STATISTICAL ANALYSIS PLAN for AUD outcome predictors

- This Statistical Analysis Plan follows the "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials" published by Gamble et al (December 19, 2017) in JAMA, complying with the ICH E9 guideline.

Administrative information:

Sponsor name	Vestfold Hospital Trust (Sykehuset i Vestfold)
Sponsor address	Tønsberg, Norway
EudraCT number / REC no	REK nr: 125666
Trial title	Patient factors predicting completion and outcome in group treatment of alcohol use disorder
Trial ID	Clinical Trials.gov ID NCT04822987
Trial registration number	

SAP and protocol version:

SAP version and date:	Version 1, January 6. 2024
Protocol version	Version 4

Protocol version	SAP version	Section number changed	Description and reason for change	Date changed
4.0	1.0	NA	NA	NA

1 Introduction

1.1 Background and Rationale

Alcohol use disorder (AUD) is a highly prevalent disorder and a significant risk factor for disease and early death. However, it is vastly undertreated, and a substantial portion of patients do not receive effective treatments. We need more effective treatments, to tailor interventions to the individual patient, to select patients to the right treatment program earlier, and to make more accurate prognostic predictions. The study aims to investigate how patient factors (psychological, demographic, and social factors) predict treatment completion and outcomes in group treatment of alcohol use disorder. Designed as a prospective longitudinal observational study on patients treated in specialist health services for AUD in Norway, we hope to maximize ecological validity.

1.2 Intervention(s)

1.2.1 Brief description of the study intervention(s)

The study examines patients in treatment in the specialist addiction treatment services in Norway. As such, it is best described as an observational study on standard group treatment of AUD where the aim is to investigate patient factors predictive of outcome, not the effect of treatment. All patients in the study participate in time-limited group treatment at the treatment sites. Recruiting from standard treatment facilities representative of the specialist health services meant we could capitalize on realistic treatment conditions. Patients receive what is regarded as standard AUD treatment in Norway, as outlined by the Norwegian Health Directorate. The therapy offered included psychoeducation (e.g., education on substance use, mental health, relapse factors, and change) and psychotherapeutic group treatment consisting of cognitive behavioral interventions (identifying risky drinking situations, situational analysis, relapse prevention), motivational interventions (e.g., pros and cons of drinking, how to achieve goals) and a focus on group dynamics and interpersonal relations. In addition, all treatment sites included a module on physical activity. All treatment sites accepted abstinence and controlled drinking/reduction as a treatment goal.

1.2.2 Control settings (if applicable)

Not applicable.

1.3 Trial Objectives

1.3.1 Primary Objective

The primary objective is to study patient factors predictive of a) treatment completion and premature treatment discontinuation (dropout) and b) outcome (changes in alcohol use) at

treatment completion, one year after treatment completion, and three years after treatment completion.

1.3.2 Secondary Objectives

The secondary objectives of this study are:

a) Is the Montreal Cognitive Assessment (MoCA) useful as a brief screening instrument for cognitive impairments in patients with AUD?

1.3.3 Exploratory Objectives (if applicable)

a) Cognitive functioning of AUD patients
b) Fitness to drive evaluations in AUD patients
c) Pain as a predictor of alcohol use and treatment outcomes
d) Associations between quality of life and alcohol use

2 Trial Methods

2.1 Trial Design

- The study is designed as a quasi-experimental prospective cohort study of patients in ordinary treatment of AUDs in Norway. The emphasis on all sites is on treatment in groups, administered in a time-limited format. Including all patients qualifying for participation in group treatment increases the external validity of the study.

2.2 Randomisation

Not applicable.

2.3 Statistical Framework

The study is designed to investigate how patient variables predict outcomes of AUD treatment.

2.3.1 Hypothesis Test

We expect that:

a. Demographic factors
b. Alcohol use
c. Other drug use
d. Maladaptive personality functioning
e. Cognitive impairment

Predict

1. Treatment completion/discontinuation

2. Alcohol use one year after treatment completion
3. Alcohol use three years after treatment completion
4. Work status and social benefits three years after treatment completion

2.3.2 Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. Appropriate correction for multiplicity will be done.

2.3.3 Decision Rule

NA

2.4 Timing of Outcome Assessments

The timing of assessments and measures are presented in the table below:

MEASURES	T1 (Pre-treatment/baseline)	T2 (Treatment completion)	T3 (Follow up after 1 year)
PRIMARY OUTCOME			
AUDIT	X	X	X
ATTENDANCE IN GROUP TREATMENT		X	
SECONDARY OUTCOMES			
DUDIT	X	X	X
SCL-90R	X	X	X
WHOQOL	X	X	X
MODERATORS			
DEMOGRAPHIC VARIABLES	X		
EARLIER TREATMENT EPISODES/DIAGNOSES	X		
MINI	X		
SIPP-118	X		
MoCA	X		
WAIS-IV (sub-tests)	X		
D-KEFS (sub-tests)	X		
TREATMENT SATISFACTION		X	
AFTERCARE ACTIVITIES			X

2.5 Statistical Interim Analyses and Stopping Guidance

There will be no interim analyses in this trial.

2.6 Timing of Main Analysis

Due to the longitudinal nature of the study, analyses will be conducted at various intervals upon the completion of data collection for each specific measurement point.

The main analyses will be conducted in three separate stages:

1. Treatment completion/dropout. These short-term outcome analyses will be performed after all patients have completed treatments (T2). Analyses will start in January 2024 and be published immediately after the article's writing is completed.

2. Outcomes 1 year after treatment completion. This is the long-term outcome and will be conducted after all patients in the study have reached T3. Analyses will start in January 2025, and the results will be published soon after that.
3. Outcomes 3 years after treatment completion. Register data on work status and social benefits will be gathered from NAV.

3 Trial Population

3.1 Screening Data, Eligibility, and Recruitment

We apply broad inclusion criteria since we want the subjects to reflect the variance and complexity in ordinary clinical settings to enhance ecological validity. *All patients with a primary diagnosis of AUDs, enrolled in treatment at one of the three sites, and who will receive group therapy as part of their treatment are eligible for inclusion in the study.* Comorbid psychiatric, personality or other SUDs do not exclude participation. The subjects will be adults above 18 years of age.

3.2 Baseline Patient Characteristics

1. **Patient pre-therapy background.** Information about earlier treatment episodes, diagnoses, and demographic variables (e.g., age, sex, education, work experience, marital status, drug-free social network, economic situation, driver's license, etc.) is retrieved from participants' medical records.
2. **Alcohol use disorders identification test (AUDIT)** (Saunders et al., 1993). Ten-item self-report questionnaire for identifying harmful drinking and dependence. Responses are scored on a scale from 0 to 4. We have added one additional question, where patients are asked to indicate how many alcoholic units they have drunk for the last 7 seven days.
3. **Drug disorders identification test (DUDIT)** (Berman et al., 2005). Eleven-item self-report questionnaire for drug problems. Responses are scored on a scale from 0 to 4.
4. **Symptom checklist 90-R (SCL-90-R)** (Derogatis, 1994). Self-report inventory, 90 questions. Scored on a 4-point scale. Measures severity of psychological symptoms/distress.
5. **World health organization quality of life scale (WHOQOL-BREF) (Kirouac et al., 2017).** It measures the quality of life in four domains: Physical health, mental health, social and environmental. Twenty-six items scored on a 1 to 5 Likert scale.
6. **The Mini International Neuropsychiatric Interview (MINI) 7.0.2** (Sheehan et al., 1998). Short structured diagnostic interview for DSM-V diagnoses.
7. **Severity indices of personality problems (SIPP-118)** (Pedersen et al., 2019). A self-report questionnaire focusing on core components of maladaptive personality functioning. 118 questions scored on a 4 point scale.
8. **Montreal cognitive assessment (MoCA) 7.1** (Nasreddine et al., 2005). A 10-minute screening tool to assist clinicians in detecting mild cognitive impairments. Yields a maximum score of 30; a cut-off under 26 indicates cognitive impairment.
9. **Wechsler adult intelligence scale (WAIS-IV)** (Wechsler, 2008). Measures core aspects of intelligence (estimate of General Ability Index). The following subtests will be administered: Similarities, information, visual puzzles, block design, and digit span.

10. **Delis-Kaplan executive function system (D-KEFS)** (Delis et al., 2001). Measures executive functioning. (Color Word Interference Test and tasks 2-4 from the Trail Making Test).

Patient demographics and baseline characteristics will be summarised using descriptive statistics (N, mean, standard deviation, median, 25/75 percentiles, minimum, and maximum) for continuous variables and the number and percentages of patients for categorical variables. All variables will be checked for normalization, and any irregularity will be handled with statistical corrections according to best statistical practice.

3.3 Withdrawal/Follow-up

- Patients will be categorized as follows:
- Patients completing treatment and follow-up
- Patients discontinuing treatment, allowing collected data to be used
- Patients discontinuing treatment, withdrawing consent. These participants' data will be removed from the analyses.
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3.4 Adherence and Protocol Deviations

3.4.1 Adherence to Allocated Treatment

Adherence is defined as completing baseline assessment and starting treatment, i.e., attending at least one group therapy session of the planned treatment episode. Premature termination is defined as a) the patient leaving the treatment before completion and b) the clinic terminating the patient before treatment completion.

3.4.2 Protocol Deviations

If a patient is included in the study and, for some reason, discontinues treatment, the case will be used for analyses, and the patient will be contacted in the one-year follow-up study. Patients who discontinued treatment but did not withdraw their consent will also be included in the 3-year follow-up with data from medical registers.

Sensitivity analysis will be conducted if patients discontinue treatment before entering group treatment. These cases will be coded as pretreatment discontinuation, and analyses will be performed to investigate if these patients constitute a particular class of cases.

It is well-established that attrition from studies and difficulties obtaining follow-up data in the planned time frame are widespread in studies on substance use disorders. However, many patients will respond to follow-up questionnaires if given more time. We will, therefore, make a note of late responders, evaluate the quality of the data, and conduct sensitivity analyses when necessary. In addition, the response rate from the one-year follow-up may be low from those that discontinued treatment and analysis of sensitivity analyses on this subsample will be conducted.

Further, if any large deviations in scores/outliers are detected in the primary analyses, these will also be subject to sensitivity analysis.

3.5 Analysis Populations

- As the study investigates treatment completion and outcomes, the full analysis set (FAS) will include all patients who complete the baseline examination. Patients who have withdrawn consent will be removed from the database.
- For the one-year follow-up, all patients who have not actively withdrawn consent will be contacted.
- FAS will be used in the three-year follow-up and the analyses of register data, as our aim at this point is to investigate the functioning of all patients and consider if there are group differences and patient factors that can predict these differences in outcome.

4 Outcome Definitions

4.1 General Definitions and Derived Variables

The following predictor variables will be examined at baseline (T1): Severity of alcohol consumption, illegal substance use, mental disorders (diagnoses), psychological symptoms, maladaptive personality functioning, cognitive function, and demographic variables.

1) *The primary outcome variable for the short-term predictor analyses (T2) is the* percentage of attendance in group therapy sessions and dropout from therapy. *The primary outcome variable* for the 1-year assessment (T3) is alcohol use reduction, measured with AUDIT.
2) *Secondary outcomes* are substance use measured with DUDIT, symptom level measured with SCL-90, and quality of life measured with WHOQOL-bref.

4.2 Primary Outcome Definition

CHANGES IN ALCOHOL USE

Change in alcohol use will be measured with the AUDIT.

TREATMENT COMPLETION

Completion of treatment will be registered as completion or dropout, and further by the percentage of treatment completed (the number of treatment sessions attended out of the total planned sessions).

Treatment completion is defined as the patient completing the planned treatment episode in agreement with the clinic. *Treatment discontinuation* is defined as the patient leaving the clinic before the planned treatment episode is completed. This applies both when the patient decides to terminate the treatment episode and in the few cases where the clinic decides to terminate the

treatment episode prematurely. The study sites code treatment completion and discontinuation on every patient participating.

4.3 Secondary Outcomes Definitions

OTHER DRUG DISORDERS

Other drug use (primarily illegal drugs) will be measured with DUDIT.

PSYCHOLOGICAL DISTRESS

Psychological symptoms will be measured by SCL-90, providing the opportunity to investigate both a general symptom index score and symptom scale scores.

QUALITY OF LIFE
The WHOQOL-BREF measures quality of life.

4.4 Overview of Outcomes

The table below presents an overview of outcomes and measurement points:

MEASURES	**T1 (Pre-treatment/baseline)**	**T2 (Treatment completion)**	**T3 (Follow up after 1 year)**
PRIMARY OUTCOME			
AUDIT	X	X	X
ATTENDANCE IN GROUP TREATMENT		X	
SECONDARY OUTCOMES			
DUDIT	X	X	X
SCL-90R	X	X	X
WHOQOL	X	X	X

5 Analysis Methods

5.1 Methods for Primary Outcome

5.1.1 Descriptive Statistics

Descriptive statistics will be calculated for demographic and predictor variables. Descriptive statistics will be based on non-imputed data.

5.1.2 Primary Inferential Analysis

TREATMENT COMPLETION

Treatment completion/discontinuation will be analyzed using a logistic regression model with completion as a dichotomous dependent variable. Alcohol use, other drug use, psychological symptoms, maladaptive personality functioning, cognitive functioning, and demographic characteristics will be entered as predictor variables.

OUTCOME FOR TREATMENT COMPLETERS, 1 YEAR FOLLOW-UP

All patients completing baseline assessment will continue to the follow-up after one year. A multiple regression model will be constructed to examine significant outcome predictors. The primary outcome variable will be alcohol use (AUDIT), and drug use, psychological symptoms, maladaptive personality functioning, cognitive functioning, and demographic characteristics will be entered as predictor variables.

OUTCOME FOR TREATMENT COMPLETERS, 3-YEAR FOLLOW-UP

We will perform the same analysis for treatment completers as in the 1-year follow-up. In addition, we aim to follow-up the discontinuation group as well, making comparisons between the two groups possible.

REGISTER DATA

Further, we will analyse register data on employment and social benefits from all participants. We will use descriptive statistics and chi-square tests to describe and compare the groups.

5.1.3 Effect Estimates

The primary effect estimate will be the adjusted risk difference computed from the logistic regression effect estimate using the delta method. The adjusted relative risk will also be reported together with the p-value of the null-hypothesis test of no difference from the logistic regression.

Effect estimates from the multiple regression model will be estimated.

5.1.4 Assumption Checks and Alternative Analyses

Appropriate tests will be applied to assess whether data are normally distributed. Where relevant, logtransformation will be performed to attain a normal distribution. In case of a considerable departure from a normal distribution, we will use non-parametric tests.

5.1.5 Missing Data

When baseline data (T1) are obtained, there will be two more assessment points at treatment completion (T2) and after one year (T3). If a patient discontinues treatment, we will know about this

consecutively. In this study, as long as baseline data are completed, we will have data on all patients and be able to do analyses. For the treatment completion analysis, there will be no missing data for this primary outcome as we have complete information about completion status.

For the one-year follow-up data, we expect to have missing data. We will assess the need for imputation; if necessary, the primary method for imputation will be multiple imputation.

5.1.6 Sensitivity Analyses

At 12-months, we will do multiple imputation based on baseline characteristics and used in the sensitivity analysis accordingly.

5.1.7 Subgroup Analyses

- As data are collected from multiple sites, we will perform subgroup analyses of patients from different sites to investigate consistency in outcomes across subgroups. No other subgroup analyses are planned.

5.2 Methods for Dichotomous Secondary Outcomes

- Follows plan for primary analysis

5.2.1 Descriptive Statistics

5.2.2 Primary Inferential Analysis

5.2.3 Effect Estimates

5.2.4 Assumption Checks and Alternative Analyses

5.2.5 Missing Data

5.2.6 Sensitivity Analyses

5.2.7 Subgroup Analyses

5.3 Methods for Continuous Secondary Outcomes

- Follows plan for primary analysis

5.3.1 Descriptive Statistics

5.3.2 Primary Inferential Analysis

5.3.3 Effect Estimates

5.3.4 Assumption Checks and Alternative Analyses

5.3.5 Missing Data

5.3.6 Sensitivity Analyses

5.3.7 Subgroup Analyses

5.4 Methods for Time to Event Secondary Outcomes

- NA

5.4.1 Descriptive Statistics

5.4.2 Primary Inferential Analysis

5.4.3 Effect Estimates

5.4.4 Assumption Checks and Alternative Analyses

5.4.5 Missing Data

5.4.6 Sensitivity Analyses

5.4.7 Subgroup Analyses

5.5 Additional Analyses

We have planned some exploratory analyses of the data. For non-continuous data (axis 1 diagnosis, gender, drug-free social network, and marital status), analyses of variance will be computed with group characteristics as independent variables and outcome as dependent. It is reasonable to assume that patients with combinations of substance use profiles, symptom levels, cognitive impairments, and demographic factors may constitute specific groups (clusters) with different prognoses.

Cluster analysis will be applied to unravel distinct combinations of factors associated with good or poor prognosis. As an experiment, one substance use measure, one symptom distress measure, one cognitive functioning measure, and one or two demographic markers will be included in the analysis. Cluster analysis is merely an explorative method designed to uncover post-hoc empirical groups with combinations of features but may discern individual patterns that will not be evident in analyses of group means.

If the 1 year follow up response rate from the subjects that dropped out of treatment is sufficiently high, the analyses of baseline predictors effects on 1 year outcome, will be performed also as mediation analyses, with treatment completion status as possible mediator.

5.6 Sample size

The planned number of participants must be sufficiently large to answer the research questions. It is a quasi-experimental design in the sense that division into subgroups is determined by attributes of the participants not under complete control by the researchers. Regarding statistical power, we have computed the following examples: With an expected effect size of .35 and four predictors in a regression analysis, one hundred and four participants will be necessary to reach a power above .80. Small effect sizes (Cohen's d: .30) will be statistically significant on the five percent level with 85 participants. If we expect that 35 % (n=42) of the participants have an axis 1 diagnosis of major depression and that this group will have somewhat over half a standard deviation (.55) higher score on AUDIT one year after completed treatment, this difference will be statistically significant on the

five percent alpha-level if there are 41 and 76 persons in the two groups (depression vs. absence of depression), which will then be within the planned sample size. Based on the above analyses, a sample size of 120 will be sufficient to answer the research questions.

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5.7 Adverse Events

Adverse events will be registered using the hospital's adverse events clinical tool. The PI will be notified.

5.8 Clinical Laboratory Parameters

NA

5.9 Vital Signs

NA

6 Statistical Software

All statistical analyses will be done in SPPS version 29 (IBM) or R version 4.2.3.

7 References

7.1 Literature References

- The trial will be using standard statistical methods.

7.2 Reference to Data Handling Plan

- Data handling and cleaning of data will be documented during the analysis and described briefly in each peer-reviewed published paper and more thoroughly in the final Ph.D. thesis.

7.3 Reference to the Trial Master File and Statistical Documentation

- NA

7.4 Reference to other Standard Operating Procedures or Documents

NA.