Protocol for a definitive, multi-centre, randomised controlled trial of Individual Placement and Support for people with alcohol and drug dependence

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Abstract

BACKGROUND: Unemployment is highly prevalent in populations with alcohol and drug dependence and current employment support is ineffective. Individual Placement and Support (IPS) is an evidence-based intervention for competitive employment. IPS has been extensively studied with people with severe mental illness and physical disabilities, but there have been no formal randomised controlled trials in alcohol and drug dependence. The Individual Placement and Support for Alcohol and Drug Dependence (IPS-AD) trial will determine definitively the effectiveness and cost effectiveness of IPS for patients with alcohol use disorder (AUD), opioid use disorder (OUD) and other drug use disorders.

DESIGN/METHODS: The IPS-AD trial is a seven-site, pragmatic, two-arm, parallel group, superiority, randomised controlled trial, with an independent process evaluation. Eligible patients – all enrolled in ongoing community treatment in England for AUD, OUD and other drug use disorders (adult, unemployed or economically inactive for at least 6 months and wishing to obtain open job market employment) – will be randomised (1:1) to receive standard employment support (treatment-as-usual [TAU]) or TAU and IPS for nine months with up to four months of in-work support. The primary outcome measure will be competitive employment status (at least one day [7 hours]) during an 18-month follow-up, determined by patient-level, trial data-linkage with national tax and state benefit databases. With an 18% target difference (for the IPS intervention), and a two-sided 5% level of statistical significance, a minimum target sample of 832 participants will give 90% power for a pre-specified, mixed-effects, multi-variable logistic regression model, using a maximum-likelihood multiple imputation approach to manage missing outcome data. IPS-AD has seven vocational secondary outcome measures: total time in competitive employment (and corresponding National Insurance contributions and tax paid); time from randomisation to first competitive employment; number of competitive job appointments; job tenure (length of longest held competitive employment); sustained employment (tenure in a single appointment for at least 13 weeks); and job search self-efficacy. A cost-benefit and cost-effectiveness analysis will be done using the primary and secondary vocational outcomes, along with a set of secondary alcohol and drug treatment-related and social and health outcomes and their associated reference costs. The study process evaluation will
address complementary questions of IPS implementation and delivery.

DISCUSSION: The IPS-AD trial is the first large-scale, superiority randomised controlled trial of IPS for people with alcohol and drug dependence. The study will provide definitive evidence for the effectiveness and cost-effectiveness of the IPS model and will have substantial implications for service delivery.

TRIAL REGISTRATION: ISRCTN Registry, ISRCTN24159790. Registered on 1 February 2018.

KEYWORDS: Individual Placement and Support, alcohol, opioids, drugs, dependence.

Background
Employment is integral to society and an important source of economic resource, personal role identity and life functioning [.]. Job loss and unemployment are associated with stress, poverty, illness and mortality [,.].

Developed by Becker, Bond and Drake and their colleagues at Dartmouth College in the USA, Individual Placement and Support (IPS) is an evidence-based intervention to facilitate participation in the open competitive labour market [,.]. IPS is founded on principles of personal preference, rapid job search, minimal pre-vocational training, and ‘in-work support’ to maintain employment. IPS has been widely studied severe mental illness and physical disability. In these populations, Frederick and VanderWeele reported a meta-analysis of 30 randomised controlled trials (RCTs) of IPS versus standard employment support [.]. Participants allocated to IPS were more likely to obtain work (relative risk 1.63; 95% Confidence Interval [CI] 1.46 to 1.82); had greater job tenure (defined as duration of longest held competitive employment; Cohen’s d 0.55; 95% CI 0.33 to 0.79); worked for longer during follow-up (d 0.46; 95% CI 0.35 to 0.57); and had more income (d 0.48; 95% CI 0.36 to 0.59).

In England in 2017/18, there was a very high rate of unemployment among people with alcohol and drug dependence (diagnosed as alcohol use disorder [AUD] and [named] drug use disorder in DSM-5 []). Among 75,800 people treated in the community with AUD, 70% were unemployed. Among 141,200 patients with OUD, 85% were unemployed; and among 24,200 patients with another drug use disorder 68% were unemployed [.]. These substantial rates of unemployment—highlighting the
ineffectiveness of current employment support provision—are in contrast to the overall rate of unemployment and economic inactivity in the United Kingdom (UK) in that year, approximately 4% and 21% respectively.

In the UK, alcohol and drug-related problems are associated with substantial social costs (£21.5bn []) and economic costs (£20bn []). These include support provided from family and carers; costs associated with the provision of non-elective National Health Service (NHS) hospital treatment (accident and emergency [A&E], outpatient and inpatient care); mortality, loss in productivity, and crime.

Aside from a single, small-scale clinical pilot study of IPS for patients receiving medication treatment for OUD [], IPS has not been definitively evaluated for people with alcohol and drug dependence. Following a UK government-commissioned independent report’s recommendations [], the Work and Health Unit (a collaboration between the Department for Work and Pensions [DWP] and the Department of Health and Social Care [DHSC]) invited researchers from Public Health England (PHE) to submit a proposal for a multi-centre, randomised controlled trial of IPS.

This article describes the protocol for the Individual Placement and Support for people with Alcohol and Drug dependence (IPS-AD) trial.

Methods
Design
IPS-AD is an investigator-initiated, pragmatic, multi-centre, two-arm, parallel group, superiority RCT, with an independent process evaluation. The aim of the study is to provide definitive evidence for the effectiveness and cost-effectiveness of IPS to help people with AUD, OUD and other drug use disorders obtain open competitive employment. These questions will be answered by analysis of primary and secondary outcomes recorded across an 18-month follow-up (from randomisation) ([Figure 1]). There are also planned analyses of outcome mediation and longer-term effectiveness.

After enrolment, all study participants will continue to receive clinical treatment for AUD or drug use disorders (co-ordinated by a clinician called a keyworker) and standard employment support (conventionally termed treatment-as-usual [TAU]—the control condition); or they will receive ongoing
clinical treatment for AUD or drug use disorder, standard employment support, and IPS—the intervention condition.

The study will be reported following the CONSORT guideline (Consolidated Standards of Reporting Trials; http://www.consort-statement.org/) extension for non-medication trials [] and the Template for Intervention Description and Replication (TIDieR) checklist for reporting interventions []. This protocol has been written following the SPIRIT checklist for intervention trials []—see Supplementary Material (Table S1).

IPS-AD will be conducted following the principles of the Declaration of Helsinki [], the Medical Research Council Guidelines for Good Clinical Practice [], and the NHS Research Governance Framework[]. Participants will have the right to withdraw from the trial at any time without giving a reason.

Study population and setting

Study populations will be adults, unemployed and economically inactive, enrolled in community treatment for AUD, OUD or another drug use disorder. The minimum total target sample will be 832 participants. There are seven clinical recruitment sites. Each site is a NHS, not-for-profit, or private organisation providing community/outpatient treatment for alcohol and drug dependence. These clinical recruitment sites are in the following locations: Birmingham, Blackpool, Brighton and Hove, Derbyshire, London Borough of Haringey, Sheffield and Staffordshire. According to the treatment capacity of each site, two or more Employment Specialists (ES) will deliver IPS.

Participant inclusion criteria

Patients will be eligible to take part if they meet the following inclusion criteria:

1. Aged 18–65 years
2. Enrolled in treatment for drug or alcohol use disorder for at least 14 days with current diagnosis of a specified drug and/or alcohol use disorder
3. Unemployed or inactive at study screening visit for at least 6 months with declared wish to obtain open job market employment
4. Able to attend the community addiction clinic as required in the protocol
5. Able to communicate (verbal and written English) at a level required to engage with a psychosocial intervention
6. Able to provide personal National Insurance Number (NINO) to facilitate data linkage
c.

Participant exclusion criteria
Otherwise eligible patients will not be able to join the study if one or more of the following exclusion criteria are met:
1. Currently receiving detoxification treatment for drug or alcohol withdrawal
2. Clinically significant (or otherwise uncontrolled) severe mental health, intellectual disability, organic brain disease or dementia, or physical disability that is judged by the local clinical lead to prevent the person accepting IPS
3. Suicide planning (past month) or suicide attempt (past 6 months)
4. Current legal proceedings which are likely to result in imprisonment
5. Enrolment in an IPS trial, or in the past 6 months
6. Previously enrolled in the IPS-AD study.

Procedure
All keyworkers and ES will complete National Institute for Health Research’s Good Clinical Practice (GCP) training. Potential participants will be referred to an ES in the clinical team to discuss the study.

An online randomisation procedure will be created and independently managed on a secure website by the King’s College London Clinical Trials Unit. Immediately after securing informed consent and completing baseline research questionnaires, the ES will access the randomisation website to assign the participant to the intervention or control group (allocation ratio: 1:1). This will be done using block randomisation (with varying block size), and stratification by site, clinical diagnosis (AUD, OUD, other drug use disorder), and work history (1 month or less versus more than 1 month of paid employment in last five years).
The randomisation system will immediately confirm the participant’s allocation to IPS or TAU by email. The ES will then inform the participant and their keyworker. Participants assigned to TAU will be given an information pack containing details of standard employment support services available locally and will have no further contact with the ES. It will not be feasible to blind clinicians to trial condition allocation.

**IPS intervention principles and delivery**

IPS will be offered as an individual (one-to-one) intervention for 9 months with up to 4 additional months of in-work support if competitive employment is attained. IPS will be provided without restriction due to job readiness, work history, qualifications, and homelessness. In weekly sessions in the first month, the ES will discuss opportunities to work while continuing to receive state benefits; develop a vocational profile of the participant’s skills, experience and employment preferences; help the participant write or update their curriculum vitae; and implement a rapid job search. As appropriate, the ES will contact local employers and help the participant with completing job applications and interview preparation. The ES will look for opportunities to develop relationships with local employers and discuss opportunities to tailor work for people recovering from alcohol and drug dependence.

Thereafter, scheduled sessions will be approximately fortnightly, with additional phone and email contact provided as needed. Once the participant starts work, the ES will offer in-work support for up to 4 months. This support will be approximately weekly contacts in the first month, then fortnightly. The ES will discuss how the participant is adapting to new job; assist with any referral for medical treatment; and, with consent, seek to discuss job flexibility issues with the employer (e.g. adjusting shift patterns to enable the participant to collect treatment medication from a retail pharmacy).

**Standard employment support control group**

Vocationally, participants randomised to the TAU control group will receive standard employment support and no IPS. For participants receiving Jobseeker’s Allowance (JSA) or Universal Credit (UC) with all work-related requirements, TAU will generally receive support from Jobcentre Plus (JCP) and/or the Work and Health Programme, or employment support provided by the alcohol and drug treatment
programme or other local services. For most participants in receipt of health-related unemployment benefits, there may be little or no contact with public employment services, although they may still be able to access employment support through the treatment partnership.

**IPS training**

Baseline training will consist of a continuing professional development accredited two day ‘Doing What Works’ course provided by the Centre for Mental Health (CMH) and a 12-week online Practitioner Skills Course provided by the USA IPS Employment Center. Sites will be encouraged to pursue continuing training and professional development for the IPS team. Opportunities to do so will include establishing links with a local IPS Centre of Excellence, facilitated by the CMH, and with IPS Grow—a capacity building network of IPS expertise funded by NHS England and the DWP, primarily to support the expansion of IPS in NHS mental health services.

**IPS fidelity**

To support delivery of IPS interventions in accordance with the intervention’s principles, the study will use the Revised Individual Placement and Support Fidelity Scale (IPS–25) [1]. The IPS–25 has been adapted to the UK employment context by the CMH [2]. The instrument has 3 sections: staffing, organization and services. Independent reviewers score items on the scale using a 5-point response format, ranging from 1 = no implementation to 5 = full implementation, with intermediate numbers representing progressively greater degrees of implementation. The maximum score is 125 points. In IPS-AD, completion of the IPS–25 involves access to multiple sources of information, including interviewing study participants; ES and managers; discussions with local employers; reviewing case records; and observing the clinical team. CMH will coordinate all fidelity reviewers with another organisation called Social Finance (SF).

From the start of the study, there will be planned fidelity reviews planned at each site at 5 to 7 months and 15 to 18 months. CMH and SF will provide each site with a detailed report of their IPS fidelity, with advice on how this can be improved.

**Independent process evaluation**

RAND Europe and the CMH will conduct an independent process evaluation. Theory-driven and
following realist principles, this investigate IPS and clinical practice and answer questions of the characteristics of patients and IPS exposure that are associated with competitive employment outcomes. An initial focus will be on any obstacles encountered during the set-up of IPS in each site and how IPS is integrated into routine procedures. The evaluation of IPS delivery will be theory-driven and will follow realist principles. In each site, RAND and CMH researchers will conduct personal interviews (each audio recorded with permission) with a random sample of participants allocated to IPS and TAU as well as a convenience sample of ES, treatment service commissioners, managers, keyworkers, local JCP staff and employers (approximately 170 interviews planned in total).

**Primary outcome measure**

The primary outcome of the study is competitive employment status. This outcome will be met if the participant obtains at least 7 hours (i.e. one day) of employment in the open competitive job market at any time following randomisation to the end of an 18-month follow-up. This outcome measure is a commonly used indicator of IPS trial efficacy and aligns with meta-analysis. We will determine if the participant has achieved this outcome by linking participant-level information with Her Majesty’s Revenue and Customs’ (HMRC) Real Time Information (RTI) and Connect databases.

**Secondary outcome measures**

**Vocational**

IPS-AD includes the following secondary vocational outcome measures:

- Total time (days) in competitive employment (total National Insurance contributions [NIC] and tax paid)
- Time (days) from randomisation to first competitive employment
- Number of competitive job appointments
- Job tenure (length of longest held competitive employment)
- Sustained employment (tenure in a single appointment for at least 13 weeks)
- Job search self-efficacy

The time and count-based vocational outcomes will be determined from extracts of the RTI and CONNECT databases using the dates of starting and stopping competitive employment, NIC and tax records from randomisation to the end of follow-up.

Job search self-efficacy (for a mediation analysis of outcome) will be assessed by the Job Search Self-
Efficacy Scale-Behaviour scale (JSSE-B []). The JSSE-B is a 6-item measure, which includes confidence in making a good impression, making a good application, and using friends and contacts to discover vacancies, and has been shown to predict job search behaviour. Site clinicians will complete this measure during personal interviews at baseline, 6 months, 12 months, and 18 months and at treatment exit (the latter if feasible).

**Alcohol and drug treatment-related**

For the secondary outcomes and economic analyses, the following outcomes will be included:

- Alcohol consumption, drug use, drug injecting
- DSM-5 AUD, OUD and other drug use disorder remission status
- Total time enrolled in alcohol and drug use disorder treatment
- Number of AUD, OUD and other drug use disorder treatment episodes
- Treatment status at end of follow-up (enrolled; left successfully; left unsuccessfully; deceased).

Alcohol and drug use (recall: past 28-days) will be self-reported to site clinicians using the Treatment Outcomes Profile (TOP)]. The TOP is the English national outcomes monitoring instrument for publicly funded treatment services for drug and alcohol dependence. TOP data is uploaded to the National Drug Treatment Monitoring System (NDTMS). The TOP uses a structured, calendar-prompt, ‘timeline follow-back’ procedure [] to maximise accuracy of drug and alcohol use reporting. The TOP will be administered by site clinicians as a structured personal interview at baseline, 1 month, 6 months, 12 months and 18 months and exit.

DSM-5 remission status will be assessed by personal interview by site clinicians at baseline, 6 months, 12 months and 18 months using the Structured Clinical Interview for DSM-5 (clinician version; SCID-5-CV []). This has a checklist of 11 symptoms (each coded ‘present ‘or ‘absent’ ) to diagnose severity: no symptoms; mild, 1-3 symptoms; moderate, 4-5 symptoms; severe, ≥6 symptoms.

We will use the American Psychiatric Association’s definition for AUD and OUD remission (i.e. zero criteria except craving and using the ‘on maintenance therapy’ specifier as appropriate and not including tolerance and withdrawal item if adherent).

NDTMS records will be used to determine each participant’s total time in treatment in the community and in prison; the number of treatment episode, and their status at the end of follow-up. For data
modelling, we will record TOP and treatment exposure data for 18-months prior to randomisation for
those members of the cohort with a history of prior treatment for alcohol and drug dependence.

Social and health

For the economic analysis, the following social and economic outcomes will be included:

Welfare payments (i.e. Job Seeker’s Allowance [JSA]; Employment and Support Allowance [ESA];
Universal Credit [UC]; and Personal Independence Payment [PIP], Tax Credits [TC]).
NHS hospital attendances and admissions (A&E, outpatient and inpatient)
EQ–5D–5L
Mortality
Convictions
Prison sentences

JSA, ESA, UC and PIP welfare payments will be determined from the dates of starting and stopping
receipt of each benefit type recorded in the following DWP databases: National Benefits Database (JSA
and ESA); Atomic Data Store (UC), and Full-Service System (PIP). Tax Credits will be determined by
use of HMRC’s General Matching System (GMS).

Hospital care will be recorded by Hospital Episode Statistics (HES; PHE is the data controller). The
Office for National Statistics’ (ONS) register of births and deaths will record mortality.

Convictions and prison sentences will be recorded from extracts from the Police National Computer
(PNC) and the National Offender Management Information System (p-NOMIS), respectively (both
operated by the Ministry of Justice).

The EQ–5D–5L is a brief generic scale recording mobility, self-care, usual activities, pain/discomfort,
anxiety/depression, and with a 0 to 100-point vertical visual analogue scale (VAS) measuring overall
health status. Site clinicians will complete this measure during personal interviews at baseline, 6
months, 12 months, and 18 months and exit. HES, DWP and HMRC welfare payments, PNC and p-
NOMIS data will be recorded from randomisation to the end of follow-up. For data modelling, we will
also record these outcomes for 18-months prior to randomisation.

The schedule of enrolment, allocation, interventions and assessments is summarised in Table 1.

Sample size

Following preliminary planning, we followed the DELTA guideline to estimate the minimum sample
size []. Frederick and VanderWeele’s meta-analysis [8] specified the important and realistic target difference for the primary outcome, together with an estimate of its uncertainty. We have included a sensitivity calculation if our assumptions prove to be mis-specified.

For comparison to the duration of the IPS intervention in IPS-AD, we used the rate of competitive employment status reported by seven superiority trials which evaluated 12 months of IPS (928 participants; outcome rate 0.36 for IPS and 0.13 for TAU; odds ratio [OR] 3.76; 95% CI 2.70 to 5.24). Conservatively, we used the lower bound of CI (i.e. 2.70; equivalent to an outcome rate of IPS 0.36 and TAU 0.18).

To achieve 90% power to detect this 18% target difference—with a two-sided 5% level of statistical significance and a 20% increase to compensate for missing or inaccurate NINO information—we estimate that 302 participants will be required with AUD and OUD (giving an expected 95% CI estimate for the OR effect within a range from 1.50 to 4.36). In the event that the observed effect falls short of the target difference, we will be able to detect a 15% difference (which we judge is still important) with 83% power (OR 95% CI 1.24 to 3.46).

Given the lower number of people in treatment with other drug use disorders, we expect to recruit fewer participants in this group, so it will be realistic to power the analysis at 80%. For the 18% target difference (two-sided, 5% level of significance and with 20% increase for attrition), 228 participants will be needed (95% CI 1.35 to 4.57).

For the secondary outcome of total time worked, four of the seven trials used for the power calculation for the primary outcome measure from meta-analysis reported the total number of hours worked (i.e. the sum of all time in all competitive employment during the trial). These four trials recruited 376 participants and the pooled mean difference was 505 hours (Hedges’ g effect size = 0.54; 95% CI 0.33 to 0.74). Using this effect size as the realistic mean target difference, the analysis of the secondary outcome for length of competitive employment will have 99% to detect this target difference for the AUD and OUD groups. For the other drug use disorder group, we will be able to detect an effect size ranging from 0.54 to 0.38 with a minimum of 82% power.

On the basis of these conservative planning assumptions, a total of 832 participants will be the
minimum number of participants recruited. Mediation analysis and longer-term follow-ups will benefit from a greater sample size, so recruitment may extend beyond this minimum.

Study governance
Following a signed charter, an independently chaired Trial Steering Committee (TSC) and Data Monitoring Committee (DMC), will oversee study integrity, recruitment, research measure completion and analysis. These committees will include members with addiction service delivery, commissioning or IPS expertise, and patient and public involvement (PPI).

The Trial Management Group will be responsible for day-to-day running of the study and members will attend meetings of the oversight committees. After approving the protocol, the TSC and DMC will meet approximately three times each year.

All serious adverse events will be promptly reported to the DMC (for the TSC) and the study sponsor. The chief investigator will have overall responsibility for the trial dataset, supported by the oversight committees. The study may be prematurely discontinued by the sponsor, or for reasons reported by the chair of the DMC to the chair of the TSC.

Information governance and data linkage
Physical case report forms will be securely stored at each site. Sites will report research data and management information securely via NDTMS. A data submission portal will transfer monthly patient information to the study. Clinical site personnel will use a two-factor authentication before access to submit data.

A bespoke Local Data Collection System (LDCS) will collect data on participant identification characteristics, scheduled and attended IPS support sessions, and self-report job data to facilitate study monitoring. LDCS will be used by the Principal Investigator and ES at each site with data sent to the study via secure file transfer. All study data will be stored in password-protected folders within a restricted area of PHE’s network, accessible only by a limited number of authorised analysts.

Additionally, there will be physical and other data security safeguards to protect the data, and audit processes.

The planned deterministic data linkage procedure will be based on the participant’s NINO for
vocational outcomes, and NHS number for health-related outcomes. If the NINO is missing, linkage will be done utilising the participant’s full first name and surname, date of birth, gender and full or partial postcode or upper-tier local authority of residence. If the NHS number is missing, linkage will be done utilising the participant’s date of birth, gender and full or partial postcode or upper-tier local authority of residence. The HES patient identifier will be used to verify that a participant has been linked to a single HES patient. Linkage with offending databases (PNC and p-NOMIS) will utilise participant’s full first name and surname, date of birth, gender and upper-tier local authority of residence. Data to enable linkage will be transferred from PHE to government departments via a strong password-protected, encrypted, file transfer protocol. This transfer and linkage protocol will be reviewed periodically and may be enhanced.

Analysis
Primary vocational effectiveness
A Statistical Analysis Plan (SAP) will be approved by the trial committees and will be published on the Open Science Framework (OSF; www.osf.io) before data-lock. The analysis of the primary outcome (completed in STATA or R) will follow the intention-to-treat (ITT) principle and include all patients in the group to which they are allocated. Alpha will be set at 5% for the primary and secondary outcomes (with associated 95% CIs). The distributions of scale and count measures may be non-normal (skewed), so test statistics and effect sizes will be computed following appropriate transformation (e.g. natural log to obtain a geometric mean).

Data from all seven sites will be pooled and the superiority effectiveness estimate for the IPS intervention (adjusted OR and CI) will be determined using a mixed-effects, multi-variable logistic regression model. The model will include the stratification variables and a random intercept for each site to account for clustering. A maximum-likelihood multiple imputation approach will be used for the management of missing data with a sensitivity comparison to the complete case dataset.

Analysis of secondary vocational and alcohol and drug treatment outcomes
The ITT analysis of the secondary vocational and clinical outcomes will be done using appropriate
mixed-effects regression models according to each measure: linear for time-based (total time in employment and treatment); Poisson family for count-based (number of appointments; days of alcohol and drug use; number of treatment episodes); logistic for binary outcomes (sustained employment; DSM-5 remission); ordinal for treatment exit status; and proportional-hazards (for time to first employment) with measure-appropriate covariates. These models will include site and employment history stratification factors and may include other background variables. Exploratory models will also be separately done for AUD, OUD and other drug use disorder groups. A causal mediation framework analysis will be used to determine evidence for a theoretical mechanism of change for the IPS intervention using the JSSE-B as a mediator of competitive employment.

After completing the analysis and reporting of the primary and secondary analyses, we plan to undertake exploratory longer-term analyse using the national registry data at 3 years and 6 years – subject to approval for a protocol amendment.

**Economic analysis**

A Health Economic Analysis Plan (HEAP) will be approved by the trial committees and will be published on the OSF before data-lock. Using all primary and secondary vocational, treatment-related, social and health outcomes, the analysis will determine whether IPS has a positive net benefit and is cost-effective compared to TAU.

Using a cost-benefit ratio, a primary social cost-benefit analysis (CBA) will estimate the extent of additional monetised benefits accrued by the public and the Exchequer from investing in IPS. Costs and benefits will be analysed at the patient-level, before and after exposure to IPS and TAU.

Taking an NHS and patient perspective, a secondary cost-effectiveness analysis (CEA) will compare outcomes at baseline and 18-months after trial enrolment to calculate the additional cost per quality-adjusted life year (QALY), using mortality data and utilities estimated using the EQ–5D–5L. An incremental cost-effectiveness ratio (ICER) will be estimated to determine if IPS is cost-effective from the perspective of the health and social care sectors.

Outcomes from national registries will be used to estimate net tax revenue benefits accrued to the Exchequer, along with wider societal and economic benefits, and QALY gains. Official government
fiscal, economic and social monetary values will be applied to the difference in events observed pre-
and post-enrolment between the control and the intervention arms. For example, hospital activity will 
be valued by attaching average unit costs per episode derived from the Personal Social Services 
Research Unit (PSSRU) [] or the national NHS reference sheet [] and criminal activity will be valued 
using the Home Office social and economic costs of crime []. All costs will be multiplied by the market 
forces factor (MFF) developed by the NHS to adjust for the unavoidable geographical cost differences 
by site and differential labour and building costs.
The unit costs of IPS at each site will be estimated from information from the provider on site delivery 
using a Staff Time Survey (STS) of direct and indirect time spent on delivering IPS and delivering 
research. This will be conducted on three occasions during the study (i.e. at 6 months, 12 months and 
18 months) to remove noise from the data collection exercise. The CBA and CEA will also include 
sensitivity checks as specified in the HEAP.
After completing the analysis and reporting of the within-trial primary and secondary economic 
analyses, we envisage undertaking an exploratory longer-term economic analysis phase of the 
national registry data at 3 years and 6 years, subject to approval for a protocol amendment.
Discussion
There is a complex and costly relationship between unemployment and alcohol and drug use and 
dependence. Harmful drinking is a risk factor for job loss [] and, in some groups, unemployment 
predicts higher levels of drinking []. During economic recession, there is evidence that some people 
start to drink more and harmfully after losing their job []. Opioid use disorder (OUD) is associated with 
chronic unemployed [,]; untreated, this disorder can deter job seeking activity and the likelihood of 
finding work [,].
IPS is a promising candidate intervention for people with alcohol and drug dependence who are 
seeking work; but there have been no formal trials. IPS-AD will provide policy makers and treatment 
service commissioners with a definitive answer to questions of effectiveness and cost-effectiveness.
There will be several challenges to undertaking a pragmatic effectiveness RCT in community 
treatment services operated by the NHS, non-governmental and commercial providers. While ES are
funded posts for the study, the keyworkers will be dividing their time between their primary clinical role and research tasks (e.g. completion of research measures). It may be challenging to secure the same rate of research follow-up between the two arms of the study. However, this will not affect the primary outcome because of the data-linkage design.

A strength of the study will be the causal mediation analysis and process evaluation to investigate IPS change mechanisms. For the former, the job-search self-efficacy concept (here measured by the JSSE-B instrument) has been frequently used in IPS research. One acknowledged limitation of the study is that we may not be able to determine competitive employment status for some participants who pursue self-employment due to the timeline for submitting self-assessment tax returns to HMRC. The current system in the UK is for 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. With the IPS-AD 18-month follow-up completed at the end of March 2021, determination of competitive employment would not be known for at least 10 months after this point (i.e. January 2022). The question of IPS effectiveness and cost-effectiveness for the sub-population of participants who register for self-employment and attain at least 7 hours of paid work will therefore be addressed in a longer-term follow-up after the analysis of the primary outcome has been reported.

In the UK, there is a high prevalence of unemployment among populations enrolled in treatment for alcohol and drug dependence, and a pressing need for effective employment interventions. If IPS is to prove effective, there will NHS health savings, crime and employment benefits annually for the economy and the Exchequer [. We anticipate that the IPS-AD trial will make a substantial contribution to policy and practice.

Declarations

Trial status

IPS-AD was registered on ISRCTN (ISRCTN24159790) on 1 February 2018. This article refers to version 1.0 of the approved protocol (23 May 2018). The first participant was enrolled in the study on 8 May 2018. The trial is ongoing and recruiting participants. The last day of participant recruitment will be 30 September 2019. The ISRCTN entry was edited on 20 June 2019 to show that participant
recruitment is to be extended to 30 September 2019.

**Ethics approval and consent to participate**

Informed consent will be obtained from all study participants. The protocol, participant information sheet, participant consent form, and research questionnaires were approved by the East of England-Cambridge East research ethics committee (reference: 17/EE/0454) and the Health Research Authority (IRAS project number: 233276). The protocol was first approved by the Ethics Committee on 21 December 2017 and amended on 23 May 2018 to incorporate the independent process evaluation (version 1.0).

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**Authors’ contributions**
JM, JK and JS conceived the study design and developed the study protocol with PA. JK (trial statistician) was responsible for information governance and GDPR compliance. JK, BE and JM developed the SAP and VW and AM developed the HEAP. DQ, BE and PA developed the data management procedure. PA, KC, JK, JM and JS developed and implemented a training protocol for each site. JM drafted the initial and subsequent drafts of this article. All authors contributed to the revision of the manuscript and gave their consent to be authors. JM took the final decision to submit the manuscript for publication.

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**Availability of data and materials**

A trial implementation guide developed by the study team is available from the corresponding author on request. This manuscript does not contain any data.

**Consent for publication**

Consent forms for the trial include consent for publication of results in peer-reviewed journals.

**Competing interests**

All authors have completed the uniform disclosure form of the International Committee of Medical Journal Editors (www.icmje.org/coi_disclosure.pdf).

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Abbreviations
A&E Accident and emergency
ADS Atomic Data Store
AE Adverse event
AUD Alcohol use disorder
CBACost-benefit analysis
CEACost-effectiveness analysis
CIClConfidence Interval
CMH Centre for Mental Health
CONNECTHMRC database
CONSORT Consolidated Standards of Reporting Trials
CPD Continuing professional development
DHSC Department of Health and Social Care
DMCD Data Monitoring Committee
DSM–5 Diagnostic and Statistical Manual of Mental Disorders (5th edition)

DWP Department for Work and Pensions

EQ-5D–5L EuroQol 5-dimension, 5 level version

ESE Employment specialist

ESA Employment and support allowance

FSS Full Service System

GCP Good Clinical Practice

GDPR General Data Protection Regulation

GMS General Matching System

HEA Health economic analysis plan

HES Hospital Episode Statistics

HMRC HM Revenue and Customs

ICER Incremental cost-effectiveness ratio

IPS Individual Placement and Support

IPS-AD Individual Placement and Support for people with alcohol and drug dependence trial

IRAS Integrated Research Application System

ITT Intention-to-treat

JCP Jobcentre Plus

JSA Jobseeker’s Allowance

JSSE-B Job Search Self-Efficacy-Behaviour scale

LDLCS Local Data Collection System

MFF Market forces factor

MOJ Ministry of Justice

NBD National Benefits Database

NDTMS National Drug Treatment Monitoring System

NHS National Health Service

NIC National Insurance contributions
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Tables

Table 1. Schedule of enrolment, allocation, interventions and assessments

| Activity/data collection                  | Instruments/interventions                  | Study Period | Baseline | R | Interventions |
|------------------------------------------|-------------------------------------------|--------------|----------|---|---------------|
| Enrolment                                |                                           | T-1          | T0       | 1m | 6m            |
| Referral                                 | Referral form                             | X            |          |    |               |
| Eligibility                              | Screening                                 |              |          |    |               |
| Informed consent                         | PIS/PCF                                   | X            |          |    |               |
| Study arm allocation                     | Randomisation form                        |              |          |    |               |
| Interventions                            |                                           |              |          |    |               |
| TAU                                      | KW                                        |              |          |    |               |
| IPS                                      | ES                                        |              |          |    |               |
| IPS ES contacts                          | LDCS                                      |              |          |    |               |
| Assessments                              |                                           |              | X        | X  | X             |
| Alcohol and drug use                     | TOP                                       | X            | X        |    | X             |
| Health status                            | EQ-5D-5L                                  | X            | X        |    |               |
| Job search self-efficacy                 | JSSE-B                                    | X            | X        |    |               |
| AUD, OUD, other use disorder             | SCID-5-CV                                 | X            | X        |    |               |
| Staff time                               | STS                                       |              |          |    |               |
| Adverse events                           | AE form                                   |              |          |    |               |
| National databases                       |                                           |              | X        | X  |               |
| Alcohol/drug treatment                   | NDTMS                                     | X            |          |    |               |
| Earnings and tax/NICs paid               | RTI                                       | X            |          |    |               |
| Self-employed earnings                   | CONNECT                                   | X            |          |    |               |
| Personal Independence Payment            | ADS                                       | X            |          |    |               |
| Tax credits                              | GMS                                       | X            |          |    |               |
| Universal credit                         | UCFS                                      | X            |          |    |               |
| Other out of work state benefits         | NBD                                       | X            |          |    |               |
| Hospital treatment                       | HES                                       | X            |          |    |               |
| Mortality                                | ONS Register                              | X            |          |    |               |
| Convictions                              | PNC                                       | X            |          |    |               |
| Prison sentences                         | p-NOMIS                                   | X            |          |    |               |

ADS, Personal Independence Payment Atomic Data Store (Department for Work and Pensions); AE form, adverse events; AUD, alcohol use disorder; EQ-5D-5L, EuroQol five-level health status; ES, employment specialist; FSS, Universal Credit Full-Service System (Department for Work and Pensions); GMS, General Matching System (Department for Work and Pensions); HES, Hospital
Episode Statistics (Public Health England); IPS, Individual Placement and Support (the experimental intervention); JSSE-B, Job Search Self-efficacy scale; KW, treatment service keyworker; LDCS, local data collection system (Public Health England); NBD, National Benefits Database (Department for Work and Pensions); NDTMS, National Drug (and alcohol) Treatment Monitoring System; ONS Register, deaths registered in England and Wales (Office for National Statistics); OUD, opioid use disorder; PIS/PCF, Participant Information Sheet/Participant Consent Form; PNC, Police National Computer (Ministry of Justice); p-NOMIS, National Offender Management Information System (Ministry of Justice); R, randomisation; RTI, Real Time Information database (Her Majesty’s Revenue and Customs); SCID-5-CV, structured clinical interview for DSM-5 (alcohol and drug use) disorders, clinician version; STS, Staff Time Survey; TAU, treatment as usual; TOP, Treatment Outcomes Profile Figures
Figure 1
SPIRIT flow of participants

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
SPIRIT CHECKLIST FOR IPS-AD TRIAL.doc