Statistical analysis plan: Alcohol misuse treatment delivered in the hepatology clinic to patients newly diagnosed with alcohol-related liver disease: a randomized controlled trial

Statistical analysis plan date: 31.10.2025

Ethical protocol version 6 of 19.08.2025, SJ-895, EMN-2022-05916

Enrollment start date: 01.11.2025

Registration at clinicaltrials.gov was conducted before enrollment began: Yes, link:

Sponsor-investigator

None

Investigator

Gro Askgaard, email: gras@regsj.dk

Emil Buch Fromberg, Emil: Ebuf@regsj.dk

Section of Gastroenterology and Hepatology, Medical Department, Zealand University Hospital, 4600 Køge, DK-Denmark

Clinical epidemiologist responsible

Matilde Winter-Jensen, email: matilde.winther-jensen.01@regionh.dk

Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region, Denmark

Content

Abbreviations

RCT Randomized controlled trial

AUD Alcohol use disorder

ALD Alcohol-related liver disease

REDCAP Research Electronic Data Capture

Introduction

Alcohol consumption is the main cause of advanced chronic liver disease in the European region, and data from 2004 suggests that alcohol is the cause of 75% of chronic liver disease in the EU **(1,2)**.

Cessation of alcohol intake is an important factor for survival in patients with alcohol-related liver disease (ALD), with an almost double 10-year survival in ALD patients with decompensated liver cirrhosis who were abstainers compared to active alcohol users (65% vs 35%) **(3)**. Today, no routine practice supporting alcohol cessation in newly diagnosed ALD patients exists in Danish hospitals and similar in several other countries. Often, alcohol use disorder (AUD) treatment is anchored in local municipalities, away from hospital settings. Observational studies found that AUD treatment in ALD patients is associated with a reduced risk of decompensation and mortality **(4)**. Still, few randomized controlled trials of AUD treatment of patients with ALD have been undertaken, and they have mainly been in the context of liver transplantation. Qualitative studies have described the diagnosis of ALD and hepatology care as a key "teachable moment", as well as AUD treatment being heavily stigmatized and potential participants having great misconceptions about what it might entail **(5)**.

In 2021, we established an observational cohort of patients with newly diagnosed ALD (<3 months). Preliminary data from our cohort suggest that less than 10% of patients currently receive

specialized AUD therapy, and 62% of patients were actively using alcohol 6 months after diagnosis (unpublished data). In addition, we found that 65% of patients expressed high motivation to cut down on alcohol consumption (unpublished data). A high rate of continuing alcohol problems and a low rate of AUD treatment in ALD patients have also been reported in the United States **(4)**. With this background, we propose a randomized controlled trial embedded in an ongoing clinical cohort study to test if an offer to an alcohol misuse treatment in the hepatology clinic to newly diagnosed patients with ALD can increase abstinence 6 months later compared to standard care.

Objective

- To evaluate the efficacy of offering AUD treatment in the hepatology clinic to newly diagnosed ALD patients on alcohol abstinence after 6 months. We will conduct a randomized controlled superiority trial with parallel group design, hypothesis blinding and blinded outcome assessment comparing A) an offer of specialized AUD treatment in the hepatology clinic (intervention) and B) standard care (control).
- The primary outcome is abstinence throughout the last 30 days assessed 6 months after randomization.

Hypotheses, endpoints, and rationale

Hypotheses and endpoints

- Null-hypothesis: We hypothesize that among patients with newly diagnosed ALD, an offer of AUD treatment in the hepatology clinic will not make a clinically significant difference to the proportion that is abstinent throughout the last 30 days at 6 months of follow-up compared to standard care.
- Alternative hypothesis: We hypothesize that among patients with newly diagnosed ALD, an offer of AUD treatment in the hepatology clinic will make a clinically significant increase in the proportion that is abstinent throughout the last 30 days at 6 months of follow-up compared to standard care from 38% to 60%.

Rationale

Alcohol cessation in ALD patients is key to avoiding the progression of the disease, but many patients with ALD continue to drink alcohol. The efficacy of offering AUD treatment in the hepatology clinic to newly diagnosed ALD patients is nearly unstudied, with data on the efficacy of AUD treatment mainly coming from studies with participants without established ALD or patients awaiting liver transplantation (6–18).

Study methods

Trial design

We have designed a randomized controlled superiority trial to investigate the effectiveness of systematically offering AUD treatment in the hepatology clinic to newly diagnosed ALD patients to increase the proportion that is abstaining from alcohol after 6 months compared to standard care. The study will be embedded in an existing observational cohort from which already included participants will be used as controls in the RCT (n = 89). Please see Figure 1 for the flow of participants in the study. From 1 November 2025, we will start randomization of eligible participants.

Randomization will take place in connection with the first visit in the observational cohort study. Study participants randomized as controls will receive standard care through their treating physicians, which consists of individualized education on the nature of ALD as well as encouragement of alcohol use cessation.

Patients in the intervention group will receive standard care and in addition an offer of AUD treatment for six months, which includes a meeting with a therapist from the AUD treatment center at the hepatology clinic from which an individualized course of treatment is developed.

As decided by the local ethics committee, those randomized as controls will receive the same offer of AUD treatment in the hepatology clinic as the intervention group, but 6 months after their baseline visit. The historical controls will not be offered AUD treatment in the hepatology clinic.

The study period for recruitment will proceed from November 2025, until 132 participants have been randomized in total, expected in autumn 2028. There is follow-up for each individual participant conducted by personnel blinded to the randomization and consisting of: 1) telephone contact with interview about alcohol consumption using the time-line follow-back method

conducted at three time points after 1, 3 and 6 months after baseline, 2) measurement of phosphatidyl ethanol after 6 months, and 3) electronic health records after 6 months. We plan to later conduct an analysis of the randomized controls who are offered AUD treatment in the hepatology clinic after 6 months, that is 6 months postponed compared to the intervention group. Furthermore, we plan to conduct long-term follow-up via healthcare registries in about 3 years after study recruitment is finished. Please see Figure 2 for clarification on trial structure.

Figure 1. Expected flow of participants in the RCT (Created in BioRender. Fromberg, E. (2025) https://BioRender.com/ Tcacppm)

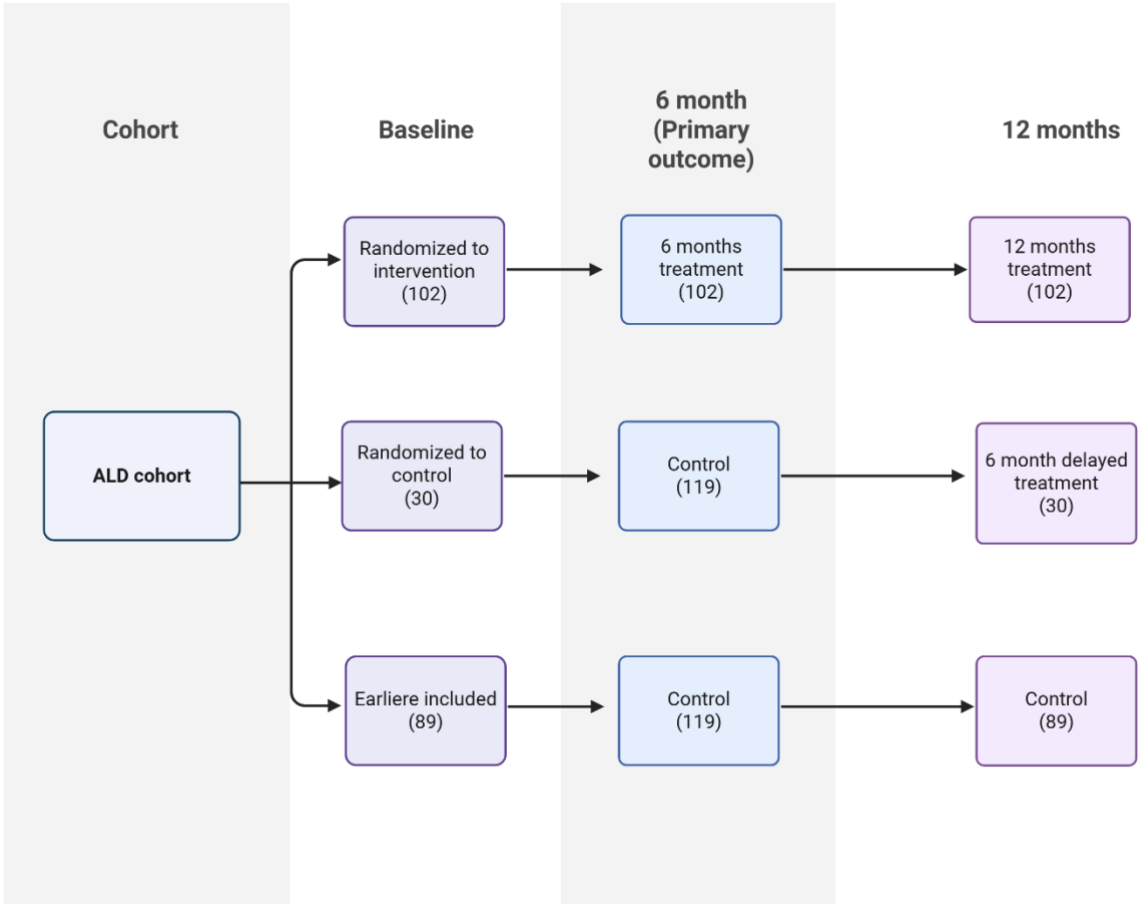
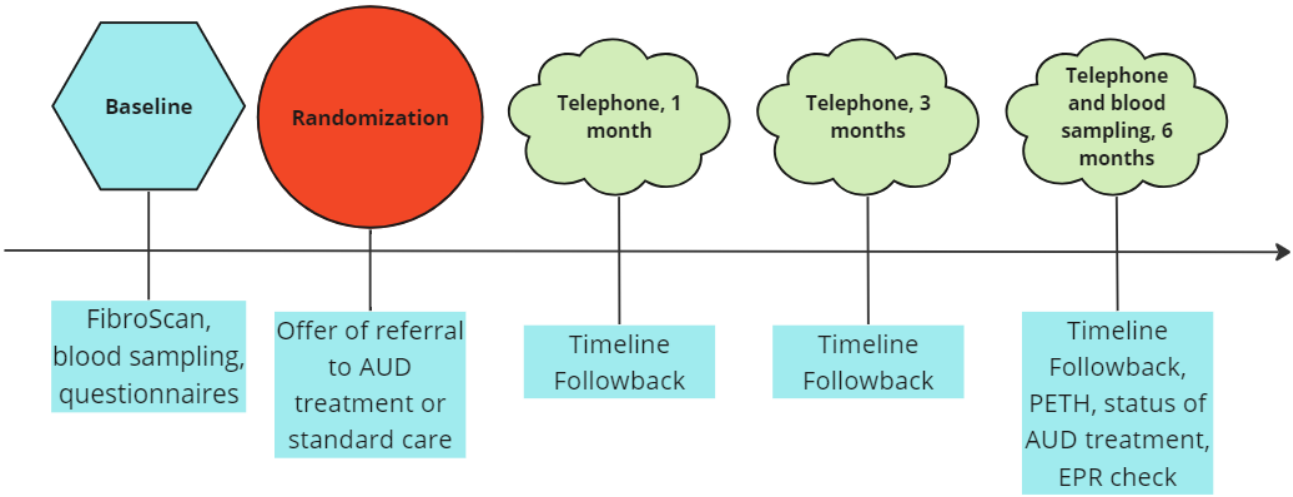


Figure 2. Study activities. Phosphatidylethanol = PETH, AUD = Alcohol use disorder, EPR = Electronic Patient Record



Randomization

Eligible participants from the existing observational cohort will be included as controls (n = 89). Before enrollment to the randomized study, a randomization sequence will be generated by Microsoft Excel 2013 and uploaded to the software program REDCap. From November 2025, participants will be continuously allocated to intervention or control group using REDCap with stratification by age (over/under 60 years), sex, and current alcohol use status (self-reported active alcohol consumer or abstinence less than 30 days vs. self-reported alcohol abstinence more than 30 days). Participants are randomized 4.4:1 to an offer of referral to AUD treatment vs. standard care to ensure that we can compare clinical characteristics in controls before and after randomization began.

Sample size

We plan to include 221 individuals in the study: 102 will be offered the intervention, and 119 will be controls. This number is based on preliminary data based on 80 patients from the observational cohort, demonstrating that 38% have been abstinent the last 30 days at 6 months of follow-up, and we want to improve this percentage to 60%. The study is a superiority trial with a margin of 5%. A superiority margin of 5% was chosen due to the expectation of no adverse effects of the intervention and because even a small improvement in abstinence is expected to improve the prognosis in ALD **(19)**. With a power of 80% and a 5% significance level, it requires 102 participants

in the intervention arm and 101 in the control arm. As 89 participants were already enrolled as controls, 12 more controls are needed, but to enhance the sub analysis of comparing the randomized control group to the historic cohort, it was chosen to increase the randomized control group to 30. Also to allow comparison for clinical characteristics in historical and randomized controls. Therefore, we need to randomize 132 new participants at a ratio of 4.4:1 to intervention:control group. We expect the loss to follow up to be 10-15%. The power calculation was performed in the software program of Excel (20).

Framework, interim analysis and stopping guidance

No interim analyses will be performed.

Timing of final analysis

Analyses will be performed in a blinded data set with treatment allocation labeled “A” and “B”. Prior to this, the statistical analysis plan will be completed, signed, and uploaded at clinicaltrials.gov, and the data set will be locked. Unblinding will not occur until all analyses are performed (expected spring 2029. This means that apart from data on long-term follow-up, all analyses will be finalized collectively.

Timing of outcome assessment

The primary outcome will be assessment of abstinence (see detailed description in Table 1) 6 months after the randomization or 6 months after the baseline visit in controls who were not randomized because they were part of the already enrolled controls. Secondary outcomes will be assessed after 3, 6 and 12 months. Later, we will conduct a secondary analysis with a longer follow-up of up to 3 years.

Statistical principles

Confidence and P-values

Level of statistical significance is set at an alpha level of 0.05 with two-sided testing and a confidence interval of 95%.

Adherence and protocol deviation

Protocol deviations will be presented in a table and divided into categories: Eligibility, study procedure, and randomization. The deviations "lost to follow-up" (in case of emigration out of Denmark) and "withdrawal" (when study participants withdraw their informed consent) are described in more detail below.

Analysis populations

The primary analysis will be performed using the intention-to-treat approach, which includes all patients included in the RCT. In a secondary analysis, the primary outcome will be investigated using the per-protocol principle, where only those participants randomized to the intervention, who accepted AUD treatment in the hepatology clinic and who were successfully contacted at the 6-month follow-up will be included in the analysis in addition to the controls. This analysis will also exclude participants who are lost to follow-up due to emigration or withdrawal from the study. Follow-up will be possible for all participants who have not emigrated (follow-up procedures are described below).

Trial population

Screening data

A CONSORT flow chart will present the flow of study participants.

Eligibility

Inclusion criteria

- Age > 18 years
- Newly diagnosed alcohol-related liver disease, defined as within six months from baseline visit.
- A liver stiffness ≥8.0 kPa with 10 successful measurements and an interquartile range of less than 30% as assessed with transient elastography.
- Excessive alcohol consumption defined as >7 units/week for women and >14 units/week for men within the previous year.
- The patient is able to understand the purpose of the study and give informed oral and written consent to participate.

Exclusion criteria

- Not enough proficiency in Danish to participate in interviews and questionnaires.
- Pregnancy
- Ongoing specialized AUD treatment. Self-help groups and AUD counselling at general practitioners are not counting as specialized AUD treatment in this study.

Recruitment

November 2025 until complete recruitment of 221 study participants.

Patients will be recruited from the Department of Internal Medicine, ZUH Køge, Denmark, with a satellite outpatient facility at Holbæk Hospital, Denmark.

Withdrawal/follow-up

See Table 1 for the description of follow-up. Four follow-up methods will be applied: Telephone interview, measurement of phosphatidylethanol in blood, review of medical chart records, and records from the alcohol treatment center. If participants are not approachable by telephone, follow-up data will be based on information from records from the hospital and alcohol treatment center alone. Withdrawal is when a study participant withdraws their informed consent for study participation.

Loss to follow-up is only in the case if the patient emigrates or if the participant withdraws consent to be followed through the health registries.

Baseline characteristics

The following characteristics will be summarized according to intervention allocation:

- Sex
- Age, median and 25-75% percentiles
- Months since last alcohol consumption, median
- Abstinence throughout the last month (yes/no)
- Years exceeding 10 units/week, groups (<5, 5-10, 10-15, 15-20, >20)
- Audit-C
- Motivation to cut down on 10 point scale, percentage answering “10”, median and IQR
- Belief in capability to cut down on alcohol, 10 point scale, percentage answering “10”, median and IQR
- Current smoking (yes/no)

Analysis

Outcome definitions

Primary endpoint

Primary outcome: Alcohol abstinence throughout the last 30 days assessed after 6 months after the randomization (randomized participants) or baseline visit (only for controls enrolled before randomization began).

Table 1. Evaluation of primary outcome of alcohol abstinence throughout the last 30 days		
	Interpreted as *not fulfilling* alcohol abstinence if indicated by *one or more* of the outcome measures below	**Interpreted as *fulfilling* alcohol abstinence the last month if indicated by all three of the outcome measures below**
1) Telephone interview with timeline follow-back method	Interview reveals any alcohol intake the last 30 days	Interview reveals alcohol abstinence the last 30 days
2) Phosphatidylethanol	Phosphatidylethanol value was $\geq$ 0.05 µmol/L	Phosphatidylethanol value was < 0.05 µmol/L
3) Electronic health record	Hospital contact the last 30 days with history that indicates current drinking: alcohol intoxication, ethanol measurement, self-reported by the patient, or death with obvious alcohol involvement recorded in patient charts. If it has not been possible to establish contact with the	Hospital contact without mentioning of alcohol consumption last 30 days. Death with no obvious alcohol involvement as reported in patient charts.

	patient using methods 1), 2), or 3) no hospital contacts.	
4) Report of alcohol consumption via specialized AUD treatment from Novavi	AUD treatment provider reports patients have ongoing alcohol consumption.	AUD treatment provider reports patients are alcohol abstinent.

Secondary outcomes:

1. Alcohol abstinence throughout the last 30 days assessed after 3 months.
2. Any treatment for alcohol use disorder after 6 months.
3. Number of received sessions of treatment for alcohol use disorder after 6 months.

Assessed as the difference between baseline visit and 3 or 6 months of follow-up:

4. Reduction in drinks per week after 3 and 6 months compared to baseline (yes or no).
5. Reduction in phosphatidylethanol value at 6 months compared to baseline (yes or no).

Analysis of the randomized control group accepting referral to AUD treatment, as part of the cohort study the participants will meet for a 1-year follow-up, performing the same tests as for the 6 months follow up.

1. Alcohol abstinence throughout the last 30 days assessed 1 year after the randomization.
2. Reduction in drinks per week after 12 months compared to 6 months (yes or no).
3. Reduction in phosphatidylethanol value at 12 months compared to 6 month follow up (yes or no).

Longer follow-up (3 years) is planned utilizing electronic medical records to investigate if the intervention improves liver outcomes and survival.

These outcomes are:

1. Time to first decompensation event, which is defined as variceal haemorrhage, ascites grade 2 or worse, or hepatic encephalopathy West-Haven grade 2 or worse, assessed as a competing risk analysis, taking death as a competing risk into account.
2. All-cause mortality.
3. Progression in liver fibrosis grade assessed by transient elastography **(21)** or progression to a worse Child-Pugh class (A to B or C and B to C), taking death as a competing risk into account.

Statistical analysis

Continuous outcomes will be assessed for normality and reported as mean (sd) or median (25th-75th percentile) and analyzed with t-test or Wilcoxon test, as appropriate. Further, outcomes will be analyzed using logistic regression, adjusted for confounders. Categorical outcomes will be reported as n (%) and analyzed using chi-square test. Linear or logistic regression will be used to adjust for confounders.

The primary outcome will be assessed using logistic regression.

The primary outcome will be assessed in the intention-to-treat population, and further, in the per-protocol population. Participants who accepted referral to alcohol abuse treatment will be regarded as fulfilling the protocol. In the latter, inverse probability of treatment weighting will be used to account for measured confounding of age and sex. Weighting will be based on accepting referral to treatment.

Secondary outcomes:

1. Alcohol abstinence throughout the last 30 days evaluated after 3 months (yes/no), assessed by logistic regression
2. Reduction in drinks per week after 3 and 6 months (yes or no), assessed by logistic regression.
3. Change in number of drinks per week after 3 and 6 months – assessed by linear regression
4. Reduction in phosphatidylethanol value by 0.05 or more at 6 months (yes or no), assessed by logistic regression.
5. Change in phosphatidylethanol value after 6 months – assessed by linear regression
6. Any treatment for AUD (yes or no), assessed by logistic regression.
7. Number of received sessions of treatment for AUD (median and IQR).

Follow-up after 1 year

1. Reduction in drinks per week after 6 and 12 months (yes or no), assessed by logistic regression.
2. Change in number of drinks per week after 6 and 12 months – assessed by linear regression
3. Reduction in phosphatidylethanol value by 0.05 or more at 12 months (yes or no), assessed by logistic regression.
4. Change in phosphatidylethanol value after 12 months – assessed by linear regression
5. Any treatment for AUD (yes or no), assessed by logistic regression.
6. Number of received sessions of treatment for AUD (median and IQR).

Longer follow-up (3 years) is planned utilizing electronic medical records to investigate if the intervention improves liver outcomes and death. Death will be taken into account as a competing risk in analyses of non-mortality outcomes.

These outcomes are:

1. Time to first decompensation event, which is defined as variceal haemorrhage, ascites grade 2 or worse, or hepatic encephalopathy West-Haven grade 2 or worse assessed by competing risk analysis, taking death as competing risk into account.
2. All-cause mortality, assessed in Cox regression
3. Progression in liver fibrosis grade assessed by transient elastography **(21)** or progression to a worse Child-Pugh class (A to B or C and B to C), assessed by competing risk analysis, taking death as competing risk into account.

Assessment of model assumptions

Logistic regression:

The assumption of linearity between log odds of outcome and the predictor is less relevant when the predictor is dichotomous, as in this study.

Linear regression:

Linear relationship between intervention and number of drinking days will be assessed by plotting the fitted values(x) vs. the residuals(y).

Normality of residuals is checked by the QQ-plot, residuals should follow the straight line.

Homoscedascity is assessed plotting standardized residuals vs. fitted values.

Influential values are not as likely, since the intervention is dichotomous, and all numbers of heavy drinking days pr. 30 days are likely.

The assumption of proportional hazards in Cox regression will be tested by cloglog-plots and/or Schoenfeld residuals.

Sensitivity analysis

Only including those who had the intervention by excluding those in the intervention group who never had any AUD treatment (per protocol analysis). Participants who are lost to follow up due to emigration will also be excluded in this analysis.

Subgroup analysis

Severity of liver disease at baseline (non-cirrhotic, compensated, decompensated)

By hospital diagnosis of ALD (inpatient admission with ALD/not admitted)

By alcohol abstinence last month at baseline

Severity of AUD, measured by AUDIT-C (over/under median)

By Liver frailty index at baseline

By sex (men/women)

By age at baseline

By motivation to cut down at baseline

By evidence of minimal hepatic encephalopathy assessed by continues reaction time

Assessment of missing data

Missing data will be investigated by producing tables that characterize patients with missing data vs. patients with information for each missing variable, as in table 2 below. There may be missing data in many variables, so variables of interest will be assessed.

Table 2: Example of assessment of missingness

	Missing (n=xx)	Not missing (n=YY)

Intervention	2%	10%
Primary outcome	12%	5%

Missingness is not expected in intervention assignment or outcome but may be present in confounders. Missingness is likely unrelated to intervention, but patterns of missingness will be assessed, if found meaningful this will be presented with a missingness directed acyclic graph, which is visual model of the causal relationships between variables and the reasons they may be missing. If patients with missing data differ from patients without missing data, it is assumed that data is missing not at random and multiple imputation may be redundant. Otherwise, multiple imputation may be used as a sensitivity analysis. Whether imputation can be used will be based on a judgment of the extent of patterns in missingness as well as degree of missingness. Imputation will not be used if missingness should be skewed or if missingness is present in less than 10% of the total dataset including the confounders to be used. All secondary outcomes will be assessed as cross tables with intervention, primary outcome, age, sex, marital status, and occupation. As a rule of thumb, differences should be less than 5% between patients with and without missing data, but the total pattern will be considered.

Tables

Table 3. Baseline demographic and clinical characteristics according to randomization outcome, values are number (%) unless otherwise stated

	Randomized to intervention (referral to AUD treatment)	Controls randomized to standard care	Controls from before implementation of RCT (received standard care)
Sex, % men			
Age, median			
Self-reported alcohol abstinence			
AUDIT-C			
Days since last alcohol consumption, median			
Years with exceeding 10 units/week, median SD			
Phosphatidylethanol			
Duration of AUD treatment in months, median			
Number of AUD treatment sessions, median.			
Smoking, % yes			

Table 4. Assessment of primary outcome N (%) at 6 months after randomization according to the four follow-up methods

	Intervention		Control	
Alcohol abstinence throughout the last 30 days	*Yes*	*No*	*Yes*	*No*
At Inclusion				
By Telephone interview				
By phosphatidylethanol				
By Electronic health record				
In total				

Table 5. Comparison of endpoints at 3- and 6-months follow-up according to randomization group

	Referral to AUD treatment (intervention)	Standard care (controls)	p-value
Alcohol abstinence last 30 days at 6 months (yes or no)			
Alcohol abstinence last 30 days at 3 months (yes or no)			
Reduction in drinks per week last 30 days in drinkers at 6 months (yes/no)			
Reduction in drinks per week last 30 days in drinkers at 3 months (yes/no)			
Change in drinks per week in drinkers since baseline (drinks) at 6 months			
Change in drinks per week in drinkers since baseline (drinks) at 3 months			

Phosphatidylethanol value at follow-up			
Change in phosphatidylethanol value since baseline at 6 months			
Received alcohol treatment for AUD yes/no), number of sessions,			
Median number of treatment sessions for AUD, total			
- Individual sessions, median			
- Group sessions, Median			

References

1. Rehm, Jürgen; Shield, K D; Rehm, M X; Gmel, Gerhard; Frick U. Alcohol consumption, alcohol dependence, and attributable burden of disease in Europe: Potential gains from effective interventions for alcohol dependence. 2012;

2. Sheron N. Alcohol and liver disease in Europe--Simple measures have the potential to prevent tens of thousands of premature deaths. Journal of hepatology. 2016 Apr;64(4):957–67.

3. Lackner C, Spindelboeck W, Haybaeck J, Douschan P, Rainer F, Terracciano L, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. Journal of hepatology. 2017 Mar;66(3):610–8.

4. Rogal S, Youk A, Zhang H, Gellad WF, Fine MJ, Good CB, et al. Impact of Alcohol Use Disorder Treatment on Clinical Outcomes Among Patients With Cirrhosis. Hepatology (Baltimore, Md). 2020 Jun;71(6):2080–92.

5. Mellinger JL, Winder GS, Dejonckheere M, Fontana RJ, Volk ML, Lok ASF, et al. Misconceptions, preferences and barriers to alcohol use disorder treatment in alcohol-related cirrhosis. 2018;

6. Saitz R, Cheng DM, Winter M, Kim TW, Meli SM, Allensworth-Davies D, et al. Chronic Care Management for Dependence on Alcohol and Other Drugs: The AHEAD Randomized Trial. JAMA : the journal of the American Medical Association. 2013 Sep 9;310(11):1156.

7. Bradley KA, Bobb JF, Ludman EJ, Chavez LJ, Saxon AJ, Merrill JO, et al. Alcohol-Related Nurse Care Management in Primary Care: A Randomized Clinical Trial. JAMA Internal Medicine. 2018 May 1;178(5):613.

8. Upshur C, Weinreb L, Bharel M, Reed G, Frisard C. A Randomized Control Trial of a Chronic Care Intervention for Homeless Women With Alcohol Use Problems. 2015;

9. Watkins KE, Ober AJ, Lamp K, Lind M, Setodji C, Osilla KC, et al. Collaborative Care for Opioid and Alcohol Use Disorders in Primary Care: The SUMMIT Randomized Clinical Trial. JAMA Internal Medicine. 2017 Oct 1;177(10):1480.

10. Oslin DW, Lynch KG, Maisto SA, Lantinga LJ, McKay JR, Possemato K, et al. A Randomized Clinical Trial of Alcohol Care Management Delivered in Department of Veterans Affairs Primary Care Clinics Versus Specialty Addiction Treatment. Journal of General Internal Medicine. 2014 Jan 1;29(1):162.

11. Coulton S, Bland M, Crosby H, Dale V, Drummond C, Godfrey C, et al. Effectiveness and Cost-effectiveness of Opportunistic Screening and Stepped-care Interventions for Older Alcohol Users in Primary Care. Alcohol and Alcoholism. 2017;52(6):655–64.

12. Drummond C, Coulton S, James D, Godfrey C, Parrott S, Baxter J, et al. Effectiveness and cost-effectiveness of a stepped care intervention for alcohol use disorders in primary care: Pilot study. British Journal of Psychiatry. 2009;195(5):448–56.

13. Finn SW, Hammarberg A, Andreasson S. Treatment for Alcohol Dependence in Primary Care Compared to Outpatient Specialist Treatment-A Randomized Controlled Trial. Alcohol and Alcoholism. 2018;53(4):376–85.

14. Ettner SL, Xu H, Duru OK, Ang A, Tseng CH, Tallen L, et al. The Effect of an Educational Intervention on Alcohol Consumption, At-Risk Drinking, and Health Care Utilization in Older Adults: The Project SHARE Study. Journal of Studies on Alcohol and Drugs. 2014;75(3):447.

15. Moore AA, Blow FC, Hoffing M, Welgreen S, Davis JW, Lin JC, et al. Primary Care Based Intervention to Reduce At-Risk Drinking in Older Adults: A Randomized Controlled Trial. Addiction (Abingdon, England). 2011 Jan;106(1):111.

16. Weinrieb RM, Horn DHA Van, Lynch KG, Lucey MR. A Randomized, Controlled Study of Treatment for Alcohol Dependence in Patients Awaiting Liver Transplantation.

17. Willenbring ML, Olson DH. A Randomized Trial of Integrated Outpatient Treatment for Medically Ill Alcoholic Men. Archives of Internal Medicine. 1999 Sep 13;159(16):1946–52.

18. Rombouts SA, Conigrave JH, Saitz R, Louie E, Haber P, Morley KC. Evidence based models of care for the treatment of alcohol use disorder in primary health care settings: a systematic review.

19. Louvet A, Bourcier V, Archambeaud I, D'Alteroche L, Chaffaut C, Oberti F, et al. Low alcohol consumption influences outcomes in individuals with alcohol-related compensated cirrhosis in a French multicenter cohort. Journal of Hepatology. 2023 Mar;78(3):501–12.

20. Chow S Chung, Shao Jun, Wang Hansheng. Sample size calculations in clinical research. Chapman & Hall/CRC; 2008. 465 p.

21. Nguyen-Khac E, Chatelain D, Tramier B, Decrombecque C, Robert B, Joly JP, et al. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: Prospective comparison with seven non-invasive laboratory tests. Alimentary Pharmacology and Therapeutics. 2008 Nov;28(10):1188–98.