%) of 135 participants in the PSI group and 124 (92%) of 135 of participants in the TAU group were receiving OAT at the clinic. There were no clinically meaningful group differences in methadone or buprenorphine dose. In the PSI group, participants on methadone were prescribed 57·2 mg/day, and those on buprenorphine were prescribed 11·5 mg/day. In the TAU group, participants on methadone were prescribed 59·3 mg/day and those on buprenorphine were prescribed 10·7 mg/day. Across the study, the PSI was delivered by five assistant psychologists. Each assistant psychologist was independently rated as competent on the CTS-R.

Analysis of the primary outcome

Overall, the median time to the endpoint interview was 19·4 weeks (IQR 12·7 to 121·0), with 10 participants interviewed between 50 and 121 weeks. The median time to endpoint in the PSI group was 22·9 weeks and 18·0 weeks in the TAU group. Due to the unforeseen long duration of follow-up, we decided to use log time from randomisation in all analyses, finding that a quadratic term improved model fit. Models were estimated using maximum likelihood with inferences judged under the assumption that the missing data generating mechanism was missing-at-random. Deviation from missing-at-random was accounted for by including variables that were predictive of missingness in the model. The number of days of opioid use at baseline was predictive of missing data, so this measure was also included in the model.

Table 2 shows the frequencies and **Figure 2A** shows the model-estimated group differences at each follow-up to endpoint. No participant refused to comply with a UDS procedure. At the endpoint, there were 22 (16·3%) of 135 participants in the PSI group and 9 (6·7%) of 135 responders in the TAU group (adjusted log odds 1·20, 95% CI 0·01 to 2·37, p-value=0·048.

Figure 2B displays shows a marginal effects plot of the magnitude of the absolute proportions. The predicted probability of being a treatment responder at primary endpoint was 0·091 in the TAU group and 0·171 in the PSI group.

With removal of endpoint assessment data after 24 weeks for the sensitivity analysis, we estimated stronger evidence of effectiveness for the PSI (adjusted log odds 2·31, 95% CI 0·62 to 4·00, p-value=0·007).

Analysis of secondary outcomes

Compared to the TAU group, the PSI group reported more opioid abstinent days (ES 0·39, 95% CI 0·15 to 0·62, p-value=0·001) and crack cocaine abstinent days (ES 0·27, 95% CI 0·27 to 0·47, p-value=0·009). There was no group difference in abstinence from cocaine powder (ES 0·12, 95% CI -1·13 to 0·36, p-value=0·344).

Figure 2D displays the Kaplan-Meier plot for retention in treatment. There was no group difference in retention, either unadjusted ($\chi^2_{[1]}$ = 1·20, p-value = 0·270) or after adjusting for study covariates ($\chi^2_{[1]}$ = 0·26, p-value = 0·610).

For keyworker contact, 99·3% of the PSI group and 92·6% of the TAU group attended the clinic to receive general counselling and support once or more. The PSI group attended 8·8 scheduled keyworker appointments (SD 5·4, range: 1-33). The TAU group attended 7·5 scheduled keyworker sessions (SD 5·1, range: 0-28). Participants in the PSI group attended

an average of 4·9 sessions (SD 4·9, range: 0-20). 79 (58·5%) attended more than one-third of their scheduled sessions and were classified as adherent.

There was a reduction in OUD-attributed social impairment on the WSAS (ES 0·27, 95% CI 0·04 to 0·50, p-value=0·016), but no group difference in cognitive function, depression or anxiety symptoms (**Table 2** and **Figure 2C**).

Economic Analysis

Complete economic data were available for 95 (70·4%) of 135 participants in the PSI group, and for 104 (77·0%) of 135 participants in the TAU group. **Table S4** in the Appendix shows mean resource use in both groups over the follow-up period. Patients in the PSI group attended an average of five therapy sessions and almost all participants continued to attend drug keyworker sessions, regardless of group allocation. There was little difference between groups in the number of keyworker sessions attended (approximately eight sessions per participant) or the proportion attending (approximately 98%). The use of secondary care, primary care and social care services was broadly similar across the two groups, although the PSI group spent a greater number of nights in hospital on average. Average doses of methadone and buprenorphine were broadly similar. There was little difference in the proportion of the groups reporting criminal activity over the follow-up period. Differences in absenteeism from work were small, with 26% of employed participants in both groups reporting days off work.

Table S5 in the Appendix shows disaggregated imputed mean costs during follow-up alongside tests for differences including multiple imputation and adjustment for pre-specified variables. OUD intervention costs were significantly higher in the PSI group (mean difference £561, SE £60, 95% CI £443 to £680, p-value<0·001), but this was off-set by lower costs of criminal activity among the participants in the PSI group (mean difference -£1,843, SE £3,109, 95% CI -£8,127 to £4,442, p-value=0·557). There was no significant difference in societal costs between the TAU and PSI groups (mean difference -£400, SE £3,416, 95% CI -£7,274 to £6,475, p-value=0·907) or in total NHS/PSS costs between the two groups (mean difference £658, SE £876, 95% CI -£1,070 to £2,388, p-value=0·453).

The probability of treatment response was significantly higher in the PSI group compared to the TAU group (average marginal effect 0·108, SE 0·048, 95% CI 0·012 to 0·238, p-value=0·025). QALYs were also significantly higher in the PSI group than TAU (mean difference 0·048, 95% CI 0·016 to 0·080, p-value=0·004) in adjusted analyses with missing data imputed. Complete case EQ-5D-3L values and QALYs are summarised in **Table S6** in the Appendix. The average value at baseline was slightly higher in the PSI group (0·674)

compared to TAU (0·649). At follow-up, the average values had declined in both the PSI group (-0·014) and TAU (-0·080).

For the primary outcome, **Figure 3** displays a scatterplot of bootstrapped cost and effectiveness pairs for PSI versus TAU with effectiveness measured in terms of treatment response. This shows points falling primarily in the North-East quadrant (PSI more effective and more expensive than TAU) and the South-East quadrant (PSI more effective and cheaper than TAU), with the point estimate and 87% of scatter points falling below the £1,000 per one percentage improvement in the probability of the cost-effectiveness threshold line. The corresponding cost-effectiveness acceptability curve (**Figure S1** in the Appendix) shows that the probability that PSI was cost-effective compared to TAU was greater than 50% at WTP levels of £30 or higher per one percentage point improvement in the probability of treatment response (range 47% at a WTP level of £0 to 87% at a WTP level of £1,000).

For QALYs, **Figure S2** (in the Appendix) shows the scatterplot of bootstrapped cost and QALYs for PSI versus TAU. The probability that PSI was cost-effective compared with TAU was 60% and 67% at the NICE WTP thresholds of £20,000 and £30,000 per QALY (**Figure S4** in the Appendix).

The sensitivity analysis based on the NICE reference case, using QALYs and taking the NHS/PSS perspective was less favourable than the societal perspective, due to the exclusion of the cost of criminal activity. However, while the probability of PSI being cost-effective compared to TAU was only 36% at the NICE threshold of £20,000 per QALY, the probability was 56% at the NICE threshold of £30,000 per QALY (**Figure S4** in the Appendix).

Adverse events

In total, 38 of 273 (13·9%) participants reported an adverse event: 20 of 136 (14·7%) in the PSI group, and 18 of 137 (13·1%) in the TAU group ($\chi^2_{[1]}$ =0·487, p-value=0·490) (**Table 3)**. There were three severe adverse events: in the TAU group, 1 [1%] of 136 died after hospital admission for drug injection-related sepsis, and 1 (1%) of 136 was hospitalised after head injury and later discharged. In the PSI group, 1 (1%) of 137 was hospitalised after a panic attack and later discharged. None of the severe adverse events was judged to be trial-related.

DISCUSSION

Among OAT-resistant patients in the ARC trial, approximately 16% of the group allocated to receive an adjunctive, case-formulation driven, personalised PSI achieved the endpoint defined measure of treatment response (i.e. biochemically-verified, self-reported abstinence from opioids and cocaine in the previous 28 days), compared to 7% of the group receiving

TAU. Participants in the PSI reported more opioid and crack cocaine abstinent days (ES 0·39 and ES 0·27, respectively), and had less social impairment (ES 0·27).

The PSI also represented good value for money, with better outcomes and lower total costs per participant compared to TAU. The probability that the PSI was cost-effective compared to TAU was 60-67% at the NICE willingness to pay thresholds of £20,000 to £30,000 per QALY. It was also cost-effective from the narrower NHS/PSS perspective but only at the upper NICE threshold. However, NICE has acknowledged that reductions in crime due to drug treatment programmes, as observed in this study, are an appropriate extension to the recommended NHS/PSS perspective [36]. Our study suggests that the economic benefits of addiction treatment are largely accounted for by reduced crime and victim costs of crime.

Previous studies of PSI have included a sample of patients with OUD in methadone or buprenorphine maintenance therapy at admission, or after some period of treatment; so a major strength of the ARC study is the focus on patients who were not responding after 26 weeks in treatment. It is also usual for intervention trials to evaluate OST on a single measure of opioid use. We believe our inclusion of cocaine alongside opioid use in the definition of the primary outcome measure was a strength, because the likelihood of abstaining from opioids during OAT has been consistently shown, in our public treatment system and elsewhere, to be strongly moderated by cocaine use.

We were able to recruit a high proportion of patients screened (78%) and at enrolment, the study groups were well-balanced on demographic and clinical characteristics. Reflecting the current standard profile of OAT at specialist OUD treatment services in England, approximately two-thirds of our sample were enrolled in methadone maintenance treatment and one-third was enrolled in buprenorphine maintenance treatment. Importantly, 93% of the PSI group were receiving OAT at the end of the study (no group difference). There were also no clinically important differences in medication dose at the endpoint or levels of keyworker contact, so it was it unlikely that fluctuations in medication accounted for our findings.

The success of our aim to motivate patients to engage in a PSI was reflected in the rate of attendance at the level set to indicate adherence: one-third or more therapy sessions (59%). This compares reasonably well to other studies (e.g. 48% non-attendance for first session of individual psychological therapy [42], and 34% commencing but then not attending [43]). In many treatment systems, clinical psychologists and psychotherapists in substance use disorder services are in short supply, so another key strength of the study is that we were able to train and supervise psychology assistants to deliver an effective PSI, all of whom were rated competent. Although it took many weeks to complete field-work, there was a relatively

low level of loss to follow-up and all participants who withdrew from the study gave their consent for their data to be used in the analysis.

ARC trial findings must be interpreted in the light of several limitations. Firstly, the number of patients interested in taking part in the study was over-estimated, and our achieved sample of 273 participants fell short of the 368 target. However, we powered the trial conservatively at 90% for the primary outcome. Second, the rate of effectiveness for our PSI was less than anticipated (18% difference in abstinence). The rate of treatment response was 16·3% in the PSI group and treatment response rate and 6·7% in the TAU group (adjusted log odds 1·20, 95% CI 95% CI 0·01 to 2·37). We believe this is a clinically meaningful finding, not least because our primary outcome was stringent, requiring UDS-verified self-reported abstinence from both opioids and cocaine to define a positive outcome response. Also, our perseverance to secure endpoint interviews was conservative for the estimate of PSI effectiveness because there was a tendency for those with long follow-up times to be identified when they re-presented for further OAT following relapse (so none achieved the primary outcome measure).

When we removed endpoint assessment data after 24 weeks for a sensitivity analysis, our estimate of positive evidence for the PSI almost doubled (adjusted log odds 2·31, 95% CI 0·62 to 4·00). There is, however, no doubt that the ARC trial highlights the challenge facing clinicians to engage patients who are retained in OAT but continue to use opioids and cocaine. Our findings set a level of expectation for future studies with this population. In the PSI group, many participants were motivated to attend a formulation assessment and to try out cognitive and behavioural interventions. However, for a small number of participants, it proved very challenging to engage with them after one or two sessions (results of our case formulation and psychological intervention selection process are reported elsewhere).

Third, we were not able to blind research assistants to study group. However, the primary outcome included a biochemical verification component, and this was supported by a 12-point increase in the ES for the opioid and cocaine abstinence collected via a field-standard structured interview. It was unfortunate that three patients who indicated interest in joining the study for a second time were not properly checked; but we identified this problem quickly, instituted preventive training, and our DMC-recommended mITT analysis strategy was conservative.

Fourth, ARC is a single-centre trial and we do not know the extent to which the findings reported here will generalise to other clinics prescribing medication for OUD. This was a pragmatic study done in a routine NHS clinical setting with minimal participant exclusion

criteria and we believe our comparator (medical management and fortnightly 30-minute drug counselling) is comparable to that offered by community treatment services in England. We have shown that a team approach with supervised psychology assistants is cost-effective and our findings lend support to this investment by treatment services.

As has been long observed in psychotherapy, the addition of an ingredient to standard care is likely to achieve only a small average effect [45]. This is reflected in the current position of the NICE that CBT should not be offered routinely to those receiving OAT [13; page 148]. This recommendation is based on the average treatment effect from samples recruited at admission or during treatment — thereby mixing current treatment responders and non-responders — and potentially masking PSI efficacy for responders. However, we have shown that a personalised PSI can be effective when targeted to non-responders, so in that sense we agree with the NICE's recommendation not to offer a CBT-type PSI *routinely*. A personalised approach in which specific behaviour change interventions are tailored to need could well prove to be a fruitful strategy for evidence-based therapeutics in addiction.

We did not observe a reduction in anxiety and depressive symptoms. Further analysis will be published elsewhere, but it appears that additional interventions may be needed. Clinical responders to OAT should also not be overlooked. They may be completely abstinent but amenable to relapse prevention-oriented PSI and support to attain other goals such as employment.

Disaggregation of the OUD clinical population is also important. There is evidence that non-responders are visible early in treatment. A US trial found that 26·4% of the sample did not stop opioid use after two weeks of buprenorphine maintenance therapy, with this non-response strongly predictive of opioid use three months later [46]. A significant minority of patients will also stay in treatment over the longer-term and continue to use opioids or relapse. A recent study of 7,719 patients who were continuously enrolled in OAT for five years [47], found that one-seventh displayed a stable pattern of non-response (opioids used on 15 of the past 28 days prior to six-monthly clinical reviews across 5·5 years). But even if drug use is not suppressed, the offer of a PSI should be kept open while the patient benefits from a reduced risk of fatal opioid-related overdose and help to receive other medical services as needed. The applied conclusion from this study is that clinicians providing OAT should assess their patients' response early once the maintenance dose has been achieved. If OAT is not giving clinical benefit, even a basic case formulation will shed important light on the reasons why and point to an intervention. We also believe there is much to be gained from using clinical scales where these provide actionable information and inform the process of selecting change methods. Clinicians should bear in mind that the patient's personal preferences are key, so

having a toolbox of psychological change methods gives flexibility and the ability to adapt treatment according to the patient's response and evaluation.

An integrated approach to assessment, stratified treatment and continuing care is now gaining momentum in behavioural medicine, where tailoring variables and decision rules is improving outcomes. At present, there is relatively limited evidence for this measurement-based care approach to adapt interventions in the substance use disorders field [48]. The ARC trial has taken an important step in that direction and has shown that this approach is effective and cost-effective.

CONTRIBUTORS

JM (chief investigator) developed the PSI concept with LM (lead investigator) and MK. All authors contributed to study design. GS managed the trial with support from CM, JK and JH. KJ and JH conducted the statistical analysis. JH designed the statistical analyses and was responsible for cleaning the data. JS and SB conducted the cost effectiveness analysis. The manuscript was drafted by JM with support from all authors, who reviewed manuscript drafts, revised for content, and approved the final version.

DECLARATION OF INTERESTS

In the past three years, JM declares research grants from the NHS England and the English Department of Health and Social Care (prison setting maintenance medication for opioid use disorder [OUD]); the National Institute for Health Research (NIHR; randomised controlled trial of depot naltrexone for OUD, and a randomised controlled trial of acamprosate for alcohol use disorder); and the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM; randomised controlled trial of novel cognitive therapy for cocaine use disorder). He has part-time employment as Senior Academic Advisor for the Alcohol, Drugs, Tobacco and Justice Division, Health and Wellbeing Directorate, Public Health England (PHE) and is a clinical academic consultant for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. JM declares an unrestricted research grant at IoPPN and SLaM from Indivior via Action on Addiction for the present study and unrestricted research grant funding at IoPPN and SLaM from Indivior for a three-year, multi-centre, randomised controlled trial of injectable depot buprenorphine (from 2019). He has received honoraria and travel support for from Merc-Serono (2015; oncology medical education); Reckitt-Benckiser (2016; treatment of OUD and PCM Scientific and Martindale for the Improving Outcomes in Treatment of Opioid Dependence conference (2015-2018; contributions and chairing). He holds no stocks in any company.

In the past three years, LM acknowledges funding from King's College London in support of his clinical research activities. He is a trustee of The Aurora Project (a charity providing peer support services for people in drug and alcohol treatment) and he has a part-time secondment (clinical psychology) at the Alcohol, Drugs, Tobacco and Justice Division, Health and Wellbeing Directorate, PHE. LM declares research grants from NIHR (randomised controlled trial of depot naltrexone for OUD); an unrestricted research grant at IoPPN and SLaM from Indivior via Action on Addiction for the present study; and an unrestricted research grant funding at IoPPN and SLaM from Indivior for a three-year, multi-centre, randomised controlled trial of injectable depot buprenorphine (from 2019). He also declares honoraria and travel support from Mundi Pharma (2016; expert panel discussion on novel pharmacotherapy for OUD.

In the past three years, MK acknowledges his honorary senior lecturer position at KCL (ongoing) and co-opted membership of the Royal College of Psychiatrists Faculty of Addictions Executive Committee (completed in 2018). He has a part-time secondment (clinical psychiatry) with the Alcohol, Drugs, Tobacco and Justice Division, Health and Wellbeing Directorate, PHE. MK declares: a research grant from NIHR (randomised controlled trial of depot naltrexone); site principal investigator status for a randomised controlled trial of extended-release buprenorphine for the treatment of OUD funded by Camerus and Braeburn pharmaceutical; research collaborator status for a study of treatment for Hepatitis C Virus (HCV) for people who inject drugs (PWID) funded by Merck Pharmaceuticals; support from Cephaid for a finger prick testing unit for HCV and HIV; an unrestricted research grant at IoPPN and SLaM from Indivior via Action on Addiction for the present study; and an unrestricted research grant funding at IoPPN and SLaM from Indivior for a three-year, multi-centre, randomised controlled trial of injectable depot buprenorphine (from 2019). He declares honoraria and travel support from Mundi Pharma (2016; expert panel discussion on novel pharmacotherapies for OUD); and Abbievie and Gilead (2017 and 2018; discussion with hepatology specialists on HCV treatment for PWID).

JH acknowledges an NIHR doctoral fellowship.

SB, JH, KJ, JK, CM, JS and GS declare no competing interests.

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DATA SHARING

Requests for sharing the anonymised trial database should be addressed to the lead author.

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***Table 1*: Sample characteristics at baseline**

Patient characteristics	**PSI** (n=136)	**TAU** (n=137)	**All** (n=273) §
Age, years	43·1 (7·8)	42·6 (7·8)	42·8 (7·8)
Sex			
Male	103 (75·7%)	102 (74·5%)	205 (75.1%)
Female	33 (24·3%)	35 (25·5%)	68 (24·9%)
Ethnicity			
White	96 (70·6%)	105 (76·6%)	201 (73·6%)
Black	18 (13·2%)	17 (12·4%)	35 (12·8%)
Other	22 (16·2%)	15 (11·0%)	37 (13·6%)
Employment status			
In full or part-time work	20 (14·7%)	9 (6·6%)	29 (10·6%)
Not working	116 (85·3%)	128 (93·4%)	244 (89·4%)
Opioid agonist treatment (OAT)			
Methadone ¶	93 (68·4%)	93 (67·9%)	186 (68·1%)
Methadone dose, mg/day	55·6 (20·0)	56·2 (24·8)	55·9 (22·5)
Buprenorphine ¶	43 (31·6%)	44 (32·1%)	87 (31·9%)
Buprenorphine dose, mg/day	12·0 (5·2)	10·7 (5·3)	11·3 (5·2)
Weeks of OAT at study enrolment †	26 (9-89)	25 (11-88)	26 (10-88)
Substance dependence *			
Opioid **	118 (86·8%)	115 (83·9%)	233 (81·7%)
Cocaine	94 (69·1%)	96 (70·1%)	190 (69·6%)
Drug use in past 28 days ‡			
Opioid (illicit or non-prescribed)	124 (91·2%)	126 (92·0%)	250 (91·6%)
Crack cocaine ¶	114 (83·8%)	114 (83·2%)	228 (83·5%)
Cocaine powder	14 (10·3%)	12 (8·8%)	26 (9·5%)
Illicit drug injecting ¶	43 (31·6%)	46 (33·6%)	89 (32·6%)
Urine Drug Screen (positive test)			
Morphine (opioid)	116 (85·3%)	115 (83·9%)	231 (84·6%)
Cocaine (benzoylecgonine)	103 (75·7%)	107 (78·1%)	210 (76·9%)
Benzodiazepine	28 (20·6%)	38 (27·7%)	66 (24·2%)

Data are mean (SD) or n (%); or † median (IQR).

TAU = treatment as usual; PSI= personalised psychosocial intervention.

§ includes three participants re-randomised in error, who were then deleted from all analysis of clinical and cost-effectiveness.

¶ Stratification variable.

* DSM-IV (past 12 months)

** remaining cases in each group in remission for opioid dependence.

‡ Report of one or more days by Treatment Outcomes Profile.

***Table 2*: Primary and secondary outcomes at 18 weeks**

	PSI (n=120)	**TAU** (n=117)	**Between-group difference †**	**p-value**
Primary outcome				
Baseline	-	-		
6-weeks	8/80 (10·0%)	6/84 (7·14%)	-	
10-weeks	7/49 (14·3%)	4/50 (12·0%)	-	
14-weeks	6/21 (28·57%)	0/15 (0%)	-	
18-weeks (endpoint)	22/120 (18·3%)	9/117 (7·6%)	1·20 (0·01 to 2·37) ¶	0·048
Secondary outcomes §				
Opioid PDA				
Baseline	52·49 (36·47)	49·92 (35·15)	-	
Endpoint	72·62 (32·85)	56·78 (37·75)	13·62 (5·84 to 21·40) **§**	0.001
Crack cocaine PDA				
Baseline	59·95 (36·13)	56·43 (38·03)	-	
Endpoint	78·98 (29·85)	67·34 (35·40)	8·74 (2·20 to 15·28) **§**	0.009
Cocaine powder PDA				
Baseline	98·94 (3·95)	99·15 (3·89)	-	
Endpoint	99·26 (3·52)	98·32 (10·70)	0·93 (-1·10 to 2·96) **§**	0.344
MoCA				
Baseline	22·28 (4·47)	21·20 (4·77)	-	
Endpoint	22·93 (3·70)	22·36 (4·51)	-0·16 (-1·06 to 0·74) **§**	0.724
PHQ-9				
Baseline	14·01 (7·73)	14·04 (7·29)	-	
Endpoint	10·91 (7·21)	12·34 (8·11)	1·33 (-0·36 to 3·01) **§**	0.136
GAD-7				
Baseline	9·84 (6·37)	10·12 (6·60)	-	
Endpoint	8·73 (6·03)	10·03 (7·17)	1·15 (-0·26 to 2·56) **§**	0.114
WSAS				
Baseline	22·35 (10·20)	21·12 (11·06)	-	
Endpoint	16·46 (12·64)	19·19 (12·60)	3·42 (0·53 to 6·32) **§**	0.016

Data n (%), mean (SD) or mean (95% CI). TAU = treatment as usual; PSI= psychosocial intervention; PDA = percent days abstinent in past 28 days; MoCA = Montreal Cognitive Assessment; PHQ-9 = Patient Health Questionnaire; GAD-7 = Generalized Anxiety Disorder Scale; WSAS = Work and Social Adjustment Scale.

† The referent group for between-group differences.

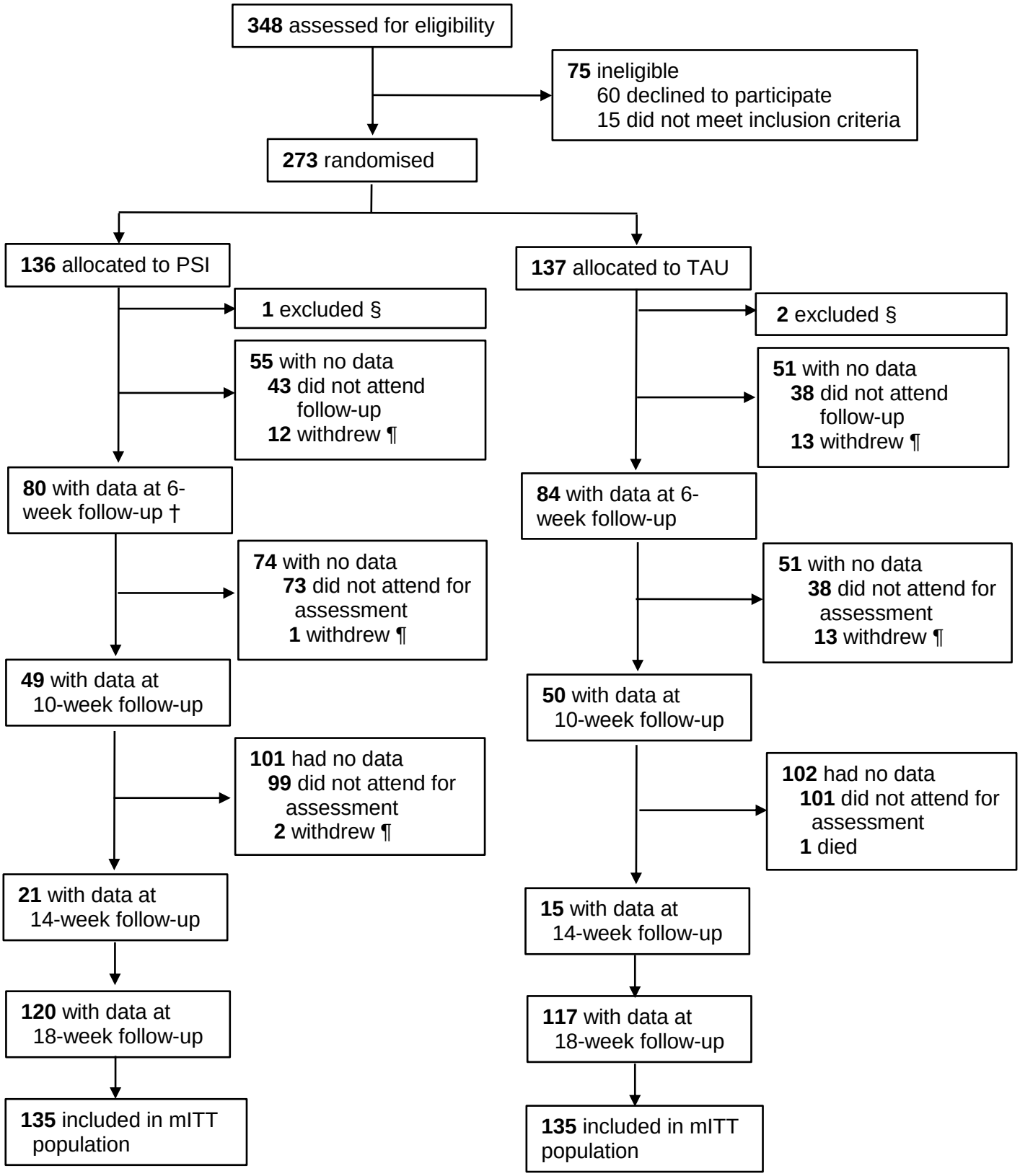
¶ Adjusted odds ratio (95% CI) from mixed-effects logistic regression model, including OAT medication (coefficient [coef.]. 0·654, standard error [SE] 0·635, 95% CI -0·590 to 1·898, p-value 0·303); baseline opioid use (coef. -0·085, SE 0·031, 95% CI -0·146 to -0·024, p-value 0.006); baseline cocaine use (coef. -1·536, SE 0·696, 95% CI -2·900 to -0·172, p-value 0.027); illicit drug injecting (coef. 0·654, SE 0·635, 95% CI -0·590 to 1·898, p-value 0.303); log time (coef. 5·719, SE 2·671, 95% CI 0·484 to 10·955, p-value 0.032); log time squared (coef. -1·014, SE 0·500, 95% CI -1·995 to -0·034, p-value 0.043); and treatment x log time (coef. -0·406, SE 0·205, 95% CI 0·004 to 0·807, p-value 0.048)

§ Adjusted difference between baseline and endpoint for scaled measures from generalised, repeated measures, linear mixed-model framework, including covariates used in the model for the primary outcome.

***Table 3**:* Adverse events by event

Event/type	PSI (n=136)	TAU (n=137)
Adverse Events (AE)		
Total number of AE (people)	22 (20)	19 (18)
Haematological	0	1
Musculo-skeletal	1	2
Neurological	0	1
Psychiatric	20 (18)	15 (14)
Immunological	1	0
Severe Adverse Events (SAE)		
Total number of SAE (people)	1	2
Hospitalisation	1	1
Death	0	1

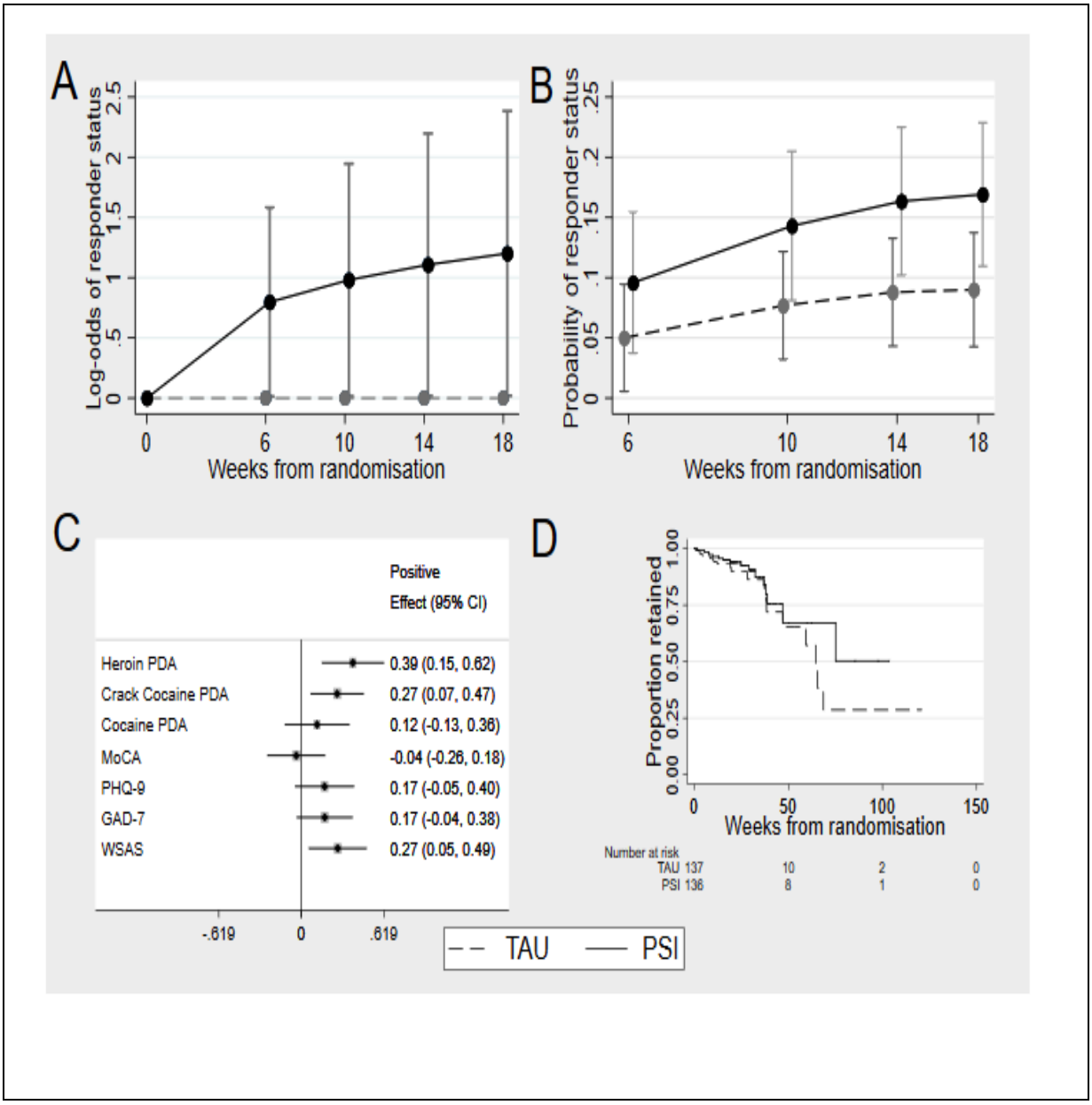
Figure 1: Trial profile



PSI = opioid agonist treatment with adjunctive personalised psychosocial intervention. All those with follow-up data attended PSI sessions. TAU = opioid agonist treatment-as-usual; mITT = modified intention-to-treat.

¶ all withdrawn participants gave consent for their available data to be included in the analysis.
§ case(s) re-randomised in error and excluded from all analysis.
† start of PSI.

***Figure 2*: Progression of response status and retention to 18 weeks**



TAU = treatment as usual; PSI= personalised psychosocial intervention.

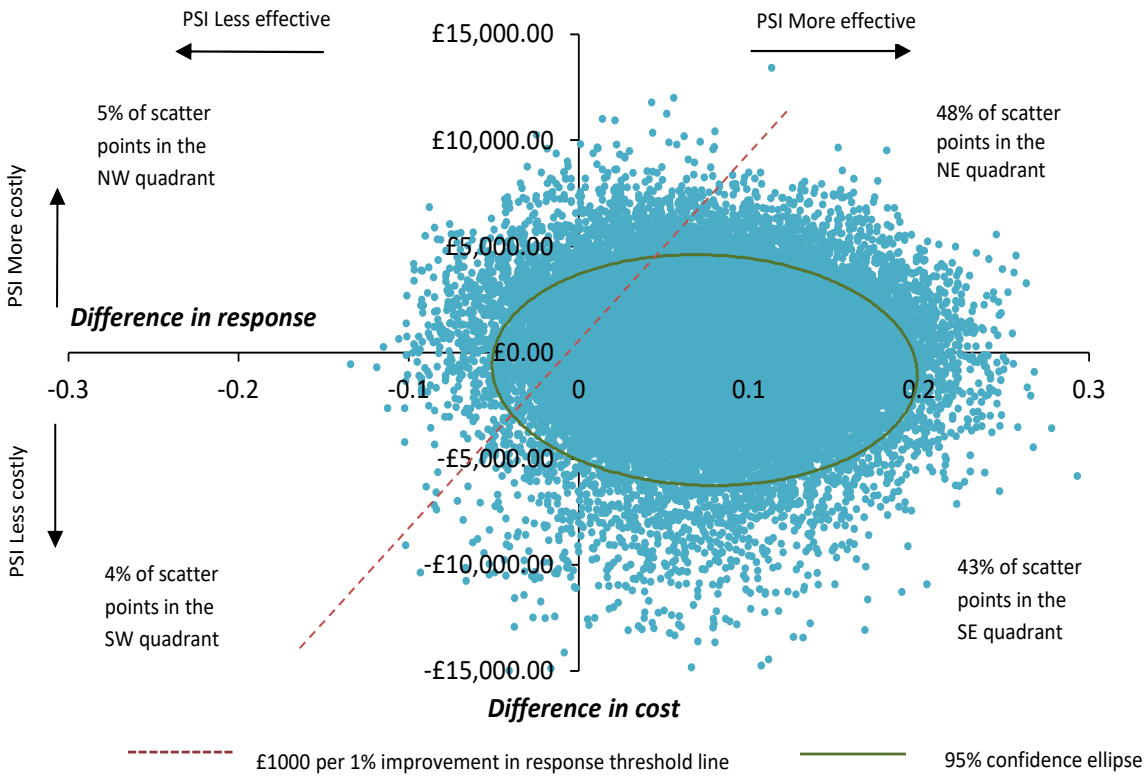
PDA = percent days abstinent in past 28 days.

Results are derived from fully adjusted mixed effects models controlling for stratification factors.

Figure 2C are Cohen's d standardised effect size estimates to allow comparisons between measures (increasing value indicates positive effect).

Figure 2D shows the number of participants at risk by group.

***Figure 3*: Scatterplot showing bootstrapped mean difference in imputed costs and effects of PSI compared with TAU**



TAU = treatment as usual;

PSI= personalised psychosocial intervention.

NE = Northeast; NW = Northwest; SE = Southeast; SW = Southwest.

APPENDIX

***Table S1*: Unit costs of health and social care services**

Item	Source	Unit cost
Intervention		
PSI therapist	Trial data – Table S2	£126 per contact hour
Drug keyworkers	Trial data – Table S2	£72 per contact hour
Accommodation		
Staffed accommodation	PSSRU 2.2 Local authority care homes for people with mental health problems §	£951 per week
Hospital services		
Hospital drug services admission	PSSRU 2016 2.1 Drug services – admitted (bed day) §	£359 per bed day
Hospital mental health admission	PSSRU 2016 2.1 Mental health care clusters (bed day) §	£373 per bed day
Non-elective inpatient long stay (>=5 days)	PSSRU 2016 7.1 NHS reference costs §	£2900 per episode
Non-elective inpatient short stay (<5 days)	PSSRU 2016 7.1 NHS reference costs §	£616 per episode
Outpatient appointments	PSSRU 2016 7.1 NHS reference costs §	£135 per attendance
Accident & emergency	Department of Health Reference costs 2015-2016 ¶	£138 per attendance
Ambulance	PSSRU 2016 7.1 NHS reference costs §	£238 per attendance
Hospital pharmacist	PSSRU 2015 13.6 Hospital pharmacist †	£101* per contact hour
Hospital nurse	PSSRU 2016 Band 5 Hospital based nurse ¶	£86 per contact hour
Community services		
General practitioner – surgery	PSSRU 201610.8b GP - unit costs ¶	£36 per 9.22 minutes
General practitioner – home	PSSRU 201510.8a GP - home visit †	£90* per visit
Practice nurse	PSSRU 2015 10.6 Nurse/GP practice †	£57* per contact hour
District nurse	PSSRU 2015 10.3 Health visitor †	£77* per contact hour
Community psychiatrist	PSSRU 2016 15.7 Consultant – psychiatric §	£138 per contact hour
Community psychiatric nurse	PSSRU 2015 10.2 Nurse (mental health) †	£76* per contact hour
Community mental health team (CMHT)	PSSRU 2016 12.2 CMHT mental health team for adults with mental health problems §	£38 per contact hour
Occupational therapist	PSSRU 2016 11.5 Community OT §	£44 per hour
Art therapy	Assumed equivalent to Community OT	£44 per hour
Accommodation keyworker	PSSRU 2016 11.4 Social Work Assistant §	£30 per hour
Counsellor	PSSRU 2015 3.4 Alcohol health worker †	£57* per contact
Family therapist	Assumed equivalent to counsellor	£57 per contact
Social worker	PSSRU 2016 11.2 Social worker §	£79 per hour
Day care/drop-in centre	PSSRU 2016 2.4 Local authority day care for people with mental health problems §	£34 per client attendance
Syringe exchange	Cost per pack	0.29 per pack
Advice service	PSSRU 2016 11.4 Social Work Assistant §	£30 per hour

cont.../

***Table S1*: Unit costs of health and social care services, cont.../**

Item	Source	Unit cost
Marriage counselling	Assumed equivalent to counsellor	£57 per contact
Helpline	http://www.thirdsector.co.uk/analysis-counting-cost-reform-samaritans/management/article/1175711	£3.96* per call
Prison/police doctor	Assumed equivalent to GP home visit	£90 per visit
Prison/police nurse	PSSRU 2016 2.1 NHS Reference costs for mental health services – Prison health adult and elderly §	£80 per contact
Dentist	PSSRU 2016 10.6 Dentist – providing-performer §	£184 per contact hour
Psychologist	PSSRU 2014 9.5 Clinical Psychologist ‡	£139* per contact hour
Group therapy, face to face	PSSRU 2015 2.9 MBCT therapy – group-based interventions †	£14* per person
IAPT	PSSRU 2016 2.1 NHS Reference costs for mental health services: Improving Access to Psychological Therapies §	£96 per contact
Dietician	PSSRU 2015 13.4 Hospital dietician ‡	£39* per contact hour
Medications		
Buprenorphine	Drug Tariff (Part VIIIA Category M) price. URL: http://www.nhsbsa.nhs.uk/PrescriptionServices/1821.aspx (accessed 24.10.18)	Pack of seven 8mg £2.90
Methadone	Drug Tariff (Part VIIIA Category M) price, URL: http://www.nhsbsa.nhs.uk/PrescriptionServices/1821.aspx (accessed 24.10.18)	1mg/ml oral solution 500ml £6.15
Controlled drug supervised dispensing fee	Methadone-Fees-Calculator-April-2013-interactive (Methasoft) Monthly fee for 14-day supervised prescriptions	£31.96* per month
Productivity losses		
Average weekly earnings	URL: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours (accessed 24.101.18).	£504

§ Curtis L, Burns A. Unit Costs of Health and Social Care 2016, Personal Social Services Research Unit. 2016?. University of Kent, Canterbury.

¶ https://socialwelfare.bl.uk/subject-areas/services-activity/health-services/departmentofhealth/179779Reference_Costs_2015-16.pdf

† Curtis L, Burns A. Unit Costs of Health and Social Care 2015, Personal Social Services Research Unit. 2015. University of Kent, Canterbury.

‡ Curtis L, Burns A. Unit Costs of Health and Social Care 2014, Personal Social Services Research Unit. 2014. University of Kent, Canterbury.

* Uprated to 2015 prices using the Hospital & Community Services Index

***Table S2*: Cost of PSI therapist and TAU keyworker time**

Item	Source	Cost/time
Therapist time		
A. Psychology Assistant salary	Therapist time use questionnaire	£25,622
B. Employers NI and superannuation	NI plus 14% pension contribution	£5,835
C. Overheads §	Study site data	£29,676
D. Wages plus overheads (**A**+**B**+**C**)	**A**+**B**+**C**	£61,133
E. Working time	Hours per year ¶	1,538
F. Cost per hour	**D**/**E**	£39.75
G. Cost per hour in direct client contact	**F**x3.03 ratio of face-to-face to indirect time	£120.44
H. Supervision/training/ preparation cost per hour	Four hours per week of clinical psychologist time	£5.34
Cost per minute in direct client contact	**G**+**H**/60 minutes	£2.10
Keyworker time		
A. Keyworker salary	Keyworker time use questionnaire	£3,2114
B. Employers NI and superannuation	NI plus 14% pension contribution	£7,575
C. Overheads §	Study site data	£2,9676
D. Wages plus overheads (**A**+**B**+**C**)	**A**+**B**+**C**	£69,365
E. Working time	Hours per year ¶	1,538
F. Cost per hour	**D**/**E**	£45.10
G. Cost per hour in direct client contact	**F**x1.47 ratio of face-to-face to indirect time	£66.30
H. Supervision/training/preparation costs per hour	Five hours per week of senior keyworker time	£5.56
Cost per minute in direct client contact	**G**+**H**/60 minutes	£1.20

NI = National Insurance

§ Including capital, administrative and managerial overhead costs.

¶ based on 37.5 hours/week for 41 weeks per year.

Table S3: **Unit costs of crime**

Item	**Source**	**Unit cost***
Burglary in a dwelling	Brand & Price §	£4,399
Burglary not in a dwelling	Dubourg, Hamed & Thorns ¶	£4,196
Robbery of personal property	Brand & Price §	£9,803
Robbery of commercial property	Brand & Price §	£9,803
Theft of a vehicle	Brand & Price §	£5,570
Theft from a vehicle	Brand & Price §	£1,155
Theft of cycle	Brand & Price §	£853
Theft from the person	Brand & Price §	£1,136
Theft from shops	Dubourg, Hamed & Thorns ¶	£155
Handling stolen goods	Dubourg, Hamed & Thorns ¶	£528
Criminal damage to a dwelling	Brand & Price §	£1,166
Criminal damage to a building other than a dwelling	Brand & Price §	£1,166
Criminal damage to a vehicle	Brand & Price §	£1,166
Serious violent offences	Brand & Price §	£14,009
Less serious wounding	Brand & Price §	£10,845
Common assault	Brand & Price §	£1,938
Harassment	Brand & Price §	£1,938
Possession of weapons	Zero rated	£0
Possession of drugs	Zero rated	£0
Trafficking in controlled drugs	Zero rated	£0
Credit and credit card fraud	Brand & Price §	£1,136
Going equipped for stealing	Zero rated	£0
Soliciting and prostitution	Zero rated	£0
Breach of peace/drunk and disorderly	Brand & Price §	£1,938
Begging	Zero rated	£0
Domestic abuse	Brand & Price §	£1,938
Kidnapped and beaten	Brand & Price §	£1,938
Indecent assault	Brand & Price §	£42,320
Indecent exposure	Brand & Price §	£1,938

§ Brand S, Price R. The Economic and Social Costs of Crime. 2000. London: The Home Office.

¶ Dubourg R, Hamed J, Thorns J. The economic and social costs of crime against individuals and households 2003/04. 2005. London: The Home Office Online Report.

* Uprated to 2016 prices using the GDP deflator

***Table S4*: Service use (unit) over follow-up by group (complete case)**

	PSI (n=95)		TAU (n=104)	
	Mean (SD)	% using	Mean (SD)	% using
PSI (sessions)	4.9 (4.9)	65.2	0.0 (0.0)	0.0
Keyworker (sessions)	8.8 (5.4)	98.3	7.4 (5.1)	97.3
Supported accommodation (weeks)	17.6 (41.3)	20.2	22.5 (44.7)	22.1
Inpatient (nights)	10.6 (11.3)	10.5	2.8 (1.2)	6.7
Outpatient appointments (number)	4.4 (5.5)	15.8	4.3 (7.9)	15.4
Accident and emergency (visits)	0.1 (0.3)	12.8	0.1 (0.3)	9.6
Ambulance (calls)	0.8 (0.5)	9.8	0.3 (0.5)	2.3
GP (contacts)	1.6 (2.7)	53.8	1.9 (3.0)	57.3
Other health and social care (contact)	17.1 (51.6)	57.9	11.5 (30.9)	55.8
Methadone (dose)	58.8 (25.0)	59.3	59.9 (25.7)	62.2
Buprenorphine (dose)	11.4 (4.6)	28.9	11.1 (5.4)	23.7
Criminal activity (offences)	60.0 (102.0)	22.1	59.1 (59.0)	18.3
Days off work over follow-up	3.3 (8.8)	26.3	1.4 (3.4)	26.3

SD = standard deviation;

PSI = personalised psychosocial intervention;

TAU = treatment-as-usual.

***Table S5*: Disaggregated imputed mean costs over follow-up**

	PSI (n=135)	**TAU** (n=135)	**Mean difference (SE) 95% CI ¶**	**p-value**
Therapist sessions	491 (510)	-	-	-
CM costs	33 (49)	-	-	-
Keyworker sessions	312 (234)	255 (239)	-12 (26) -63 to 39	0.646
Methadone	93 (120)	85 (115)	11 (11) -10 to 33	0.313
Buprenorphine	31 (64)	20 (44)	-9 (5) -20 to 2	0.090
OAT dispensing	195 (128)	161 (117)	-1 (9) -18 to 16	0.905
Intervention total	**1,155 (53)**	**521 (35)**	**561 (60) 443 to 680**	**<0.001**
Accommodation	2,048 (490)	2,888 (565)	-283 (737) -1,740 to 1,173	0.701
Hospital services	503 (199)	147 (47)	351 (191) -27 to 729	0.069
Community health & social care services	661 (168)	534 (161)	30 (234) -433 to 494	0.898
Total NHS/PSS costs	**4,367 (586)**	**4,090 (665)**	**658 (876) -1,070 to 2,388**	**0.453**
Absenteeism	499 (196)	132 (46)	359 (191) -32 to 751	0.070
Victim of crime	448 (201)	592 (252)	-136 (343) -818 to 545	0.691
Criminal activity	2,507 (1,344)	4,014 (2,362)	-1,843 (3,109) -8,127 to -4,442	0.557
Total societal costs	**7,822 (1,648)**	**8,828 (13,524)**	**-400 (3,416) -7,274 to 6,475**	**0.907**

Data are mean (standard error, SE) in GB pounds.

PSI = personalised psychosocial intervention;

CM = contingency management (shop vouchers);

OAT = opioid agonist treatment;

TAU = treatment-as-usual;

Mean difference, 95% CI and p-values adjusted for baseline covariates and duration of follow-up with missing data imputed.

***Table S6*: EQ-5D-3L scores and QALYs by group (complete case)**

	PSI (n=95)	TAU (n=104)	Unadjusted difference
Baseline EQ-5D-3L score	0.674 (0.296)	0.649 (0.280)	0.025
Follow-up EQ-5D-3L score	0.660 (0.335)	0.569 (0.346)	0.091
QALYs	0.298 (0.175)	0.216 (0.109)	0.082

PSI = personalised psychosocial intervention;

TAU = treatment-as-usual.

Figure S1: Cost-effectiveness acceptability curve showing the probability that PSI is cost-effective compared to TAU for different values of willingness-to-pay for a one percentage point improvement in the probability of a positive treatment response

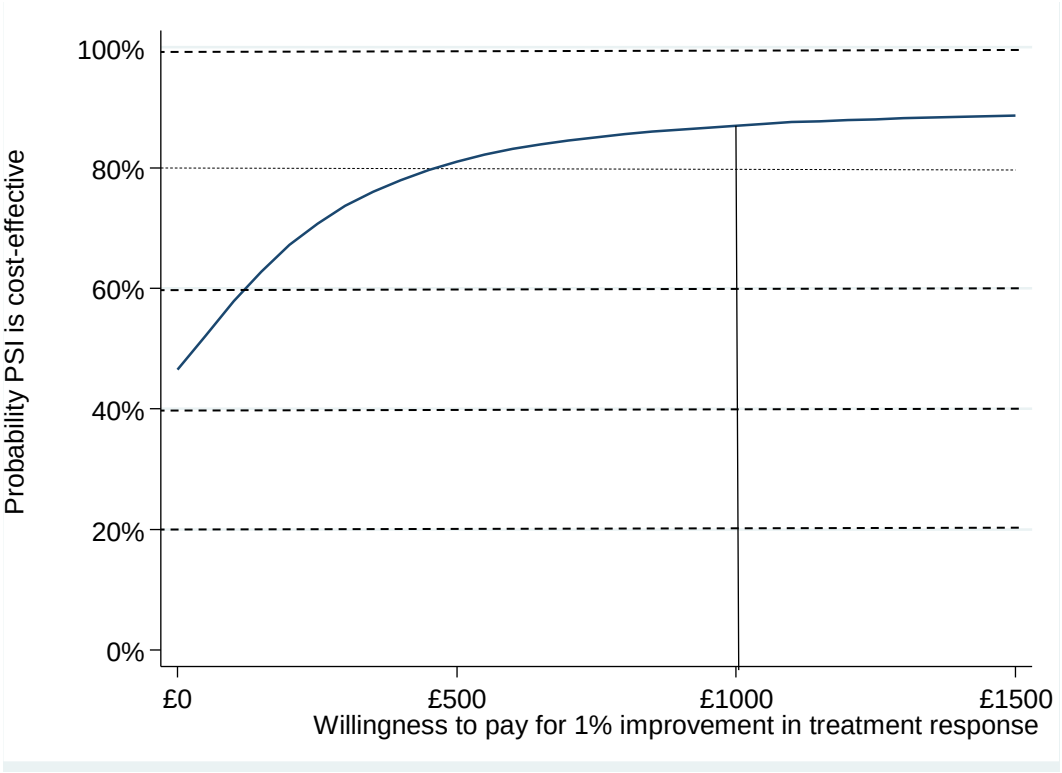
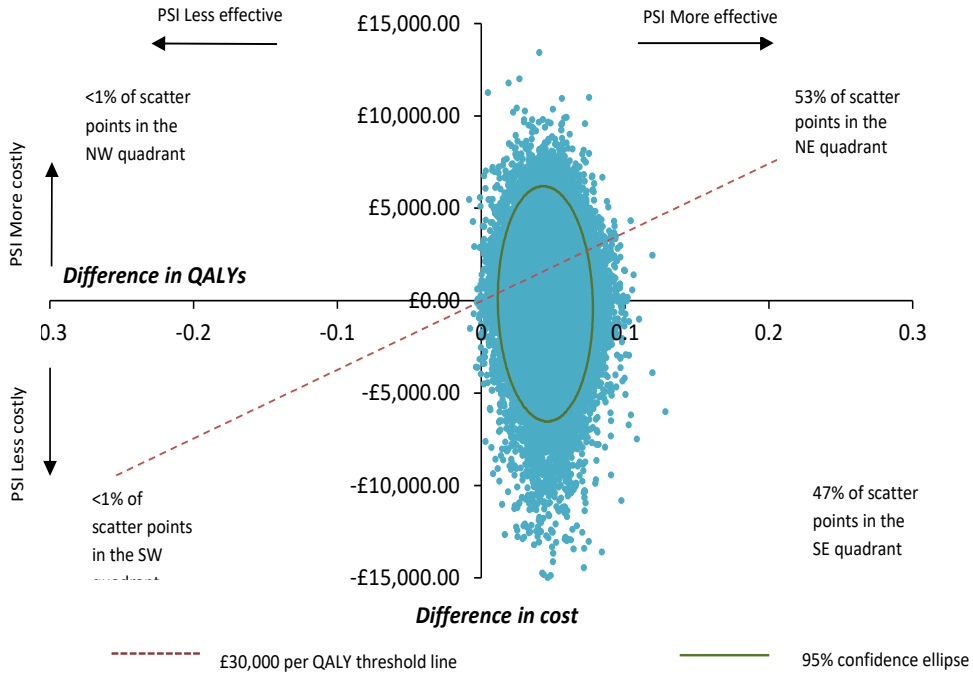


***Figure S2*: Scatterplot showing bootstrapped mean difference in QALYs for PSI compared with TAU**



TAU = treatment as usual; PSI= personalised psychosocial intervention.

NE = Northeast.

NW = Northwest.

SE = Southeast.

SW = Southwest.

Figure S3: Cost-effectiveness acceptability curve showing the probability that PSI is cost-effective compared to TAU from the NHS/PSS perspective for different values of willingness-to-pay for a unit improvement in QALYs

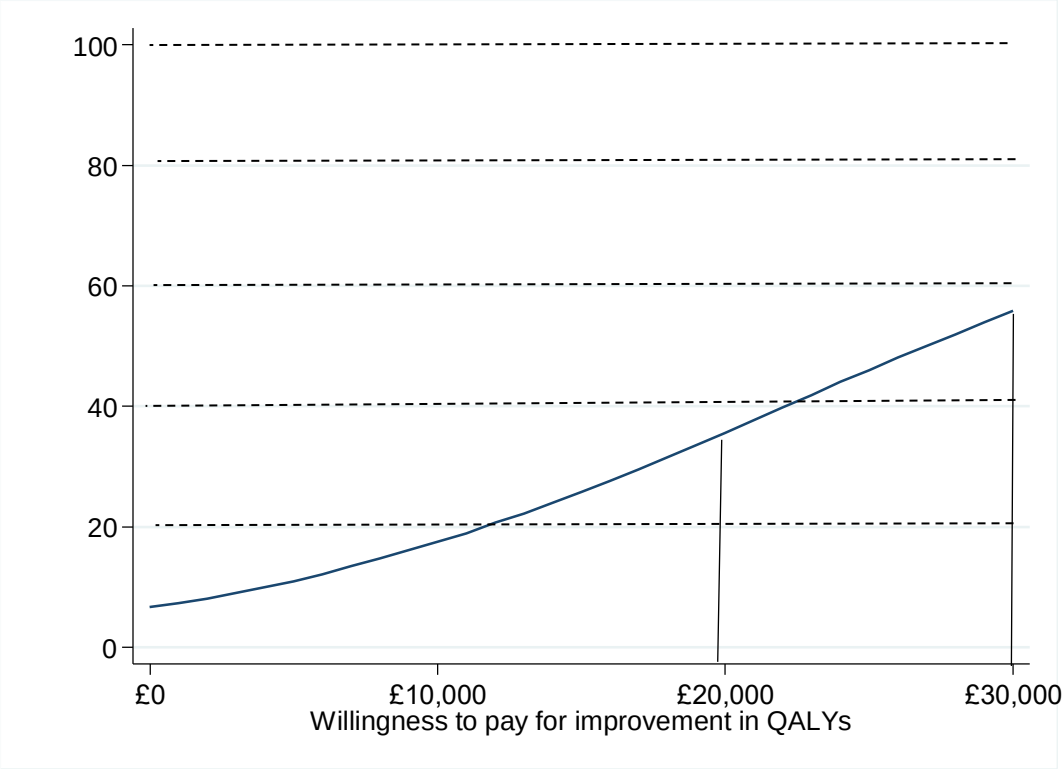


Figure S4: Cost-effectiveness acceptability curve showing the probability that PSI is cost-effective compared to TAU for different values of willingness-to-pay for a unit improvement in QALYs