Superiority and cost-effectiveness of Individual Placement and Support versus standard employment support for people with alcohol and drug dependence: a pragmatic, parallel-group, open-label, multicentre, randomised, controlled, phase 3 trial

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Summary

Background Individual Placement and Support (IPS) is a specialist intervention to help people attain employment in the open competitive labour market. IPS has been developed in severe mental illness and other disabilities, but it is of unknown effectiveness for people with alcohol and drug dependence. The Individual Placement and Support—Alcohol and Drug (IPS-AD) is the first superiority trial to evaluate effectiveness and cost-effectiveness.

Methods IPS-AD was a pragmatic, parallel-group, multi-centre, randomised, controlled, phase 3 trial of standard employment support (treatment-as-usual [TAU]) versus IPS. IPS was offered as a single episode for up to 13 months. The study was done at seven community treatment centres for alcohol and drug dependence in England. Study participants were adults (18–65 years), who had been enrolled for at least 14 days in treatment for alcohol use disorder (AUD), opioid use disorder (OUD), or another drug use disorder (DUD; mostly cannabis and stimulants); were unemployed or economically inactive for at least six months; and wished to attain employment in the open competitive labour market. After random allocation to study interventions, the primary outcome was employment during 18-months of follow-up, analysed by mixed-effects logistic regression, using multiple imputation for the management of missing outcome data. There were two cost-effectiveness outcomes: a health outcome expressed as a quality adjusted life year (QALY) using £30,000 and £70,000 willingness-to-pay [WTP] thresholds; and additional days of employment, with a WTP threshold of £200 per day worked. The study was registered with ISRCTN (ISRCTN24159790) and is completed.

Findings Between 8 May 2018 and 30 September 2019, 2781 potentially eligible patients were identified. 812 were excluded before screening, and 1720 participants were randomly allocated to TAU or IPS. In error, nine participants were randomised to study interventions on two occasions—so data for their first randomisation was analysed (modified intention-to-treat). A further 24 participants withdrew consent for all data to be used (full-analysis set therefore 1687 participants [70.1% male; mean age 40.8 years]; TAU, n = 844; IPS, n = 843 [AUD, n = 610; OUD, n = 837; DUD, n = 240]). Standard employment support was received by 559 [66.2%] of 844 participants in the TAU group. IPS was received by 804 [95.37%] of 843 participants in the IPS group. IPS was associated with an increase in attainment of employment compared with TAU (adjusted odds ratio [OR] 1.29; 95% CI 1.02–1.64; p-value 0.036). IPS was effective for the AUD and DUD groups (OR 1.48; 95% CI 1.14–1.92; p-value 0.004; OR 1.45, 95% CI 1.03–2.04, p-value 0.031, respectively), but not the OUD group. IPS returned an incremental QALY outcome gain of 0.01 (range 0.003–0.02) per participant with no evidence of cost-effectiveness at either WTP threshold—but QALY gains were cost-effective for the AUD and DUD groups at the £70,000 WTP threshold (probability 0.52 and 0.97, respectively). IPS was cost-effective for additional days of employment (probability 0.61), with effectiveness relating to the AUD group only (probability >0.99). Serious Adverse Events were reported by 39 participants (13 [1.5%] of 844 participants in the TAU group and 23 [2.7%] of 43 participants in the IPS group). There was a total of 25 deaths (1.5%; 9 in the TAU group and 16 in the IPS group)—none judged related to study interventions.

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Interpretation In this first superiority randomised controlled trial of IPS in alcohol and drug dependence, IPS helped more people attain employment in the open competitive labour market than standard employment support. IPS was cost-effective for a QALY health outcome (£70,000 WTP threshold) for the AUD and DUD groups, and for additional days of employment for the AUD group (£200 per day worked WTP threshold).

Funding UK government Work and Health Unit.

Keywords: Individual placement and support; Employment support; Alcohol use disorder; Opioid use disorder; Drug use disorder

Research in context

Evidence before this study

A search of OVID MEDLINE, Social Policy and Practice, APA PsychInfo and the Cochrane Library for 1 January 1995–30 April 2023 for literature in English, for publications evaluating the effectiveness and cost-effectiveness of Individual Placement and Support (with keywords including: "Individual Placement and Support"; "IPS"; "supported employment"; "vocational rehabilitation"; "substance* or substance misuse or drug* or alcohol* or cannabis or heroin or opioid* or cocaine or stimulant* or methadone"). There have been reported studies of populations in which substance-related problems are prevalent (e.g., people in contact with the criminal justice system), but only one small-scale randomised controlled trial with patients with a primary opioid use disorder—a methadone maintenance programme in Oregon at which 45 patients were randomly allocated to IPS or a 6-month waitlist—which reported a 50% competitive job rate for IPS versus 5% in the waitlist.

Added value of this study

The first superiority randomised controlled trial of IPS for people enrolled in treatment for alcohol and drug dependence, IPS helped more people attain employment in the open competitive labour market than standard employment support. IPS was cost-effective for QALY health outcome at a £70,000 willingness-to-pay threshold, and £200 willingness-to-pay threshold per additional day of employment for participants with alcohol use disorder and drug use disorder (mostly cannabis and stimulants), but not for participants with opioid use disorder.

Implications of all the available evidence

IPS is an effective intervention for people enrolled in treatment for alcohol and drug dependence (but not opioid dependence) who wish to attain employment in the open competitive job market.

Introduction

Employment is an essential personal role giving financial and social status, while job loss and unemployment is linked to poverty and illness.[1,2] Most people with alcohol and drug dependence see employment as a reflection of a desired productive and meaningful life spent in recovery[3]; but there is a high prevalence of unemployment among these populations. For example, in 2021–2022, National Health Service (NHS) or third-sector providers in England treated 38,495 people with alcohol dependence and 22,234 people with opioid (mainly heroin) dependence. Six-month national outcome monitoring data showed reporting that 33.7% and 16.1%, respectively were working thereby highlighting considerable room for improvement in outcome, and differences in the likelihood of employment attainment for clinical groups.[4] This outcome is also of concern because it has been reported that many people with alcohol and drug dependence believe they are not welcome applicants for competitive appointments.[5]

Individual Placement Support (IPS) is an intensive psychosocial intervention to help people find and maintain employment in the open competitive labour market.[6,7] IPS is delivered by an Employment Specialist and—in contrast to traditional vocational rehabilitation approaches—principles of personal occupational preference are followed including rapid job search, preparation for interview, and in-work support. IPS has been developed and successfully evaluated among populations with severe mental illness and physical disabilities. A meta-analysis of 30 randomised controlled trials (RCT) of IPS compared with standard employment support concluded that IPS was associated with work attainment (relative risk 1.63; 95% Confidence Interval [CI] 1.46–1.82); longer time employed (Cohen's *d* 0.46; 95% CI 0.35–0.57); and longer time employment in a single appointment (*d* 0.55; 95% CI 0.33–0.79).[8] There is mixed evidence on the effectiveness of IPS from health-related quality of life perspective. Three studies in severe mental illness, autism spectrum disorder and affective disorders have reported that IPS was effective,[9–11] but a fourth in

mood and anxiety disorders did not do so.[12] Cost evaluations have reported that IPS is either more effective and less costly compared with standard employment support,[9,13] or it is more effective, but more costly.[14,15]

Successive United Kingdom (UK) government strategies have sought to reduce the social and economic costs associated with alcohol- and drug-related problems—which have been estimated to be around £22bn and £20bn each year, respectively.[16] In 2015, a UK government-commissioned independent review saw IPS as an intervention of promise, noting that it was unavailable in alcohol and drug dependence treatment services, and called for research.[17]

The aim of the **I**ndividual **P**lacement and **S**upport—**A**lcohol and **D**rug (IPS-AD) trial was to determine the effectiveness and cost-effectiveness of IPS compared with standard employment support. Given the evidence for IPS in severe mental health and physical disability populations, we hypothesised that IPS would be superior in helping people receiving community treatment for alcohol and drug dependence attain employment in the open competitive labour market. We also expected participants allocated to IPS would achieve better clinical treatment outcomes.

Methods

Study design

IPS-AD was a pragmatic, open-label, parallel-group, seven-centre, superiority, randomised, controlled, phase 3 trial of standard employment support (treatment-as-usual [TAU]) versus IPS. After participants were randomly allocated (1:1) to TAU or IPS, we estimated vocational effectiveness, and cost-effectiveness over 18-months of follow-up. The study was registered with ISRCTN (ISRCTN24159790) and is completed. The study protocol has been published.[18]

Ethics

On 21 December 2017, the IPS-AD protocol, participant information sheet, and the written informed consent and other research materials were approved by the UK Health Research Authority (IRAS project number: 233,276) via the East of England–Cambridge East research ethics committee (reference: 17/EE/0454).

The study was initiated in community treatment centres each offering standard-of-care pharmacotherapies and psychosocial interventions.[19] These were recruited for the study via an open call. Local authority public health commissioners selected an IPS provider from among their substance use treatment partnerships. Standard employment support was available in all community treatment centres; none had provided IPS before. Research oversight was provided by an independent Trial Steering Committee (TSC) and a Data Monitoring Committee (DMC).

The Statistical Analysis Plan (SAP) and Health Economic Analysis Plan (HEAP) were published on the Open Science Framework on 15 February 2022 (https://osf.io/zjdqa/and https://osf.io/4rtw8, respectively) and data analysis occurred immediately after. Reporting adhered to the CONSORT guideline for pragmatic trials[20]; the Template for Intervention Description and Replication (TIDieR) checklist for complex behavioural interventions[21]; and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline for cost-effectiveness evaluations.[22] The IPS-AD protocol included an independent qualitative process evaluation; a planned analysis of IPS effect mediation, and a cost-benefit analysis over a longer horizon. These will be reported elsewhere.

Participants

Participants were adults (18–65 years)—approached by centre clinical staff at an appropriate point after completion of their treatment admission process, or from the electronic health record—who were unemployed or economically inactive for at least six months, and wished to obtain employment in the UK open competitive labour market. They were evaluated on DSM-5 diagnostic criteria (mild–severe; or in early remission) for alcohol use disorder (AUD), opioid use disorder (OUD), or another drug use disorder (DUD).[23] Otherwise eligible patients were excluded if they were: (1) receiving clinical management for alcohol or a drug withdrawal syndrome (but they could join after its successful completion); (2) they reported a suicide plan in past month or a suicide attempt in past six months; (3) had clinically significant (or otherwise uncontrolled) severe mental health, intellectual disability, organic brain disease or dementia, or physical disability that was judged by the local clinical lead to mean IPS would be inappropriate; (4) they had criminal justice involvement risking incarceration; or (5) they had been previously enrolled in a study of IPS effectiveness.

Randomisation and masking

The King's Clinical Trials Unit programmed and hosted a bespoke web-based randomisation service and produced reports for data verification. Immediately after completion of baseline measures, centre clinical staff accessed the randomisation system to allocate the participant to one of the two study interventions. The randomisation system used varying block lengths of two or four, and stratified participants by IPS centre, DSM-5 diagnosis, and employment history (defined as working for ≤1 month or >1 month in the past five years). The employment history stratification variable was used because it predicts lower likelihood of job attainment and negative health outcomes.[24,25] The participant was immediately informed of their study intervention allocation. With the exception of the senior statistician, it

was not feasible to mask centre staff and study researchers to study interventions.

Procedures

At each centre, a baseline, face-to-face, staff-administered interview recorded the participants demographic and alcohol and drug treatment information, and completed the following measures:

EQ-5D-5L,[26] a brief generic scale of mobility, self-care, usual activities, pain and discomfort, and anxiety and depression symptoms (each dimension scored 1–5 [no problems–extreme problems]). The scale includes a 0–100-point measure of overall health status, but this was not used.

Job Search Self-Efficacy Scale-Behaviour (JSSE-B),[27] a six-item measure including confidence in completing job applications and making a good impression at interview, with higher scores reflecting greater self-efficacy. The JSSE-B was included for a planned analysis of primary outcome effect mediation.

Structured Clinical Interview for DSM-5 Disorders—clinical version (SCID-5-CV),[28] including 11 symptoms to diagnose the patient's AUD, OUD, and other DUD status as mild (two or three symptoms); moderate (four or five); severe (six or more); or 'early remission' (no symptoms met discounting craving).

Treatment Outcomes Profile (TOP),[29] the English national instrument for alcohol and drug dependence treatment outcome monitoring. The TOP incorporates a structured, calendar-prompt, timeline follow-back procedure to record alcohol and drug use in the past 28 days. TOP data was uploaded electronically by the centres to the National Drug Treatment Monitoring System (NDTMS) and then incorporated in the study dataset.

After completion of this interview, participants were invited to visit their centre to complete the EQ-5D-5L, JSSE-B, SCID-5-CV and TOP at 6-month, 12-month and 18-month follow-up, and before leaving treatment, if this was feasible. Study data reported by participants was recorded using an MS Access database. The majority of study measures were collected from national databases and because study research questionnaires were very brief and were collected at a routine visit, participants did not receive any payments for taking part in the study.

For the cost-effectiveness analysis, we developed a Staff Time Survey (STS) for completion by each Employment Specialist. The STS recorded an estimate of direct and indirect time spent delivering IPS. The survey was sent by email to approximately coincide with the three research follow-ups.

Interventions

TAU (standard employment support)

On allocation to TAU, participants were given information on the standard employment support services at the centre and locality. In all study areas, but dependent on personal circumstances and type of state benefits received, each participant could access the UK public employment service (called Jobcentre Plus [JCP] (https://www.gov.uk/contact-jobcentre-plus); the Work and Health Programme (WHP; https://www.gov.uk/work-health-programme); or other employment programmes commissioned by the UK Government's Department for Work and Pensions. These TAU supports are also available in other areas across England as standard. During follow-up, the number of contacts each participant had with the JCP service and the WHP was recorded.

IPS

On allocation to IPS, each participant was allocated to an Employment Specialist to offer IPS for up to nine months. If the participant attained employment, they were offered four additional months of in-work support. The total duration of IPS was therefore 9–13 months contingent on employment attainment and preference.

IPS commenced with four sessions with the Employment Specialist in the first month at the centre to review the skills, experience, and participant's employment preferences; to offer help with writing or updating their curriculum vitae; to implement a job search strategy; and prepare for interviews. After the first month, the frequency of IPS sessions was approximately fortnightly, with telephone or email contacts if preferred. In-work support was four meetings or telephone contacts in the first month then fortnightly, or as requested. During follow-up, the number of IPS sessions attended and the number of contacts with standard employment support services was recorded.

In consultation with its developers,[6] we developed IPS training materials (available from the corresponding author). The Employment Specialists were expected to build contacts with local employers to discuss the practical and medical needs of people with alcohol and drug dependence (e.g., need for assistance to travel to work; adjustment of shift hours to enable attendance at the pharmacy for medication dispensing) to increase opportunities for employment. Each Specialist completed a two-day training course at the Centre for Mental Health (CMH; https://www.centreformentalhealth.org.uk/), and a 12-week online Practitioner Skills Course from the IPS Employment Center in the USA (https://ipsworks.org).

Fidelity to IPS delivery principles was evaluated by the UK-adapted, 25-item Individual Placement and Support Fidelity Scale (IPS-25).[30] The IPS-25 was completed by two independent practitioners from the CMH and IPS Grow (https://ipsgrow.org.uk); a capacity building network of IPS expertise set up to support the expansion of IPS in UK NHS mental health services) during a one-day visit to each centre after the IPS service had been running for 5–7 months and for 15–18 months.

Reviewers completed the IPS-25 after interviewing a sample of IPS participants, Employment Specialists, centre managers, local employers; reviewing a sample of case notes; and observing the IPS team at work. Each service was rated overall on staffing, organization, and delivery dimensions using a five-point scale: 1, no implementation–5, full implementation (total score range: 25–125; fidelity classification: not IPS, 73 or less; fair, 74–99, good, 100–114; exemplary, 115–125). After each review, reviewers submitted a report to the centre offering recommendations for delivery improvement.

Outcomes

The primary outcome was attainment of employment in the open competitive labour market during the 18-month follow-up. This was defined as work for at least 7 h (i.e., one day). Among participants who achieved this outcome, there were five secondary vocational outcomes: (1) number of days of employment (and National Insurance [NI] contributions and tax paid); (2) number of days from randomisation to first employment; (3) number of job appointments (operationalised as 1 only versus 2≥); (4) number of days of longest held employment (i.e., job tenure); and 5) whether employment was sustained (i.e., tenure in a single appointment for at least 13 weeks).

From the NDTMS, there were seven secondary alcohol and drug treatment-related outcomes up recorded during follow-up or at the latest point in follow-up: 1) alcohol consumption in the AUD group (grams per day of alcohol consumed in the past 28 days); (2) opioid use and drug injecting in the OUD group (number of days in the past 28 days); (3) use of the primary drug in the other DUD group (number of days in the past 28 days); (4) AUD, OUD and other DUD DSM-5 status; 5) number of days enrolled in alcohol and drug treatment; (6) number of alcohol and drug treatment episodes; and (7) status at the end of follow-up (i.e., enrolled in treatment; exited treatment with a successful outcome; exited treatment with an unsuccessful outcome; deceased).

We obtained data to estimate primary and secondary employment outcomes using deterministic data-linkage methods. The participant's NI number was used for a search of records in databases operated by the Department for Work and Pensions (DWP) and HM Revenue and Customs (HMRC). If the NI number was not recorded (or appeared to have been entered incorrectly on the clinical research form), data-linkage was attempted using the participant's given name(s), family name, date of birth, sex (at birth), postcode, and name of the upper-tier local authority of their home address. Secondary alcohol and drug treatment outcomes were recorded by data-linkage with the NDTMS using the same procedure. For each participant that could be matched to records in the DWP, HMRC and NDTMS databases, we received outcome data for a period of 18-months before study enrolment and for the 18-months of follow-up.

The following information was used for the cost-effectiveness analysis: (1) the cost of IPS per participant; (2) the number of standard employment contacts recorded by DWP on the Universal Credit and the Labour Market System databases; (3) the number of alcohol and drug treatment contacts recorded on the NDTMS; and (4) attendances at Accident and Emergency services, other outpatient clinics, and inpatient admissions recorded by NHS Hospital Episode Statistics. We used the participant's NHS number to obtain health-related outcomes, and their NI number or personal identifiers to obtain all other outcomes.

Each centre asked participants to report safety events during follow-up.

Statistical analysis

We followed the DELTA[2] guideline to estimate the minimum sample size to detect a realistic target difference for the primary outcome, with an estimate of its uncertainty.[31] The number of participants needed for the primary outcome was guided by meta-analysis[8] of seven randomised trials with mental illness populations that evaluated IPS over 12-months (928 participants; using conservatively the lower bound of 95% CI to give a pooled employment attainment rate of 0.36 for IPS and 0.18 for standard employment support). With 90% power to detect this difference, a two-sided 5% level of statistical significance—and a 20% increase to compensate for missing or inaccurate information for data-linkage—we estimated that a minimum of 302 participants with AUD and OUD would be needed to obtain a range of the 95% CI for the OR effect from 1.50–4.36. Given that there are fewer people in treatment with other DUD, we powered the analysis for this group at 80% (requiring a minimum of 228 participants). We planned to recruit well above this target to facilitate the IPS effect mediation study and other analyses.

The SAP was implemented in Stata (version 14.1) and followed the intention-to-treat principle. Reports to the DMC were prepared by analysts BE and PH. Senior Statistician (JK) remained blinded to intervention group allocation until the primary endpoint and clinical group analysis was completed.

Statistical tests were two-sided and performed with a 5% significance level, reporting 95% CI and the p-value of the effect. There was no adjustment for multiple comparisons.

Missing outcome data for the effectiveness analysis was managed following a full-information, maximum likelihood approach, with generation of 20 probabilistic datasets containing all study variables for predictive mean matching (PMM). The primary analysis model was repeated to evaluate IPS effectiveness for the AUD,

OUD and DUD groups using the OUD group as the referent.

For the full-analysis set, the primary outcome measure was analysed by a mixed-effects logistic regression model which included fixed-effects for the AUD, OUD and other DUD groups, the participant's five-year employment history, and study intervention allocation; and a random intercept for the community treatment centre (Stata command meqrlogit). The intervention effect parameter was the adjusted odds ratio for attainment of employment. We also planned a complete case sensitivity analysis for all participants with primary outcome data.

Recruitment occurred during the COVID-19 pandemic, and we anticipated that the government's public health restrictions would exert a substantial negative impact on study participants' ability to seek employment. Following the CONSERVE statement for trials affected by extenuating circumstances,[32] we twice repeated the primary analysis: first, by removing participants unaffected by the pandemic (i.e., their end-of-study date was before 16 March 2020, the start of the first 'lockdown' in England); second, by including a pandemic exposure covariable to represent the potential degree the participant might have been affected by the public health restrictions (coded: 0–3; 0, not impacted [enrolled in study during 8 May 2018–25 September 2018]; 1, low potential impact [tertile 1, enrolled in study during 26 September–5 February 2019]; 2, medium potential impact [tertile 2, enrolled in study during 6 February 2019–18 July 2019]; and 3, high potential impact [tertile 3, enrolled in study during 19 July 2019–30 September 2019]).

Available data for the complete case exploratory analysis of the secondary vocational and alcohol and drug treatment outcomes was analysed by mixed-effects regression (including fixed-effects for the AUD, OUD and other DUD clinical groups, the participant's employment history, and their study intervention allocation; and a random intercept for treatment centre). Each model related to the nature of the outcome measure: linear regression for alcohol consumption and drug use (Stata command *mixed*); count-based outcomes were assumed to have an underlying Poisson distribution (Stata command *mepoisson* or *menbreg*, depending on the observed distribution); logistic regression for binary measures (e.g., DSM-5 early remission status) with the success probability inferred from the logistic cumulative distribution function (Stata command *meqrlogit*); and a parametric survival-time model for the number of days to first employment (Stata command *mestreg*).

The Health Economic Analysis Plan (HEAP) was implemented in Stata (version 14.1).

The within-trial cost-effectiveness analysis (CEA) was done from the NHS and patient perspective. We estimated the costs of study interventions, alcohol and drug treatment, and health services received. IPS delivery costs were calculated using information provided by centre management on staff salaries, on-costs, and overheads, and from the STS. Derived unit costs were multiplied by the total days of each participant's IPS episode. Standard employment support services were estimated from the type, number, and duration of contacts with using DWP data on Universal Credit and the Labour Market System database for legacy benefit claimants.

Alcohol and drug dependence treatment and hospital care costs were obtained from national daily unit costs by service type using the most recent year of publication. A cost per participant was calculated by multiplying the reported resource use by the unit cost for each service type. Where unit cost data was only available for earlier financial years, they were inflated to 2020–2021 prices using the ONS GDP deflator.[33] All costs were valued in 2020–2021 prices and, because the study follow-up was less than two years, they were not discounted. Using a Market Forces Factor adjustment—apart from the intervention costs which were only incurred for the IPS trial arm and were local costs—all costs were measured and monetised for 18-months before allocation to study interventions and follow-up. Estimated costs before participant randomisation were included as model covariables.

We included exploratory analyses of the AUD, OUD, and other DUD group and the study centres. There were two outcome measures: a health outcome; a quality of life outcome (expressed as a quality-adjusted life year [QALY; one QALY equal to one year of life in perfect health, measured in terms of the person's ability to carry out daily life activities free from pain or mental ill health]); and the number of additional days in employment during follow-up. Cost-effectiveness was determined using a threshold value for the economic concept called Willingness-To-Pay (WTP). A WTP threshold value is the amount of money that a consumer is willing to pay for an improvement in an outcome.

For the value of a QALY in 2020–2021, incremental cost-effectiveness ratios (ICERs) were valued against the National Institute for Health and Care Excellence's (NICE) willingness-to-pay (WTP) threshold of £30,000[34] and HM Treasury's WTP threshold of £70,000.[35] As recommended by NICE,[36] QALY values were estimated at the study baseline assessment and each participant's latest follow-up used EQ-5D-5L crosswalk values for the UK.[37] To account for those who did not complete the full 18-month follow-up period, we calculated the percentage of the follow-up period that each participant completed. The health outcome value was the change in total QALYs over the trial period, calculated as the average QALY crosswalk value at baseline and latest follow-up, multiplied by the duration spent within that health state. A standardised WTP threshold was not available to value each additional day of employment, so we

followed the same methodology as an IPS trial which used a series of net benefit values ranging between £0–1000 in £200 increments.[13]

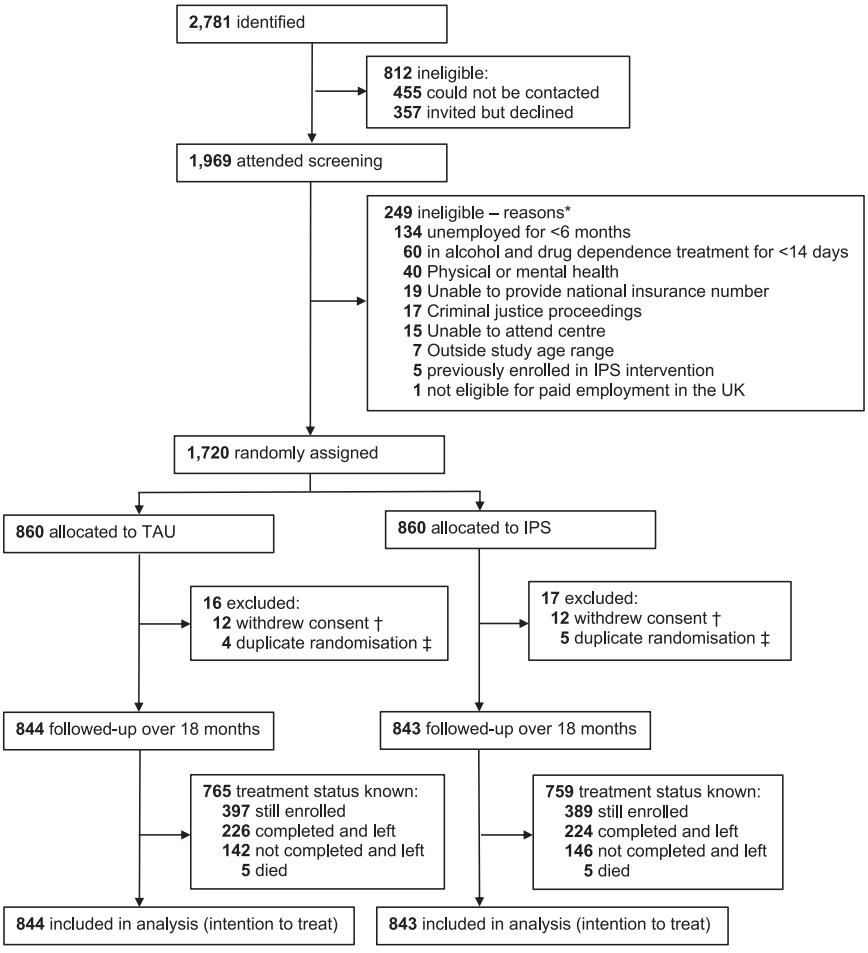
Missing outcome data for the CEA was managed using a full-information, maximum likelihood approach with multiple imputation and PMM with 20 probabilistic datasets containing all study variables. The CEA used a mixed-effects generalised linear model, with fixed-effects for AUD, OUD and other DUD group, the participant's employment history, and study intervention allocation, and a random intercept for treatment centre. We determined if models would run with bootstrapped and imputed data and evaluated their specifications through inspection of Akaike Information Criteria values and standard errors. Bootstrapping with 10,000 replications was done to produce cost-effectiveness acceptability curves.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between 8 May 2018 and 30 September 2019, 2781 potentially eligible patients were identified. Of these, 812 were excluded, most commonly due to a failure to contact or the patient declined to be screened (Fig. 1). 1720 [87.4%] of 1967 who consented for screening completed it, and they were randomly allocated to TAU or IPS. During the study, 24 participants withdrew their consent for all their data to be used and were removed. In error, a further nine participants were re-randomised to study interventions on two occasions. After discussion with the study oversight committees, we included



IPS, Individual Placement and Support; TAU, treatment as usual;

* Some participants met more than one criterion;
† These 24 participants withdrew their consent for all their data to be used for the analysis;
‡ Participants re-randomized in error and excluded from all analysis.

Fig. 1: CONSORT Flow chart of participants.

data for the first randomisation for these participants and deleted all data for their second randomisation (the analysis was therefore modified intention-to-treat).

The full-analysis set constituted 1687 participants (TAU, n = 844; IPS, n = 843). The last participant completed follow-up on 31 March 2021.

The location of the alcohol and drug treatment centres, their IPS provider(s), was as follows: Birmingham (Change Grow Live [CGL]); Blackpool (Blackpool Council); Brighton and Hove (Cranstoun at study initiation, then CGL to end of study); Derbyshire (Intuitive Thinking Skills); Haringey (St. Mungo's); Sheffield (Sheffield Health and Social Care NHS Trust); and Staffordshire (ADS at study initiation, then Humankind to end of study). The number of Employment Specialists in each centre was as follows: Birmingham (5); Blackpool (3); Brighton and Hove (3); Derbyshire (4); Haringey (3) Sheffield (4); and Staffordshire (4). Six of the seven centres recruited 144–288 participants. Birmingham recruited 432 participants.

Participants in the TAU and IPS groups were comparable on demographic and clinical characteristics (Table 1). OUD represented the largest clinical group (837 [49.6%] of 1687 participants). The other DUD mainly involved cannabis use disorder or stimulant (amphetamine or cocaine) use disorder. Typically, participants had received one previous completed alcohol or drug dependence treatment episode in the past 18 months (1270 [77.0%] of 1650 participants with available data). Most participants had severe DSM-5 diagnosis of alcohol or drug use disorder at admission to their current treatment episode (1091 [67.6%] of 1615 participants with available data). During the follow-up, 57 [0.3%] of 1687 participants were imprisoned (30 participants in the IPS group for a total of 3–432 days, and 27 in the TAU group for a total of 4–447 days).

TAU (standard employment support)

559 [66.2%] of 844 participants in the TAU group had at least one standard employment support contact during the follow-up (range: 1–73; median 13 [IQR 6–26]).

IPS intervention

804 [95.37%] of 843 participants in the IPS group received at least one session of IPS. Among these 804 participants, the duration of the IPS episode ranged from 1 to 276 days (mean 211.03 days; SD 81.39). On average, participants had 14.49 contacts (SD 13.19) with their Employment Specialist. The lowest number of contacts was recorded for the Sheffield centre (mean 9.22; SD 8.70). The highest number of sessions was recorded at the Staffordshire centre (mean 25.40; SD 17.21). 566 [67.1%] of 843 participants in the IPS group had at least one contact with standard employment support services during the follow-up (range: 1–65; median 15 [IQR 5–24]).

For the first fidelity review, IPS delivery in all seven centres was rated as 'fair' (IPS-25 total score range: 77–98). After 18 months of operation, all services increased their score (total score increase ranged from nine in Derbyshire to 31 in Staffordshire), with two services retaining their 'fair' rating, and five centres increasing to a rating of 'good fidelity' (IPS-25 total score range at second review: 88–111).

Primary outcome

We were able to successfully link 1403 [83.2%] of the 1687 participants in the full-analysis set to the DWP and HMRC databases to secure data for the primary outcome (706 [83.6%] of the 844 participants in the TAU group and 697 [82.7%] of the 843 participants in the IPS group). In the full-analysis set (n = 1687; Table 2), with multiple imputation, there was a statistically significant IPS effect (OR 1.29; 95% CI 1.02–1.64; p-value 0.036). While there was evidence of IPS effectiveness for the AUD and DUD clinical groups (OR 1.48; 95% CI 1.14–1.92; p-value 0.004, and OR 1.45; 95% CI 1.03–2.04; p-value 0.031, respectively), it was ineffective for the OUD group.

In the complete case sensitivity analysis of the primary endpoint (n = 1403; Table 2; characteristics of full-analysis set and complete case samples shown in the Appendix, Table S1, page 2), 175 [24.8%] of 706 participants in the TAU group attained employment versus 207 [29.7%] of 697 participants from the IPS group. There was evidence of effectiveness for the AUD and DUD clinical groups and ineffectiveness for the OUD group. The effectiveness of each of the seven study community treatment centres is shown in the Appendix, Table S2, page 4.

Including only those participants with follow-up occurring during the COVID-19 'lockdown' restrictions (753 [44.6%] of 1687 participants), had the effect of widening the confidence interval for IPS effectiveness to include the null (OR 1.34; 95% CI 0.94–1.89; p-value 0.103). However, in the full-analysis set with the addition of the 'lockdown' restrictions exposure covariable, the overall IPS effect was not attenuated (OR 1.30; 95% CI 1.02–1.65; p-value 0.034), and it was statistically significant for the AUD and DUD groups (OR 1.46; 95% CI 1.12–1.91; p-value 0.005 and OR 1.46; 95% CI 1.03–2.05; p-value 0.031, respectively).

With 566 [67.1%] of the 843 participants in the IPS group also receiving at least one contact with employment support services, we judged it important to do an exploratory post-hoc complete case analysis of the primary outcome. In this model, we separated participants allocated to the IPS group that received IPS only (277 [32.9%] of 843 participants) and those that received IPS and had one or more contacts with employment support services (566 [67.1%] of 843 participants). Compared with the overall primary endpoint, there was evidence of an additive effect for participants allocated to IPS who

Characteristic	TAU (n = 844)	IPS (n = 843)	Overall (n = 1687)
Community treatment centre—recruitment[a]			
Birmingham	216 (25.6)	216 (25.6)	432 (25.6)
Blackpool	84 (10.0)	87 (10.3)	171 (10.1)
Brighton and Hove	96 (11.4)	97 (11.5)	193 (11.4)
Derbyshire	144 (17.1)	144 (17.1)	288 (17.1)
Haringey	71 (8.4)	73 (8.7)	144 (8.5)
Sheffield	114 (13.5)	114 (13.5)	228 (13.5)
Staffordshire	119 (14.1)	112 (13.3)	231 (13.7)
Participant—demographic characteristics			
Age—years	41.1 (9.3)	40.4 (9.6)	40.8 (9.5)
Sex—at birth[b]			
Male	592 (70.4)	588 (69.8)	1180 (70.1)
Female	249 (29.6)	254 (30.2)	503 (29.9)
Ethnicity[b]			
White	669 (85.2)	688 (87.9)	1357 (86.5)
Asian	45 (5.7)	28 (3.6)	73 (4.7)
Black	40 (5.1)	35 (4.5)	75 (4.8)
Mixed	26 (3.3)	25 (3.2)	51 (3.3)
Other	5 (0.6)	7 (0.9)	12 (0.8)
Employment history—past five years[a]			
Worked ≤1 month	375 (44.4)	382 (45.3)	757 (44.9)
Worked >1 month	469 (55.6)	461 (54.7)	930 (55.1)
Participant—clinical characteristics			
Referral source[b]			
Self or family	436 (53.0)	406 (49.6)	842 (51.3)
Treatment, health, and social care services	249 (30.3)	271 (33.1)	520 (31.7)
Criminal justice system	101 (12.3)	93 (11.4)	194 (11.8)
Other	36 (4.4)	49 (6.0)	85 (5.2)
Number of alcohol and drug dependence episodes—in past 18 months[b]			
0	20 (2.4)	22 (2.7)	42 (2.5)
1	642 (77.5)	628 (76.4)	1270 (77.0)
2	133 (16.1)	137 (16.7)	270 (16.4)
>3	33 (4.0)	35 (4.2)	68 (4.2)
Duration of current episode—median days	272 (88–546)	275 (86–546)	274 (87–546)
Primary dependence treated[a]			
AUD	306 (36.3)	304 (36.1)	610 (36.2)
OUD	416 (49.3)	421 (49.9)	837 (49.6)
DUD	122 (14.5)	118 (14.0)	240 (14.2)
DSM-5 substance use disorder status[b]			
Early remission	88 (10.9)	83 (10.2)	171 (10.6)
Mild	109 (13.6)	108 (13.3)	217 (13.4)
Moderate	72 (9.0)	64 (7.9)	136 (8.4)
Severe	535 (66.5)	556 (68.6)	1091 (67.6)
EQ-5D-5L health status[b]			
Mobility	1.5 (0.9)	1.4 (0.9)	1.5 (0.9)
Self-care	1.3 (0.8)	1.2 (0.7)	1.2 (0.7)
Usual activities	1.6 (1.0)	1.5 (0.9)	1.5 (0.9)
Pain and discomfort	1.8 (1.0)	1.9 (1.1)	1.8 (1.0)
Anxiety and depression	2.5 (1.1)	2.5 (1.1)	2.5 (1.1)

Data are n (%); mean (SD); median (IQR). AUD, alcohol use disorder; CaUD, cannabis use disorder; CoUD, cocaine use disorder; DUD, drug use disorder (mostly cannabis and stimulant); IPS, Individual Placement and Support; OUD, opioid use disorder; TAU, treatment-as-usual (standard employment support). Sex: 3 participants in TAU and 1 participant in IPS; Ethnicity: 59 participants in TAU and 60 participants in IPS; Referral source: 22 participants in TAU and 24 participants in IPS; Treatment episodes: 16 participants in TAU and 21 participants in IPS; DSM-5 SUD status: 40 participants in TAU and 32 participants in IPS; EQ-5D-5L health status: Mobility, 41 participants in TAU and 29 participants in IPS; Self-care, 40 participants in TAU and 29 participants in IPS; Usual activities, 40 participants in TAU and 29 participants in IPS; Pain and discomfort, 41 participants in TAU and 29 participants in IPS; Anxiety and depression, 40 participants in TAU and 30 participants in IPS. [a]Stratification variable. [b]Variables with missing data.

Table 1: **Baseline characteristics of the full-analysis set.**

Analysis	Adjusted estimate	p-value
Primary outcome measure—full analysis set (n = 1687)		
Attained competitive employment	1.29 (1.02–1.64)	0.036
Clinical group—full analysis set		
Attained competitive employment		
OUD (referent)	–	–
AUD	1.48 (1.14–1.92)	0.004
DUD	1.45 (1.03–2.04)	0.031
Past five years employment history		–
Worked ≤1 month (referent)	–	
Worked >1 month	2.28 (1.76–2.96)	<0.001
Complete case analysis (n = 1403)[a]		
Primary outcome measure—attained competitive employment	1.31 (1.03–1.66)	0.031
Clinical group—attained competitive employment		
OUD (referent)	–	–
AUD	1.55 (1.19–2.02)	0.001
DUD	1.48 (1.02–2.14)	0.039
Worked ≤1 month in past five years (referent)	–	–
Worked >1 month in past five years	2.31 (1.79–2.99)	<0.001
Participants affected by pandemic restrictions (n = 753)[b]		
Primary outcome measure—attained competitive employment	1.34 (0.94–1.89)	0.103
Clinical group—attained competitive employment		
OUD (referent)	–	–
AUD	1.58 (1.06–2.34)	0.025
DUD	1.48 (0.82–2.66)	0.197
Worked ≤1 month in past five years (referent)	–	
Worked >1 month in past five years	2.39 (1.66–3.44)	<0.001
Extent of impact of pandemic restrictions—full analysis set (n = 1687)[c]		
Primary outcome measure—attained competitive employment	1.30 (1.02–1.65)	0.034
Clinical group—attained competitive employment		
OUD (referent)	–	–
AUD	1.46 (1.12–1.91)	0.005
DUD	1.46 (1.03–2.05)	0.031
Worked ≤1 month in past five years (referent)	–	–
Worked >1 month in past five years	2.27 (1.75–2.94)	<0.001
Extent of possible impact—attained competitive employment		
Not impacted (referent)—follow-up completed before 26 March 2020	–	–
Low—tertile 1	1.13 (0.81–1.57)	0.484
Medium—tertile 2	0.72 (0.51–1.02)	0.064
High—tertile 3	0.99 (0.72–1.38)	0.970

IPS intervention effect is adjusted odds ratio (95% CI). AUD, alcohol use disorder; DUD, drug use disorder (mainly cannabis or stimulant); IPS, Individual Placement and Support; OUD, opioid use disorder; TAU, treatment-as-usual (standard employment support). [a]HMRC data available for primary outcome measure (TAU [n = 706]; IPS [n = 697]). [b]Recruitment to study after 25 September 2018 (i.e., follow-up during UK COVID-19 pandemic restrictions). [c]Covariable included to estimate the extent of potential impact of UK pandemic restrictions.

Table 2: **Primary endpoint analysis, analysis of clinical groups, complete case analysis, and analysis of impact of UK COVID-19 pandemic restrictions.**

also received standard employment support (OR 1.55; 95% CI 1.19–2.01; p-value 0.001).

Secondary outcomes

For the 382 participants who achieved the primary outcome, there was no statistically significant effect for IPS for the number of days to first appointment, whether they attained two or more appointments, nor the total days employed and the tenure and sustained employment outcomes. Table 3 displays the statistically non-significant IPS intervention effect for these outcomes.

The exploratory analysis of the alcohol and drug treatment outcomes indicated no statistically significant evidence of an IPS effect for alcohol consumption (grams per week; data available for 326 [53.4%] of 610 participants with AUD [mean TAU versus IPS group difference −3.78; 95% CI −136.66 to 129.09; p-value

Analysis	Days to first appointment	Attained ≥2 appointments	Total days employed	Tenure[a]	Sustained employment[b]
TAU (n = 175)	201.1 (151.9)	65 (37.1)	130.4 (137.3)	114.2 (126.0)	73 (41.7)
IPS (n = 207)	179.7 (142.6)	78 (37.7)	132.6 (141.6)	110.2 (120.9)	87 (42.0)
Adjusted effect	HR 1.15 (0.94–1.41)	OR 1.12 (0.96–1.31)	4.36 days (−23.63 to 32.36)	−2.33 (−27.05 to 22.39)	OR 1.05 (0.69–1.58)
p-value	0.176	0.151	0.760	0.854	0.830
Adjusted effect for clinical group[c]					
AUD	HR 0.93 (0.75–1.16)	OR 1.09 (0.92–1.30)	−8.51 days (−38.59 to 22.29)	−12.16 (−39.03 to 14.71)	OR 0.87 (0.55–1.36)
p-value	0.527	0.299	0.600	0.375	0.529
DUD	HR 1.07 (0.78–1.45)	OR 1.15 (0.92–1.44)	−13.20 days (−55.58 to 29.19)	−25.15 (−62.57 to 12.27)	OR 0.84 (0.45–1.57)
p-value	0.685	0.231	0.542	0.188	0.580

Data are n (%); mean (SD). AUD, alcohol use disorder; DUD, drug use disorder (mostly cannabis and stimulant); HR, hazard ratio (TAU versus IPS); IPS, Individual Placement and Support; OR, odds ratio (IPS versus TAU); OUD, opioid use disorder; TAU, treatment-as-usual (standard employment support). [a]Duration in days of longest held employment during the 18-months of study follow-up. [b]Whether employed for 13 weeks or longer in any one competitive appointment during study follow-up. [c]OUD group is referent.

Table 3: **Secondary vocational outcomes among participants who attained employment, by study intervention group and clinical group (n = 382).**

0.956]); days of opioid use (data available for 582 [69.5%] of 837 participants with OUD [mean group difference –0.37; 95% CI –1.71 to 0.97; p-value 0.592]); days of drug injecting (data available for 551 [65.8%] of 837 participants with OUD [mean group difference –0.15; 95% CI –0.99 to 0.68; p-value 0.718]); days of cannabis use (data available for 129 [53.8%] of 240 participants with DUD [mean group difference 0.53; 95% CI –2.75 to 3.81; p-value 0.753]); number of days used amphetamine or cocaine (data available for 164 [68.3%] of 240 participants with DUD [mean group difference 1.80; 95% CI –1.72 to 5.33; p-value 0.983]); nor for DSM-5 remission status (data available for 327 [53.6%] of 610 participants with AUD, 508 [60.7%] of 837 participants with OUD, and 99 [41.3%] of 240 participants with DUD [OR 0.14; 95% CI –0.12 to 0.41; p-value 0.296]).

There was available data on alcohol and drug dependence treatment at endpoint for 828 [98.1%] of the 844 participants in the TAU group (mean days enrolled in treatment 331.23 [SD 213.10]; mean number of episodes 1.16 [SD 0.85]; with 226 [27.9%] of 811 participants with available data successfully completing and exiting treatment), versus 822 [97.5%] of the 843 participants in the IPS group (mean days enrolled in treatment 335.26 [SD 212.59]; mean number of episodes 1.17 [SD 0.97]; with 224 [27.8%] of 805 participants with available data successfully completing and exiting treatment). Table 4 displays the statistically non-significant IPS intervention effect for these clinical treatment outcomes.

Cost-effectiveness

During the 18-months before allocation to study interventions, there was a negligible mean cost per person difference for alcohol and drug dependence treatment and hospital care for the participants in the TAU and IPS groups of £5002.7 (95% central range [CR] £4880.3–5125.0) and £4994.4 (95% CR £4867.1–5121.6), respectively (mean group difference £8.3 [95% CR –£168.1 to 184.7]) (Appendix, Table S3, page 5). During the follow-up, the average annual cost of IPS was £1157 per participant. During the 18-months after allocation to study interventions, the mean cost per person difference for alcohol and drug dependence treatment, hospital care and study interventions for the participants were highest in Staffordshire in the TAU and IPS groups £6168.9 [95% CR £5841.2–6496.8] and £7401.6 [95% CR £7068.5–7734.6], respectively (mean group difference £1232.6 [95% CR £767.6–1697.5]) (Appendix, Table S4, page 6).

For the QALY analysis, the bootstrapped estimate for the cost-effectiveness plane fell in the northeast quadrant indicating greater cost (with little variation in cost), and an incremental QALY outcome gain of 0.01 (range 0.003–0.02) per participant relative to the TAU group (Fig. 2, panel A; Appendix, Table S5, page 7 shows the primary and sensitivity analysis). This marginal gain in QALY returned a very low likelihood of cost-effectiveness at the WTP £30,000 threshold (probability <0.001) and the WTP £70,000 threshold (probability 0.003). No SUD group was cost-effective at the lower WTP threshold (AUD probability <0.001; OUD probability <0.001; DUD probability 0.30). However, the AUD and DUD group did achieve cost-effectiveness at the £70,000 WTP threshold (probability 0.52 and 0.97, respectively) (Fig. 2, panel B and C; Appendix, Figure S1, page 9 shows the cost-effectiveness by study centre).

We estimated that the IPS intervention was associated with an additional seven days of employment per participant. The bootstrapped estimate for the cost-effectiveness plane fell in the northeast quadrant indicating greater cost (with little variation in cost), and greater incremental employment relative to the TAU group (Fig. 3, panel A; Appendix, Table S6, page 8 shows the primary and sensitivity analysis), and a 0.61 probability of cost-effectiveness at the WTP threshold of £200 per additional day in employment (Fig. 3, panel B) shows the WTP thresholds from £0 to £1000 in £200 increments). At the WTP £200 threshold, IPS was

Analysis	DSM-5 remission status (n = 934)	Days in treatment (n = 1650)	Number of treatment episodes (n = 1650)	Successful completion of treatment[a] (n = 1616)
Adjusted IPS effect	0.14 (−0.12 to 0.41)	1.72 (−14.77 to 18.21)	0.00 (−0.09 to 0.09)	0.02 (−0.22 to 0.26)
p-value	0.296	0.838	0.927	0.879
Adjusted effect for clinical group				
OUD (referent)	–	–	–	–
AUD	−0.64 (−0.93 to −0.34)	−251.84 (−270.17 to −233.51)	−0.14 (−0.24 to −0.05)	2.34 (2.04–2.64)
DUD	−0.56 (−1.01 to −0.10)	−257.67 (−283.04 to −232.30)	−0.27 (−0.40 to −0.11)	2.17 (1.81–2.54)

AUD, alcohol use disorder; DUD, drug use disorder (mostly cannabis and stimulant); IPS, Individual Placement and Support; IRR, incidence rate ratio; OR, odds ratio (IPS versus TAU); OUD, opioid use disorder; TAU, treatment-as-usual (standard employment support). [a]Number of participants still in treatment at end of follow-up: 397 in TAU, 389 in IPS.

Table 4: **Secondary alcohol and drug dependence treatment-related outcomes by study intervention and clinical group (n = 1687).**

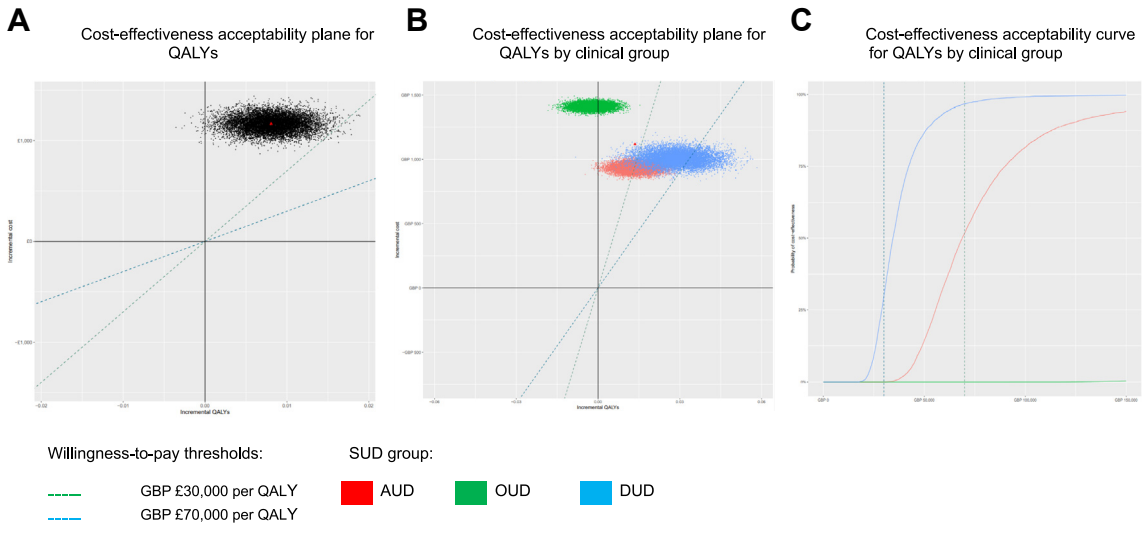
cost-effective for AUD (probability >0.99), but not for OUD and DUD (probability 0.02 and 0.41, respectively). Fig. 3, panel C and D, shows the probability of cost-effectiveness in £200 increments (Appendix, Figure S2, page 10 shows the cost-effectiveness by study site). The DUD group has a relatively widespread across the northeast and northwest quadrants of the cost-effectiveness plane and attained a break-even point at a WTP threshold of £600 (Fig. 3, panel D, dotted line). The OUD group did not reach a break-even point until the WTP threshold reached £1000.

Finally, exploratory analyses of cost-effectiveness by study centre indicated that one centre was cost-effective for the QALY outcome at the WTP £30,000 threshold (probability 0.58) and three centres were cost-effective at the WTP £70,000 threshold (probability range: 0.67–0.95). For the additional days of employment outcome, five of seven centres were cost-effective at the WTP £200 threshold. One of the two cost-ineffective centres reached a break-even point at the WTP £400 threshold; the other did not attain cost-effectiveness at any evaluated threshold.

Safety events are shown in Table 5. Serious Adverse Events were reported by 39 participants (13 [1.5%] of 844 participants in the TAU group and 23 [2.7%] of 843 participants in the IPS group. There was a total of 25 deaths (1.5%; 9 in the TAU group and 16 in the IPS group)—none judged related to study interventions.

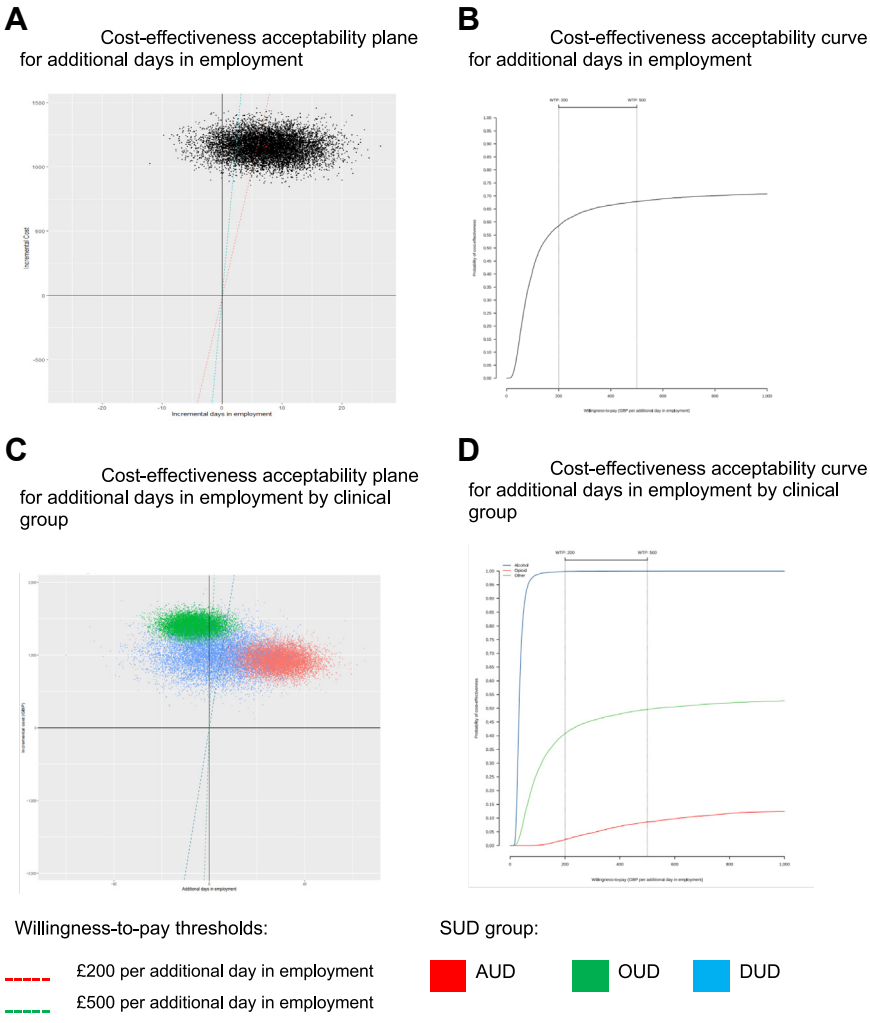
Discussion

In this first superiority randomised, controlled trial of IPS for people enrolled in treatment for alcohol and drug dependence, IPS achieved more employment in the open competitive labour market than standard employment support. Standard employment support was available to all participants, and an exploratory post-hoc complete case analysis suggested that among participants who were assigned to IPS who also received standard support, there was a stronger intervention



AUD, alcohol use disorder; DUD, drug use disorder (mostly cannabis and stimulant); OUD, opioid use disorder; QALY, quality adjusted life year.

Fig. 2: Cost-effectiveness analysis for health-related quality of life.



AUD, alcohol use disorder; DUD, drug use disorder (mostly cannabis and stimulant); OUD, opioid use disorder.

Fig. 3: Cost-effectiveness analysis for additional days in employment.

effect than for IPS alone (OR 1.55; 95% CI 1.19–2.01; p-value 0.001).

IPS was effective for AUD and other DUD, but not for OUD. Previous research that has identified chronic employability problems in this latter clinical disorder[38,39]). Our complete case analysis highlighted the disappointing finding for the OUD group (21.6% of the 356 participants allocated to TAU attained employment compared with 22.9% of the 349 participants assigned to IPS). This was a weaker IPS effect for OUD than expected, and a stronger effect for standard employment support.

Our randomisation procedure included a simple marker of employment history for the past five years (worked ≤1 month versus >1 month). Including this covariable in the analysis proved fortuitous because there was a strong independent association for job attainment for those who had worked for longer than a month (OR 2.28; 95% CI 1.76–2.96; p-value <0.001). At least on the alcohol and drug dependence populations, employment history is a strong moderator and appears—as one would straightforwardly expect—to affect the strength and direction of an IPS episode. Further work is needed to investigate how IPS might be adapted for those with little to no recent employment experience.[40]

We expected the pandemic restrictions to have a major negative impact on the primary outcome as this affected 44.6% of the total sample; and while our sensitivity analysis did return a statistically non-significant IPS effect (OR 1.34; 95% CI 0.94–1.89), the

Safety event	TAU (n = 844)	IPS (n = 843)
Adverse events		
Number of participants reporting	5	4
Number of adverse events	5	4
Type of adverse event		
Arrested	1	–
Assaulted	–	1
Despondent on allocation to study intervention	3[a]	–
Distress when completing research questionnaires	1[a]	1[a]
Drug overdose antidepressant	–	1
Minor injury	–	1
Serious adverse events		
Total number of participants reporting	13	23
Total number of serious adverse events	13	24
Type of serious adverse event		
Acute injury—head trauma	1[c]	–
Acute injury—road traffic accident	–	1[c]
Acute injury—haemorrhage after fall	–	1[c]
Other injury	1[d]	1[c]
Heart disease	–	4[c]
Heart disease—alcohol-related	–	1[c]
Liver disease	1[c]	1[c]
Liver disease and tuberculosis	–	1[c]
Liver disease—alcohol-related	1[c]	–
Liver and heart disease	–	1[c]
Multiple organ failure	–	1[c]
Psychiatric disorder—suicide attempt	–	1
Completed suicide	–	1[c]
AUD relapse after losing job	–	1[d,a]
Not known	5[c]	3[c]
Drug poisoning/overdose		
Drug class not reported	1[d]	2[d,b]
Alcohol	–	1[d]
Opioid	1[c]	2[d,b]
Antidepressant	1[d]	–
Painkillers and antidepressants	1[d]	
Non-steroidal anti-inflammatory	–	1[d]

Data are number (percentage). IPS, Individual Placement and Support; TAU, treatment-as-usual (standard employment support). [a]Adverse event judged probably related to study. [b]One drug poisoning/overdose was reported to be unintentional; other reported to be intentional (all other non-fatal drug poisoning events reported to be unintentional). [c]Participant died. [d]Participant was discharged after receiving hospital treatment.

Table 5: **Safety events (full analysis set).**

exposure variable did not attenuate the adjusted effect in the full-analysis set (OR 1.30; 95% CI 1.02–1.65). In the context of a study initiated during periods of restrictions in response to the pandemic, we believe the study findings are important, and will hopefully encourage people in recovery from alcohol and drug dependence to seek specialist IPS support.

We estimated that IPS was not associated with QALY outcome gains at the WTP thresholds used, but the additional days of employment outcome was cost-effective at the WTP threshold of £200 per additional day.

It is important to recapitulate the nature and variability of the IPS intervention effect in the study. In five of the seven centres, complete case effectiveness ranged from 26.9%–37.3%, but at the Birmingham centre (which had the largest IPS team and recruited 25% of the study sample) effectiveness was identical to standard employment support (employment attained by 41 [22.5%] of 182 participants in the TAU group and 40 [22.7%] of 176 participants in the IPS group); and was in favour of the TAU group at the Sheffield centre (31 [33.7%] of 92 participants in the TAU group attaining employment versus 26 [27.7%] of 94 in the IPS group).

In this pragmatic study, participants allocated to the IPS group were at liberty to obtain standard employment support and in the event, this was received by the majority (67.1%). This gave a rationale to explore if the combination of IPS and standard employment advice was more effective than IPS alone, and it turned out to be so (OR 1.55; 95% CI 1.19–2.01; p-value 0.001). We did not plan this adjunctive intervention analysis, so we caution against over-interpreting its important—but this does suggest a 'real world' marker of effectiveness.

In contrast to expectation, we did not find evidence that IPS was associated with behavioural and alcohol and drug dependence treatment episode outcomes. Compared with the OUD group, the AUD and DUD groups were also more likely to successfully complete and exit their clinical treatment interventions—but it should be appreciated that longer-term, retention-oriented pharmacotherapy is the norm for the former disorder. It would seem that a more intensive or enhanced IPS approach may be needed to help patients enrolled in OUD attain employment. Clinical delivery and effectiveness of interventions for OUD may also moderate IPS acceptance and effectiveness. There is evidence that strengthening case management and augmenting IPS with psychological therapies can deliver better retention and outcomes,[41,42] so this approach could be valuable for people with OUD, and others with complex needs.

The study has some strengths. This was a relatively large cohort with national database determination of primary and secondary vocational outcomes. Study findings also need to be considered in the light of several limitations. Firstly, the IPS service was new to all centres, and we commenced participant recruitment giving the teams and their management support little time to bed in. That said, the Employment Specialists were experienced, and all centres were independently evaluated, and all achieved a rating of fair IPS fidelity (five increasing to 'good' fidelity at second review). Second, we were not able to collect primary care and social care costs, and this may have restricted our ability to detect cost-savings. Third, it is possible that we did not detect all self-employment during the follow-up. This is because the UK tax system requires a paper tax return to be submitted within 6 months after the end of a tax year and 9 months if the tax return is online. Our longer-horizon cost-benefit analysis will address this. Fourth, although the 18-month follow-up was relatively long in comparison to psychosocial intervention evaluations for people with alcohol and drug dependence, it may not have been long enough to detect improvements in quality of life, and longer-term follow-up may be needed. Fifth, although we did not detect any statistically significant impact of the COVID-19 pandemic restrictions on the primary outcome, these may well have negatively impacted on the economic analysis, especially for health-related quality of life. Sixth, we were not able to link prison status or death to the primary endpoint model to evaluate if this were undercurrent effects for the primary endpoint analysis. However imprisonment (57 [3.4%] of 1687 participants) and death (25 [1.5%] of 1687 participants) were rare events and would be very unlikely to attenuate the intervention effect. Seventh, it would be straightforwardly expected that adverse events would outnumber serious adverse events; but this turned out to not be the case. We lack data on reasons for this, so we must acknowledge that either study participants were not asked about adverse events, or they were asked but attributed the question to only relate to study interventions.

In conclusion, in this first superiority randomised controlled trial of IPS for people enrolled in treatment for alcohol and drug dependence, IPS helped more participants attain employment in the open competitive labour market than standard employment support. IPS was cost-effective for QALY health outcome at a £70,000 WTP for the AUD and DUD groups, and a WTP threshold of £200 per additional day of employment.

Contributors

JM, JK and JS designed the study and developed the protocol with PA. PA, JK, JM and JS developed and implemented a training protocol for each site with support from Kyriacos Kolocassis. JK, BE and JM devised the SAP and AM, CS and WC devised the HEAP. PA, PH and BE developed the data management procedure. BE, JK, PH, JM, CS and WC had access to the dataset, and BE, PH, CS and WC analysed the data. JM had access to the dataset; he wrote the manuscript with contributions from the other authors, and he took the decision to submit the report for publication.

Data sharing statement

Deidentified patient data cannot be accessed because in order to protect participant privacy, the data use agreement with DWP and HMRC did not permit participant-level registry data relating to employment, taxes and state benefits to be made publicly accessible.

Declaration of interests

In the past three years, JM declares research grants for the following clinical trials: the National Institute for Health Research (NIHR; trial of behavioural reinforcement of acamprosate for alcohol use disorder [AUD]; sponsor: King's College London [KCL]); Indivior (phase 3 randomised controlled trial of extended-release pharmacotherapy for opioid use disorder; sponsor: KCL and South London & Maudsley NHS Trust); and Beckley PsyTech (phase 2a trial of 5-MeO-DMT for alcohol use disorder [AUD]; sponsor: Beckley PsyTech). He is the senior academic advisor for the Office for Health Improvement and Disparities, English Department of Health and Social Care, and a clinical academic consultant for the US National Institute on Drug Abuse, Clinic for Clinical Trials Network. JM declares honoraria and travel support from PCM Scientific, OPEN Health, and Indivior to contribute to scientific and educational meetings. He holds no stocks in any company.

No other authors declare any competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102400.

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