

Social Phobia and Evasiveness: Randomized Controlled Feasibility and Superiority Trial of the Effect of Modified Collaborative Assessment vs. Standard Assessment on Patients' Readiness for Psychotherapy (CO-ASSM-RCT).

Statistical Analysis Plan

Primary and secondary analyses

Version 1.0 May 30th, 2023

Introduction

This statistical analysis plan (SAP) describes the methods to be used to analyze the primary and secondary outcome data from the CO-ASSM-RCT trial. The plan is based on the study protocol (Hovmand et al., 2022) registered at www.clinicaltrials.gov (NCT2021001). Analyses follow the ICH-9 statistical guidelines for clinical trials and updated CONSORT reporting guideline extensions for non-pharmacological trials [1, 2].

The statistical analysis plan will be open to adjustments after the blind review, however finalized and registered as an amendment to the study protocol before unmasking the data.

Research objectives and hypotheses

The main objective of this study is to investigate the efficacy of Modified Collaborative Assessment (MCA) compared with standard assessment for psychiatric outpatients with a primary diagnosis of evasive personality disorder or social phobia. Main outcome is motivation to change measured with the contemplation subscale of the University of Rhode Island Change Assessment Scale at the end of the intervention with MCA/AAU. Other outcomes are symptom levels, psychological measures and clients' evaluation of the intervention.

We hypothesize that motivation to change will be improved following MCA. Apart from the main objective, we investigate the effects of the MCA on symptom levels, social functioning and self-efficacy.

Study methods

Design

Please see study protocol (Hovmand et al., 2023)[3].

Randomization

Please see study protocol (Hovmand et al., 2023).

Sample size

Please see study protocol (Hovmand et al., 2023).

Timing of outcome assessments

Baseline characteristics will be assessed at the time of inclusion. Outcome measures will be assessed at the end of the intervention for (T1) at the end of the intervention for the patients randomized to MCA (at approximately four weeks after inclusion and for patients randomized to AAU at four weeks after inclusion. T2 will be administered after four-sessions psychotherapy intervention (time depending of the waiting-list in the given psychiatric clinic).

Timing of final analysis

Primary and secondary outcomes are analyzed at the end of the intervention after all randomized patients have completed (T1). Data will be unmasked following the conclusion of the primary outcome analysis.

Statistical principles

Data presentation

We will analyze and report primary and secondary outcomes in accordance with CONSORT reporting guidelines for reporting parallel group randomised trials [1, 2]. Results from the primary analysis will be reported as between group mean differences with two-sided 95% confidence intervals. For secondary analyses, results will be reported as within and between group mean differences with two-sided 95% confidence intervals. Effect sizes (Cohens *d*) are calculated for each measure between groups. A two-sided p-value < .05 is considered significant.

No adjustment for multiplicity will be undertaken. Since outcomes are interrelated, adjustment will be overly conservative.

The analysis population

In superiority trials, the Intention-to-treat (ITT) analysis is considered the conservative choice to minimize possible type I-errors, that is falsely concluding that the one intervention is superior to another. The ITT population includes all patients randomized and allocated to intervention whether they violated the protocol or dropped out of the intervention or not. In superiority trials, the null-hypothesis asserts that there is no difference between the two interventions being compared. The alternative hypothesis being tested is that the two intervention are different by some prespecified value.

For this analysis plan, the per protocol population is defined as patients completing the MCA (i.e. completing a full MCA-intervention) or AAU (all patients randomized to AAU will be completers upon randomization due to them already having been administered AAU).

Trial population

Eligibility

Please see study protocol (Hovmand et al., 2023).

Recruitment

Please see study protocol (Hovmand et al., 2023).

Participant flow

The number of patients screened, randomized, completed the intervention, and completed follow-up outcomes, will be summarized in a CONSORT flow diagram [2].

Baseline characteristics

The following demographic and illness burden variables will be summarized by intervention condition in Table 1: age, sex, level of employment, level of education, comorbidity, completers)

Analysis

Primary outcome

The primary outcome is self-reported subjective motivation to change as assessed with the self-reported outcome **University of Rhode Island Change Assessment Scale (URICA), contemplation subscale** [4], assessed at the end of the intervention (T1) (approximately four weeks after randomization; single score continuous outcome).

Secondary outcomes

The following outcomes are secondary outcomes, all measured at T1:

- General social anxiety symptomatology assessed with the self-reported outcome **Liebowitz Social Anxiety Scale-Self-Report (LSAS-SR)** (single score continuous outcome)
- Self-esteem assessed with the self-reported outcome **Rosenberg Self-Esteem Scale (RSES)** (single score continuous outcome)
- Self-efficacy assessed with the self-reported outcome **General Self-Efficacy Scale (GSES)** (single score continuous outcome)
- Patient satisfaction assessed with the self-reported outcome **Client Satisfaction Questionnaire (CSQ-8)**
- Motivation to change assessed with the self-reported outcome **Rhode Island Change Assessment Scale (URICA) Readiness for Change score**

Exploratory outcomes

- The following outcomes are exploratory outcomes, measured at T1:
- Motivation to change assessed with the self-reported outcome **University of Rhode Island Change Assessment Scale (URICA) sub scales** Pre-contemplation, Contemplation, Action, and Maintenance (single score continuous outcome).
- Readiness for psychotherapy assessed with the self-reported outcome **Readiness for Psychotherapy Index (RPI) Overall Readiness** (single score continuous outcome)
- General well-being assessed with the self-reported outcome **WHO-5 Well-Being Index**

- Social function assessed with the self-reported outcome **The Work and Social Adjustment Scale (WSAS)**

The following outcomes are exploratory outcomes, measured at T2:

- General social anxiety symptomatology assessed with the self-reported outcome **Liebowitz Social Anxiety Scale-Self-Report (LSAS-SR)** (single score continuous outcome)
- Self-esteem assessed with the self-reported outcome **Rosenberg Self-Esteem Scale (RSES)** (single score continuous outcome)
- Self-efficacy assessed with the self-reported outcome **General Self-Efficacy Scale (GSES)** (single score continuous outcome)
- Changes in assigned primary diagnosis of patients (yes/no) (single score categorical outcome) at the end of intervention (approximately four weeks after randomization)
- Rate of no-shows during the first four sessions of psychotherapy (single score continuous outcome) for those the patients that have been offered a psychotherapy course.

Feasibility outcomes

The following outcomes are feasibility outcomes, all measured at T1:

- Acceptability: The feasibility criterion for acceptability in patients is supported if 25% of patients who are found eligible for inclusion and who have received formal information (information meeting with the first author) about the trial agree to participate in the trial.
- Satisfaction: The feasibility criterion for satisfaction in patients is supported if the mean CSQ-8 score is ≥ 3 (single score continuous outcome)
- Adherence: The feasibility criteria for adherence in patients is supported if 75% complete the MCA intervention (attend all MCA sessions including feedback-session).
- Time spent on the intervention: We evaluate the resources used to complete the study by recording the time with spent in direct contact with the patient used to complete the MCA intervention

Analysis methods

Descriptive analyses

Baseline equivalence for the two groups compared will be assessed descriptively. No formal significance testing will be conducted, since we assume that differences between randomized groups could have occurred by chance.

Primary analysis

The primary analysis will compare the primary outcome (URICA, contemplation subscale) between MCA and AAU conditions at the end of the intervention (approximately four weeks after randomization).

We will use a two-sided 95% CI interval ANCOVA approach to test for superiority between conditions on continuous outcomes. The two-sided 95% CI for the between group difference point estimate at the end of the intervention will be calculated. Superiority of MCA compared to AAU will be accepted if the lower bound of the 95% CI lies above 0.

In addition to this will Effect sizes (Cohens d) [5] for pre-post differences between intervention conditions be calculated to evaluate the magnitude of difference. We will interpret Cohen d 's effect sizes using the following general guidelines: small (0.2), medium (0.5), and large (0.8) [6].

Categorical outcomes will be analyzed with logistic regression.

Secondary analyses

For secondary analyses we will again use ANCOVA to test for superiority between intervention conditions at the end of the intervention. Effect sizes (Cohens d) for pre-post differences between intervention conditions will be calculated, and interpreted as mentioned earlier.

Exploratory analyses

For secondary analyses, we will again use ANCOVA to test for superiority between intervention conditions at the end of the intervention. Effect sizes (Cohen's d) for pre-post differences between intervention conditions will be calculated and interpreted as described above.

Sensitivity analyses

We will run a sensitivity analysis without imputed data to assess the potential impact of imputation on the trial findings and assess the impact of missingness by loading the primary analysis using an extreme scenario countering our hypothesis (i.e. imputing the data based on values from the 10% and 90% fractile population). Procedure for handling of missing data is described below.

Additional analyses (sensitivity analysis)

Analysis of primary and secondary outcomes will be repeated exploratory at T2. At T2, we will only analyze the patients who still fulfill the inclusion criteria (have a primary diagnosis of social phobia or evasive personality disorder), and who have been offered psychotherapy. Those who have been rediagnosed as a result of AAU or MCA will be excluded from T2 analyses.

The analyses at T2 will be conducted both with and without waiting time between T1 and T2 in weeks as a covariable.

Model checking and validation

We will check the robustness of models by examining residuals.

Handling of missing data and blinding

The first author extracts data from electronic health records entry according to the main study protocol. All other outcomes are patient-reported and are entered directly into REDCap by the included patients.

However, due to an error in procedure, patients randomized to MCA, that informed the researcher, that they did not have time to attend the intervention sessions, were treated as if they dismissed participating further in the study. Hence they were not contacted anymore, and not given the opportunity to fill in questionnaires at T1 and T2. Due to this, can the T1 and T2 data from these patients not be said to be missing at random, however this procedure error has occurred in two MCA cases, and it is less than 5% of the sample, hence we allow the assumption that data is missing at random.

We will undertake a blinded analysis of missing data and outliers to evaluate how to deal with missing data and outliers, and to explore possible predictors of missing data which should be controlled for in the primary and secondary analyses. The analysis of the primary and secondary outcomes will be conducted with the intervention allocation blinded by an external statistician. In the data extraction for the primary analysis, the intervention type is concealed. The intervention and control arm will randomly be coded as '1' and '2'. Deciphering will not be done before all analyses at the end of the intervention (T1) have been performed, and conclusions for the primary outcome has been formulated.

For this analysis plan, we define missing data as those variables with the absence of data at T1 or T2. .

Missing baseline data values will be handled by multiple imputation with chained equations (m=100) using stratification variables, post-baseline values and variables predicting missing baseline URICA as predictors in the imputation model.

In the secondary analyses, missing data will be handled by multiple imputations with chained equations (m=100) using baseline values of the scales in question, variables predicting missing data, and stratification variables, as auxiliary variables in the imputation models. In cases where other scales are theoretically strongly correlated to the missing data, these scales will also be used as auxiliary variables in the imputation models.

Statistical software

All analyses will be undertaken in SPSS and STATA.

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31/5-23

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Date

Signature

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30 may 2023



Date

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31/5 2023



Date

Signature

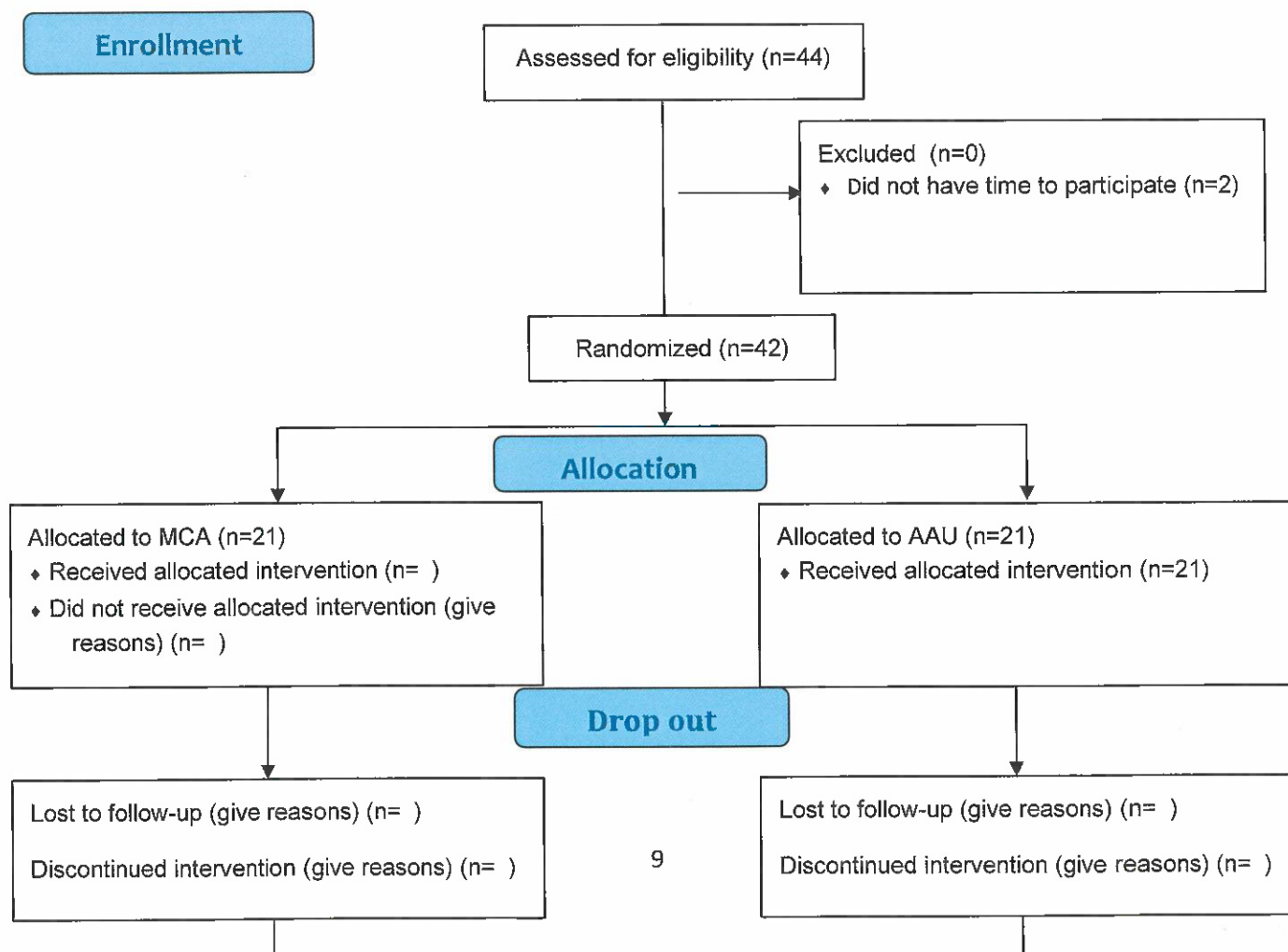
	Total (N=42)	MCA (N=21)	AAU (N=21)
Age, years			
Female			
Employment/Studies			
Full-time			
Part-time			
Sick leave			
Unemployed			
Psychiatric clinic			
Næstved			
Maribo			
Slagelse			
Highest completed education			
Elementary school			
Secondary education			
Short tertiary education			

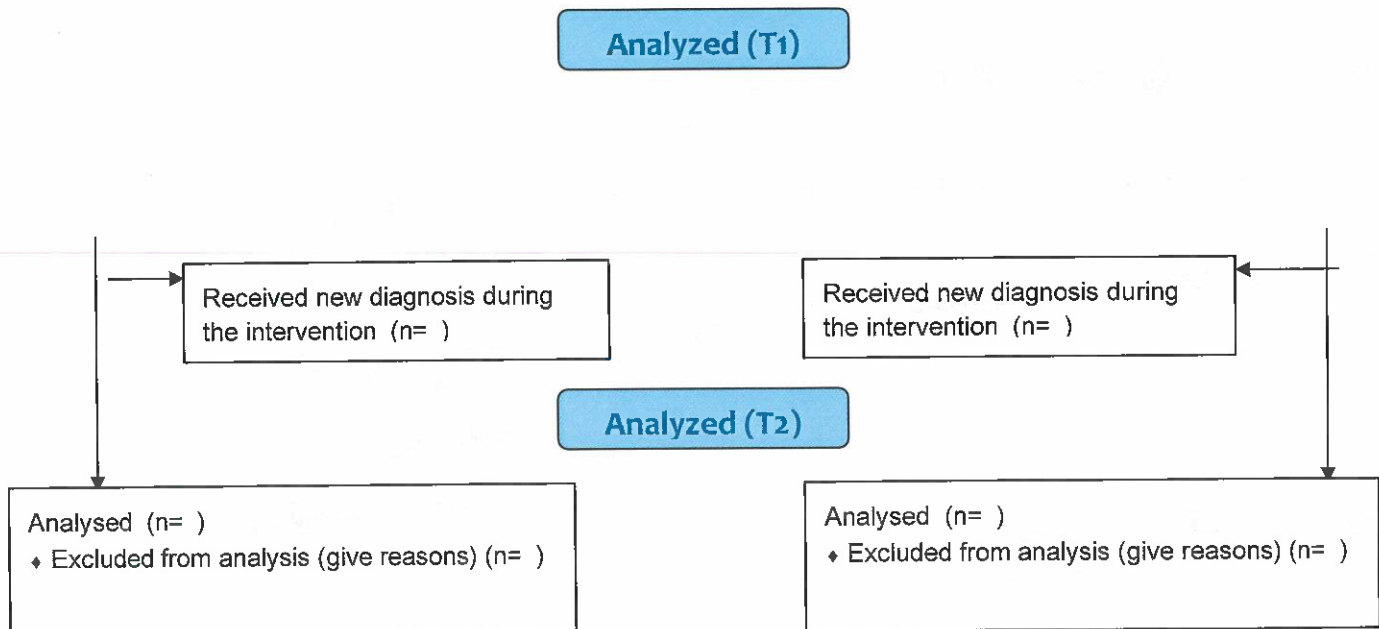
Long tertiary education			
Primary diagnosis			
Social Phobia			
Evasive Personality Disorder			

Table 1: Baseline demographic and diagnostic characteristics within and across conditions

Data are presented as n (%) or mean (SD) from data observed in the intention-to-treat population. MCA, Modified Collaborative Assessment; AAU, Assessment As Usual.

CONSORT 2010 Flow Diagram





References

1. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P; CONSORT Group., *Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration*. Ann Intern Med. 2008 Feb 19;148(4):295-309., 2008.
2. Schulz KF, Altman DG, Moher D; CONSORT Group., *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials*. BMJ. 2010 Mar 23;340:c332. doi: 10.1136/bmj.c332. PMID: 20332509; PMCID: PMC2844940., 2010.
3. Hovmand OR, Reinholt N, Dichmann K, Borisov R, Arnfred S., *Social Phobia and Evasiveness: Trial Protocol for a Randomized Controlled Feasibility and Superiority Trial of the Effect of Modified Collaborative Assessment vs. Standard Assessment on Patients' Readiness for Psychotherapy (CO-ASSM-RCT)*. In press at Pilot and Feasibility Studies, 2023.
4. SO., DiClemente CC and Hughes, *Stages of change profiles in alcoholism treatment*. Journal of Substance Abuse, 2, 217-235., 1990.
5. SV., McGough JJ and Faraone, *Estimating the size of treatment effects: moving beyond p values*. Psychiatry (Edgmont). 2009 Oct;6(10):21-9., 2009.
6. Cohen, J., *Statistical power analysis for the behavioral sciences*. 1977, New York, NY.: Academic Press.