STATISTICAL ANALYSIS PLAN for the IPS-SUD trial

Administrative information:

Sponsor name	Section for Clinical Addiction Research (RusForsk), Oslo University Hospital
Sponsor address	Mailbox 4950 Nydalen, 0424 Oslo, Norway
REC no	2019-54204
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PRINCIPAL/COORDINATING INVESTIGATOR:

Eline Borger Rognli, PhD. Oslo University Hospital.

Signature

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Date

ABBREVIATIONS

AA-registry	The State Register of Employers and Employees
EQ-5D-5L	Quality of Life questionnaire
Europ-ASI	European Addiction Severity Index
HADS	Hospital Anxiety and Depression Scale
SUD	Substance Use Disorder
RCT	Randomised Controlled Trial
IPS	Individual Placement and Support
NAV	Norwegian Welfare and Labour Administration
OUH	Oslo University Hospital
REC	Regional Ethical Committee
TAU	Treatment As Usual
WSAS	Work and Social Adjustment Scale

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1 Introduction

1.1 Background and Rationale

Employment is associated with better outcomes of substance use treatment and protects against relapse after treatment completion. Unemployment rates are high for people with substance use disorders (SUD) who undergo treatment, with Norwegian estimates ranging from 81 % to 91 %. Evidence-based vocational models are lacking for patients in SUD treatment but exist for patients with psychosis in terms of Individual Placement and Support (IPS). The aim of the IPS for substance use disorders (IPS-SUD) trial is to investigate the effect of IPS in a SUD population.

1.2 Intervention(s)

1.2.1 Brief description of the study intervention(s)

IPS: Participants will be referred to an employment specialist (ES), whose main goal is to help the patient, or job candidate, achieve employment of choice in the open job market. This will be done through intensive and personalized high-quality employment support, in this trial lasting up to 13 months. The candidate and ES will together make a vocational profile based on the candidate's strengths, experiences and job preferences. The ES will aid in targeted job seeking and provide close follow-up support according to needs to both the employee and the employer once work is obtained. The ES will work systematically in networking and developing relations with local employers with the aim of identifying job opportunities for their candidates. The IPS team will be directly integrated in the health service, with the employment specialists located in the same office space as the health service, participating in the clients' treatment teams and using a shared case management and documentation system. In order to give sufficient support, the ES's client portfolio will have a capacity of maximum 20 participants.

1.2.2 Control settings (if applicable)

The control group will receive a self-help guidebook, with a supplemental workshop to aid the use of the guidebook. The guidebook will be given to the participant immediately after the randomization allocation. The workshop will take place in the facilities of the health service and consist of three 3-hour sessions of didactic teaching and some practicing, and the number of participants will be between eight and twelve. The participants will also be offered one session of individual consultation with the workshop facilitator. The goal is that the participants will be enabled to make use of the services of the Norwegian Labour and Welfare Administration (NAV), which are extensive but may feel inaccessible to this patient group.

The standard employment support provided by NAV may vary in its content, scope and length, but consists of career counselling (individual or through workshops), help with job applications, and usually vocational training.

1.3 Trial Objectives

1.3.1 Primary Objective

The primary objective of this study is to assess if IPS is effective in helping people with SUD obtain and keep employment. The primary outcome will be in accordance with most IPS-trials: at least 1

day of competitive employment during the 18-month follow-up period after inclusion in the trial (AA-registry).

This operationalization will include even the briefest employments, and gives a general description of employment rate in the intervention group versus the control group.

1.3.2 Secondary Objectives

Secondary employment-related outcomes obtained during the 18-month follow-up will capture the pattern and extent of employment:

- Total time worked (days/hours)
- Time from inclusion to first employment
- Number of different jobs
- Duration of longest employment

12-months non-employment related outcomes will capture functioning related to mental health, substance use and quality of life:

- Engagement in education, training or other job-preparing activity
- Mental distress (using the Hospital Anxiety and Depression Scale)
- Past month substance use (Using the e-section of Europ-ASI)
- Quality of life (using the EQ-5D-5L and Work and Social Adjustment Scale)

1.3.3 Exploratory Objectives (if applicable): NA

2 Trial Methods

2.1 Trial Design

The IPS-SUD study is designed as a randomized, controlled, parallel-group superiority trial. Treatment allocation is a 1:1 ratio. Patients are randomised to either IPS or an enhanced TAU condition.

2.2 Randomisation

Eligible patients are allocated in a 1:1 ratio between IPS and enhanced TAU, using a computer randomization procedure with no stratification, and with randomly varying block sizes.

2.3 Statistical Framework

2.3.1 Hypothesis Test

This trial is designed to investigate the superiority of IPS compared to enhanced TAU with regard to obtaining and keeping competitive employment for people with SUD.

The primary null hypothesis is that IPS is non-superior to enhanced TAU with regards to the proportion of patients who obtain employment during 18 months of treatment.

2.3.2 Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the corresponding treatment group difference will be denoted as statistically significant. All efficacy estimates will be presented with two-sided 95% confidence intervals. As there is only one primary null hypothesis to be tested in this trial, there will be no adjustments for multiplicity.

For secondary outcomes, appropriate correction for multiplicity will be done.

2.3.3 Decision Rule

This trial is designed to address a single primary outcome. Superiority is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided).

2.4 Timing of Outcome Assessments

The main outcome, employment, will be retrieved from a national registry, with continuous data capture from the date of inclusion and during the 18-month follow up.

Assessments of secondary non-employment related outcomes will be obtained at 6 and 12 months after inclusion.

2.5 Statistical Interim Analyses and Stopping Guidance

There will be no interim analyses in this trial.

2.6 Timing of Main Analysis

The main analysis is planned at 18 months after the last participant is included, when our collected data has been linked with outcome data from the AA registry, and the primary database has been locked.

3 Trial Population

3.1 Screening Data, Eligibility and Recruitment

The total number of patients assessed for eligibility and reasons for not entering the trial will be summarised and tabulated.

A CONSORT flow diagram (appendix A) will be used to summarise the number of patients who were:

- assessed for eligibility
- not eligible
- eligible and randomised

- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

3.2 Baseline Patient Characteristics

The patient demographics and baseline characteristics to be summarised include age in years, gender, employment-related and educational background, source of income, living condition, substance use, quality of life and mental health.

Patient demographics and baseline characteristics will be summarised by randomised treatment arm and overall using descriptive statistics (N, mean, standard deviation, median, 25/75 percentiles, minimum, and maximum) for continuous variables, and number and percentages of patients for categorical variables. There will be no statistical analysis of group difference. Any clinical important imbalance between the treatment groups will be noted.

3.3 Withdrawal/Follow-up

Data for main outcome is drawn from a registry with no missing data. Four groups for withdrawal/lost to follow-up will be reported:

- Withdrawal of consent and deletion of data*
- Deceased during trial period
- Withdrawal from intervention but continued use of data*
- Other reasons

*Reasons for withdrawal will be presented.

3.4 Adherence and Protocol Deviations

3.4.1 Adherence to Allocated Treatment

Adherence to the intervention group with IPS is defined as having had at least one meeting with the employment specialist. Adherence to IPS for the service as a whole is evaluated by an external evaluation team on the international fidelity scale for IPS. Adherence to the control group intervention is defined as having received the self-help work book, which was the case for all participants who were allocated to the control group.

3.4.2 Protocol Deviations

The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:

- Not giving the self-help handbook to all participants randomised to the control group
- Not ever meeting with the employment specialist for those randomised to the intervention group

Protocol deviations will be summarized, and sensitivity analyses will be conducted to explore the impact of potential protocol deviations. All participants will be included in ITT analyses according to the group to which they were randomised.

3.5 Analysis Populations

The Full Analysis Set (FAS) will be defined as all patients randomly assigned to a treatment group, who have not withdrawn consent, and who are still alive 18 months after randomisation. As we do not have a complete dataset (those who withdrew and those who died are left out), this will not be a strict Intention to Treat (ITT) analysis dataset, but a dataset that follows the intention to treat principle.

The Per Protocol Analysis Set (PPS) will exclude randomised participants with major protocol deviations. In the intervention group, this is defined as not having met even once with the employment specialist. In the control group, this is defined as not having received the self-help guide book.

4 Outcome Definitions

4.1 General Definitions and Derived Variables

The outcome analyses on employment will be based on employment data from the AA registry.

4.1.1 Employment

Employment is defined as competitive employment in the ordinary labour market, where the employee receives payment. Work training or employment in protected environments are not counted.

4.2 Primary Outcome Definition

The primary outcome is the proportion in each randomised group who has at least 1 day of competitive employment during the 18 month follow-up period after inclusion in the trial, as registered in the AA-registry.
This operationalization is used in most IPS-trials, and will include even the briefest employments, and gives a general description of employment rate in the intervention group versus the control group.

4.3 Secondary Outcome Definition

4.3.1 Total time worked

Total time worked is defined as the total number of days and hours a person has worked from the date of randomisation and 18 months onwards.

4.3.2 Time from inclusion to first employment

Time from inclusion to first employment is defined as the time in days from randomization until a person has had his or her first day of employment.

4.3.3 Number of different jobs

Number of different jobs is defined as the number of different employment relationships a person has held from the date of randomisation and 18 months onward.

4.3.4 Duration of longest employment

Duration of longest employment is the length in days of the longest kept employment from randomisation and 18 months onward.

4.3.5 Sustained employment

Sustained employment is defined as tenure in a single job for at least 13 weeks.

4.3.6 Engagement in education, training, or other job preparing activity

This information is obtained from Statistics Norway's registries at 18 months. One variable will indicate engagement in education, and one variable will indicate engagement in training or other job-preparing activity. This variable is also defined as self-reported response at 6 and 12 months follow-up assessments: the proportion of participants who during the past six months have engaged in education, training, or other job preparing activity.

4.3.7 Mental distress

Mental distress is measured with the Hospital Anxiety and Depression Scale (HADS), a 14 item questionnaire consisting of an anxiety subscale (7 items) and a depression subscale (7 items). HADS is completed at baseline and at 6 and 12 months follow up. Mental distress is defined as mean score on the HADS questionnaire at 6 months and 12 months after baseline, and we will primarily use the 12-months measure.

4.3.8 Quality of life

Quality of life is measured with the EQ-5D-5L and WSAS. EQ-5D-5L is a five-item instrument that captures health related quality of life on five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) based on how the respondent feels today. The questionnaire also contains a visual analogous scale where the respondent can mark current quality of life from 0 to 100. WSAS is a five-item instrument that asks to which extent trouble with mental health has impaired the person in five different domains. Quality of life is defined as mean score at EQ-5D-5L, the visual-analogous scale, and WSAS, at 6 and 12 months follow up and we will primarily use the 12-months measure.

4.3.9 Substance use

Substance use is measured with the e-section of the Europ-ASI interview. It asks about lifetime use, age of onset, route of administration, use past six months and use past month of all commonly used substance groups, as well as about injecting behaviour. The E-section of Europ-ASI is conducted at baseline, and questions about use past six months and use past month are repeated at 6 and 12 months. Substance use is defined as use of substances (different types reported separately) during the past month and past six months, at 6 and 12 months follow up and we will primarily use the 12-months measure.

4.4 Overview of Outcomes

Level	Outcome	Timeframe	Type
Primary	At least one day of employment	18 months	Dichotomous
Secondary	Total time worked	18 months	Continuous
	Time from inclusion to first employment	18 months	Continuous
	Number of different jobs	18 months	Continuous
	Duration of longest employment	18 months	Continuous
	Sustained employment	18 months	Dichotomous
	Engagement in education, training or other job-preparing activity	18 months	Dichotomous
	Mental distress	12 months	Continuous
	Quality of life	12 months	Continuous
	Substance use, any use last six months	12 months	Dichotomous
	Substance use, any use last month	12 months	Dichotomous
	Substance use, number of days used past month	12 months	Continuous

5 Analysis Methods

5.1 Methods for Primary Outcome

5.1.1 Descriptive Statistics

We will present baseline characteristics with regard to clinical, educational and employment-related background and current status using descriptive statistics (mean, standard deviation, numbers and percentages) for the sample as a whole. To investigate baseline balance we will also present background characteristics according to randomization group. Descriptive statistics will be based on non-imputed data.

5.1.2 Primary Inferential Analysis

For the primary outcome, data from the seven sites will be pooled, and the superiority effectiveness estimate for the IPS intervention (OR and CI) will be determined using a mixed-effects logistic regression model. The model will include a random intercept for each site to account for clustering.

5.1.3 Effect Estimates

The primary effect estimate will be the risk difference between the two groups, using the logistic regression effect estimate (OR, 95% CI).

5.1.4 Assumption Checks and Alternative Analyses

Appropriate tests will be applied to assess whether data are likely from a normal distribution. Comparison of mean will be done using the t-test if variables have a normal distribution. In case of large departure from normality distribution, we will use non-parametric tests.

5.1.5 Missing Data

There are two sources of missing data for the main outcome:

1. Participant has died
2. Participant has withdrawn consent

It is explicitly stated in the consent form that participants can withdraw their consent at any time, upon which all data will be deleted. Therefore, we have not kept any data on those who withdrew their consent. These individuals will hence be excluded from all analyses.

Those who died will be kept out of the analyses.

Our primary analysis of the main outcome will be complete case analysis, excluding those who withdrew consent and those who died.

5.1.6 Sensitivity Analyses

As sensitivity analyses of the main outcome, we will do effect analysis with the Per Protocol Analyses Set.

There are no planned subgroup analyses.

5.2 Methods for Dichotomous Secondary Outcomes

5.2.1 Descriptive Statistics

Number and percentage, chi square test

5.2.2 Primary Inferential Analysis

Logistic regression model with mixed effects

5.2.3 Effect Estimates

Odds ratios (OR) with 95% confidence interval (CI)

5.2.4 Assumption Checks and Alternative Analyses

There will be no assumption checks and no alternative analyses

5.2.5 Missing Data

There are three sources of missing data on the secondary outcomes:

1. Participant has died
2. Participant has withdrawn consent
3. Participant did not respond to 6- or 12 months assessments

Those who have withdrawn consent and those who have died will be excluded from analyses.

Our primary analysis of the secondary employment-related outcomes will be complete case analysis, excluding those who withdrew consent and those who died.

Our primary analysis of the non-employment related outcomes, which are obtained at 12-months, will be mixed models for repeated measures, which are robust to handle data missing at random (MAR).

5.2.6 Sensitivity Analyses

There will be no sensitivity analyses for the employment-related secondary outcomes.

As sensitivity analyses on the non-employment related outcomes, which are obtained at 12-months, we will do multiple imputation based on baseline characteristics variables and randomization group.

5.2.7 Subgroup Analyses

We have no plans for subgroup analyses.

5.3 Methods for Continuous Secondary Outcomes

5.3.1 Descriptive Statistics

Comparison of means and t-test for normally distributed variables, or non-parametric tests if variables are not normally distributed.

5.3.2 Primary Inferential Analysis

Linear mixed model

5.3.3 Effect Estimates

Regression coefficient with 95% confidence interval

5.3.4 Assumption Checks and Alternative Analyses

Appropriate tests will be applied to assess whether data are likely from a normal distribution. Comparison of mean will be done using the t-test if variables have a normal distribution. In case of large departure from normality distribution, we will use non-parametric tests.

5.3.5 Missing Data

There are three sources of missing data on the secondary outcomes:

1. Participant has died
2. Participant has withdrawn consent
3. Participant did not respond to 6- or 12 months assessments

Those who have withdrawn consent and those who have died will be excluded from analyses.

Our primary analysis of the secondary employment-related outcomes will be complete case analysis, excluding those who withdrew consent and those who died.

Our primary analysis of the non-employment related outcomes, which are obtained at 12-months, will be linear mixed models for repeated measures, which are robust to handle data missing at random (MAR).

5.3.6 Sensitivity Analyses

There will be no sensitivity analyses on the employment-related secondary outcomes.

As sensitivity analyses on the non-employment related outcomes, which are obtained at 12-months, we will do multiple imputation based on baseline characteristics variables and randomization group.

5.3.7 Subgroup Analyses

We do not plan to conduct any sensitivity analyses.

5.4 Methods for Time to Event Secondary Outcomes

Time from inclusion to first job

5.4.1 Descriptive Statistics

Mean and t-test

5.4.2 Primary Inferential Analysis

Cox regression analyses and Kaplan Meyer plot

5.4.3 Effect Estimates

Hazard Ratio and 95% confidence interval

5.4.4 Assumption Checks and Alternative Analyses

Assumptions for Cox regression proportional hazard analysis will be checked, and stratified analyses or other more suitable analyses will be chosen if assumptions are not met.

5.4.5 Missing Data

There are two sources of missing data on the variable “time from inclusion to first job”: Participant has died or participant has withdrawn consent. In both cases, we will exclude the participants from the analysis. Missing data will hence be handled by using complete case analysis.

5.4.6 Sensitivity Analyses

There are no planned sensitivity analyses for the-time to-event outcome.

5.4.7 Subgroup Analyses

There are no planned subgroup analyses for the-time to-event outcome.

5.5 Additional Analyses

There are no plans for additional outcome analyses.

5.6 Sample size

The estimates below are used to calculate the required sample size necessary to detect a group difference on the primary outcome:

- Estimate for the primary outcome intervention group: 37 %
- Estimate for the primary outcome control group: 15 %

- Significance level: 5 %
- Power: 90 %
- Group allocation ratio: 1:1

Based on these estimates and parameters, we need 82 participants in each group to be able to detect a difference of 22% on the main outcome. By aiming for 100 participants in each group and a total sample size of 200, we will be able to detect a 20% difference on the main outcome with 90% power or a 17% difference with 80% power. A smaller difference in the main outcome is not considered clinically relevant, given the cost of the IPS intervention. We aim to recruit 100 participants in each group – a total of 200. Background for sample size estimates can be found in the protocol, PMID 34654464.

6 Safety Analyses

There are no planned safety analyses.

6.1 Adverse Events

Adverse events will be listed.

6.2 Clinical Laboratory Parameters

Not applicable

6.3 Vital Signs

Not applicable

7 Statistical Software

All statistical analyses will be done in SPSS, Stata or R.

8 References

8.1 Literature References

1. Gamble, C., Krishan, A., Stocken, D., Lewis, S., Juszczak, E., Dore, C., … & Loder, El. (2017). Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *Jama, 318*(23), 2337-2343.
2. Rognli, E. B., Aas, E. M., Drake, R. E., Marsden, J., Anders, P., Bond, G. R., ... & Arnevik, E. A. (2021). The effect evaluation of Individual Placement and Support (IPS) for patients with substance use disorders: study protocol for a randomized controlled trial of IPS versus enhanced self-help. *Trials*, *22*(1), 1-9.

8.2 Reference to Data Handling Plan

The project group will not receive any paper records. Questionnaires will be filled out by research assistant using computer or ipad, using Viedoc, a secure system for data capture and transference used by clinical trials at Oslo University Hospital. Data will be transferred to Oslo University Hospital's safe server for research data.

The list linking the project-generated ID number with the Norwegian national identity number will be stored in a separate and secure server (Medinsight).

Data will be cleansed before unblinding. An independent data monitor unit at OUH will ensure that the master file is unchanged after unblinding.

8.3 Reference to the Trial Master File and Statistical Documentation

The steps taken to cleanse data will be documented in a separate log. All syntaxes for statistical analyses based on the Trial Master File will be kept in a separate log. These Statistical Documentation logs will be kept five years after project end, as defined in the approval from REC.

8.4 Reference to other Standard Operating Procedures or Documents

Not applicable.