Statistical Analysis Plan for The Self-Match Study: a randomized controlled trial to assess if treatment outcome is improved if patients match themselves to treatment options

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Abstract

Background: There is growing emphasis on involving patients in their own treatment, however, research has been limited on the benefit of having patients choose their treatment from among options, in contrast to being assigned to a treatment by experts. Consequently, we designed a rigorous test of patient self-matching to determine whether it does improve retention, adherence and outcome in alcoholism treatment.

Method: The present study is conducted as a superiority randomized controlled trial. 401 consecutive patients aged 18 or more is enrolled and randomized to either self-matching or expert-matching to one of five different treatment approaches. The following instruments was administered at intake to provide standardized measures of alcohol problems: Addiction Severity Index, Time Line Follow Back, WHO quality of life questionnaire, NEO Five-Factor inventory-3 and Personal Happiness Form. Methods of statistical analysis are described, including the handling of missing data.

Outcome: For each outcome measure, two analyses will be conducted. Intention-to-treat analyses (ITT) will be carried out with all patients, irrespective of whether they completed the interventions or were re-interviewed. Regarding incomplete data, multiple imputations will be used together with ITT. Completer analyses will also be carried out with patients who complete their respective interventions.

Primary outcome: Decrease in number of monthly excessive drinking days 6 months after initiation of treatment.

Secondary outcomes: (1) Compliance. (2) Quality of life.

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Key words: Alcohol addiction, binch drinking, Alcohol treatment, informed choice, randomized controlled trial.

Background

International attention to involve patients in their own treatment in most medical fields, including addiction treatment, is increasing [1, 2]. The main point is that treatment regimens should encourage that patients have an active role in treatment planning [3-6]. In alcohol treatment, Project MATCH [7] and the UKATT Research Team [8], has tested the paternalistic approach to treatment planning and found that the best 'guesses' of some of the field's most experienced alcoholism treatment researchers in two nations were little better than chance when it came to choose the best treatment approaches for patients. In sum, experts matching patients to treatment based on patient characteristics is doubtful for improving treatment outcome[9] [10].

The opposite approach is to allow patients to match themselves, that is to make an informed choice from a menu of evidence-based treatment options. In large treatment regimens where more than one treatment option can be provided it would be feasible to allow patients to choose for themselves. Patient preference is increasingly being considered as good practice in healthcare, leading to implementation of shared decision making and informed choice, which is feasible when patients can be given a fair description of the options open to them and permitted to make an informed choice as to which treatment they prefer.

It is, however, still not clear if these approaches improve treatment outcome. A systematic review of the literature on shared decision making in treatment of substance use disorder [11] found that only 3 out of 25 trials found a significant effect when treatments were matched to patients preferences. The result should, however be interpreted with caution due to heterogeneity of the included studies.

To our knowledge, research is limited when it comes to clarify the benefit of having patients, suffering from alcohol addiction, freely choose their treatment approach from among options. Therefore, as a part of the RESCueH-studies[12], this randomized clinical trial will compare the efficacy of patient self-matching versus treatment-as-usual expert matching.

Purpose and hypotheses

The primary purpose of this randomized controlled trial is to determine if patient self-matching to psychotherapy treatment methods improves 1) drinking outcome, 2) compliance and 3) quality of life for patients being treated for alcohol problems compared to assignment as usual, which is by the means of expert matching.

A priori hypotheses

1. Patients who choose their own treatment will show significantly greater reductions in alcohol consumption (measured by number of days with excessive drinking) at follow-up, when compared to patients assigned to treatment by expert match.

2. Patients who choose their own treatment method will show significantly better compliance in treatment (measured by retention) when compared to patients assigned to a specific treatment method by expert match.

Material and methods

Study Design

The study is conducted as a superiority randomized controlled trial. 401 consecutive patients aged 18 or more are enrolled. All new patients fulfilling the inclusion criteria receive oral and written information about the study. Patients are randomized to either expert matching (algorithm) or self-matching. See the study protocol for more information on referral routines[13].

Study procedures

Information about the study is presented when the potential participant first attends the treatment center. If the patient needs treatment for withdrawal symptoms, the information is not given until those symptoms are sufficiently treated.

The baseline interview is divided into two sessions to avoid fatigue during a long assessment. This is already standard procedure in the clinic for everyone receiving treatment regardless of participation in this study. Upon written and oral

consent patients are randomized to either choosing their own treatment among five options or being assigned to one of these options by means of an algorithm[14] and expert opinion. Patients participating in the study will be re-interviewed 6 months after initiation of treatment.

Getting patients to participate in studies and getting a high follow-up rate is usually an obstacle in research, thus we have designed the study routines as similar as possible to the usual assessment routines in the participating treatment institution. The only difference for those participating in this study is the 45-minute follow-up interview. To ensure a high follow-up rate we collect phone number, e-mail and home address on patients and their next of kin. If patients decide to be anonymous, we underline the importance of their responsibility to contact the treatment center 6 months after treatment start.

Randomization and blinding

Patients are assigned to conditions by REDCap (Research Electronic Data Capture) from Open (Odense Patient Data Explorative Network), a computer-based randomization system. The interviewer in charge of the first baseline interview will activate the randomization, when the patient has agreed to participate in the study. The patient witness' the randomization and the result are revealed immediately.

A case report for each participant will be prepared and labeled with participant number. All case reports will be stored in a locked storage inaccessible to the therapists, who are to remain uninformed of how patients were assigned to treatment. Patients are urged not to reveal their group assignment.

Data

The following instruments will be administered to provide standardized measures of alcohol problems, quality of life and personality traits:

- Addiction Severity Index (ASI) is an assessment tool for addiction problems [15].
- Time Line Follow Back (TLFB) is an assessment tool for measuring drinking days the last 30 days [16].
- WHO quality of life 26-item questionnaire (WHOQOL-BREF) [17].

- NEO Five-Factor inventory-3 (NEO-FFI-3) is a tool for measuring personality traits [18].
- Personal Happiness Form (PHF) is a tool for assessing well-being [19].

These validated and widely-used instruments will allow direct comparisons with mainstream clinical trials.

Statistical analyses and sample size

A multiple regression model will be used to model percent of days with drinking/excessive drinking. If the model validation shows that Gaussian multiple regression does not fit due to severely non-normal data, a multiple quantile regression model will be used instead. Both modeling approaches allow for inclusion of additional explanatory variables. A two-sided alternative will be used with a significance level of p=0.05. We expect that proportion of patients assigned to the five treatments will differ between the two groups; hence, type of treatment, sociodemographic data and problem severity will be integrated in the analysis as explanatory variables.

Power calculation

To our knowledge no similar experimental studies have been conducted. The power calculation is therefore estimated from what clinicians' regard to be a clinically meaningful difference in outcome. A study by Miller and Manuel [20] found that clinicians estimated the difference between two treatment methods to be meaningful for implementation in daily practice if the continuous outcome measures (e. g. number of days with excessive drinking) were halved. The power calculation is based on the number of days with excessive alcohol abuse over the last 30 days after 6 months of treatment.

Currently, patients at the participating outpatient clinic drink on average excessively 5.7 days (SD=9.7) over the last 30 days after 12 months of treatment. With the new methods for assigning treatment to patients, we seek to halve the number of days with excessive drinking to an average of 5.7/2 = 2.85 days, i.e. a reduction of 2.85 days. We assume the standard deviation will be the same for the reduced number of days. Most likely, it will be smaller since less than zero days of excessive drinking is impossible, i.e. the method is conservative. As stated by Miller & Manuel [20] this power calculation is based on practitioners' judgment of a meaningful difference in outcome, rather than statistical significance based on other studies. By this approach, a total sample of 200 patients in each group is needed to have 90% power of detection a difference of this magnitude using a 0.05% level of statistical significance (Figure 2).

Sensitivity analyses

Complete case and worst-case computation will be carried out.

Interim analyses and stopping rule

An Independent Data Monitoring Board was assigned to carry out interim analyses. In case of significant and clinically relevant difference the study will be terminated due to ethical responsibility to provide the best treatment possible.

Start of data analyses

Data analyses will start primo January 2020.

Level of confidence and *p* values

A confidence level of 95% and *p* value of 0.05 is assigned.

Missing data

Incomplete follow-up data are assumed to be missing at random (MAR) and will be addressed by the MICE (multivariate imputation by chained equations) method of multiple multivariate imputation. Appropriate auxiliary variables will be included in the imputation model, the resulting datasets will be analyzed separately, and results will be combined using the rules of Rubin.

Outcome measures

For each outcome measure, two analyses will be carried out:

1. Intention-to-treat analyses (ITT) will be carried out on all patients, irrespective of whether they completed the interventions or were re-interviewed. Regarding incomplete data, multiple imputations is used together with ITT but there will be some caveats.
2. Completer (on-treatment) analyses will be carried out on patients who completed the respective interventions.

Results will be published regardless of our findings.

Primary outcome:

Number of excessive drinking days 6 months after initiation of treatment.

Secondary Outcomes:

1. Compliance measured by retention. At 6 months follow up the number of sessions attended is measured.

2. The four dimensions of Quality of life as measured by WHOQOL.

Tabel 1. Demographics and baseline data.

	Self-Match	Expert match (TAU)	Significance level
Demographics			
Current age mean (SD)			
Male			
Currently cohabiting or married			
Full or part time employment			
Annual income Mean (SD)			
Education (>high school)			
Treatment related to AUD and substance use			
Previously received AUD treatment			
Previously received SUD treatment			
Currently suffering from SUD			
Use of alcohol			
Number of heavy drinking days last 30 days			
Number of drinking days last 30 days			
Overall amount of alcohol consumption last 30 days			
Quality of Life			
Physical domain (sum score)			
Psychological domain (sum score)			
Social domain (sum score)			
Environment domain (sum score)			

Table 2. Follow up data

	Self-Match group	Control Group	Significance level
Follow up rate			
Percentage completed follow up			
Drinking outcome			
Heavy drinking days last 30 days			
Number of drinking days last 30 days			
Overall alcohol consumption last 30 days			
Retention			
Compliance (drop out)			
Average number of sessions completed			
Quality of Life			

Physical domain (sum score)			
Psychological domain (sum score)			
Social domain (sum score)			
Environment domain (sum score)			

Table 3: Treatment success of selfmatch compared to expert match. Treatment success defined as 50% reduction in heavy drinking days.

	Heavy drinking days		Number of drinking days		Overall consumption		Compliance (drop out)		Number of sessions completed		QoL physical domain		QoL psychological domain		QoL social domain		QoL environment domain	
	OR	CI	β	CI	β	CI	β	CI	β	CI	β	CI	β	CI	β	CI	β	CI
Expert-match																		
Self-match																		
Intercept																		

Trial status

The second version of the protocol was accepted the 17th of November 2016. The study was accepted by the Regional Scientific Ethical Committee for Southern Denmark the 24th of Marts 2017. Recruitment began 22nd of May 2017 ended the 5th of April 2019.

Trial registration: ClinicalTrial.gov identifier: NCT03278821

Declarations

Ethics approval and consent to participate

The Study was presented for the Regional Scientific Ethical Committee for Southern Denmark, who decided that the study did not need formal approval from the committee. Reference number: S-20170027. All procedures in the study are in accordance with the second Declaration of Helsinki.

Both oral and written information will be given to patients by the person who undertakes first baseline interview. Patients must sign informed consent document if they want to participate in the study.

All appointments in Center for Alcohol Treatment Odense are situated in private rooms with quiet and calm atmosphere and there will be no interruptions.

Availability of data and materials

All data collected in the study will be treated and stored strictly confidentially in REDCAP, OPEN. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Anette Søgaard Nielsen (PI), Anna Mejldal and Morten Ellegaard Hell are employees of the University of Southern Denmark and Region of Southern Denmark. Morten Ellegaard Hell is employed at the psychiatry of Region Syddanmark. None of researchers have competing interests to declare.

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