Statistical Analysis Plan (SAP)

Study Title

The Effect of an Integrated Care Intervention of Multidisciplinary Mental Health Treatment and Employment Services for Trauma-Affected Refugees: A Randomised Controlled Trial

Authors

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Trial Registration and approvals

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Danish Data Protection Agency: P-2019-327

Ethics Committee for The Capital Region of Denmark: H-19067136.

1. Introduction

This Statistical Analysis Plan (SAP) outlines the detailed statistical methodology for analysing data from the randomised controlled trial (RCT) evaluating the effect of an integrated care intervention combining multidisciplinary mental health treatment and employment services for trauma-affected refugees diagnosed with post-traumatic stress disorder (PTSD). The SAP is developed in accordance with the study protocol[1] and aims to ensure transparency and reproducibility of the analyses.

2. Study objective

To investigate the treatment effect of an add-on multidisciplinary integrated care intervention on outcomes of functioning, quality of life, mental health symptoms, and level of post-migration stressors compared to TAU.

3. Study design

This study is a pragmatic, parallel-group, two-arm superiority RCT with a 1:1 allocation ratio. Based on calculation of sample size (see below) a total of 197 participants will be enrolled and randomised to either the intervention group receiving the integrated care intervention or the control group receiving treatment as usual (TAU)[1].

4. Hypothesis and null hypothesis

This superiority trial hypothesises that the add-on integrated care intervention will lead to better outcomes across all measures compared to the TAU group.

The corresponding null hypothesis states that there is no significant difference in outcomes between the add-on integrated care intervention and the TAU group.

5. Randomisation and blinding

Participants will be randomly assigned to one of the two study arms using a centralised web-based system (REDCap) with varying block sizes. The allocation sequence is generated by a researcher not directly involved in the trial and is unavailable to the investigator, sponsor, and clinicians. Randomisation is stratified by the municipality of home address (Copenhagen, Gladsaxe, Lyngby-Taarbaek, Hillerød, Frederikssund).

Due to the nature of the intervention, blinding of participants and clinicians is not feasible.

All co-authors are blinded to group assignments until the primary analyses are completed. The actual randomisation group allocation is concealed, with values X and Y representing group assignments in the blinded dataset. The formula for converting the randomisation allocation variable will remain undisclosed until unblinding and is securely managed by a co-worker who will not be involved in conducting or assisting with any analyses.

6. Sample size

From study protocol[1]:
"A minimal clinically important difference (MCID) score for the WHODAS 2.0 has not yet been established. It is difficult to find studies with populations comparable to the present study in the literature. Based on clinical experience and the sparse available literature, a conservative minimal clinically important difference was taken to be five scale points on WHODAS 2.0 12-item version, and within-groups SD was taken to be 10 scale points. With a power level of 80% and alpha of 0.05, we estimate a sample size of each group of 64 and a total of 128. The completion rate in the preceding randomised trials at the CTP was two thirds, and we, therefore, set the expected drop-out rate to 35% for this study. The investigators increased the number of patients included to 128 × (1/ (100%-35%)) and, consequently, estimated a total sample size of 197 patients. Inclusion stops when approximately 197 patients are included in the trial. In the case that an MCID for WHODAS 2.0 is established during the time frame of the trial, this will be considered in the analyses. For the secondary outcome measures with a Cohen's d of 0.5, we have 80% power to detect a change of 0.21 on HTQ, 3.03 on HDRS, 3.77 on HARS, 0.25 on HSCL, 3.0 on SDS, 8.0 on WHO-5, 4.05 on GAF-F, and 2.85 on GAF-S."

In 2022, the Danish Health Authority assessed the MCID for the WHODAS 2.0 12-item and chose a standardised mean difference (SMD) of 0.3[2]. Based on this, we will revise the MCID from 5 scale points to 3 scale points to align with the Danish Health Authority when interpreting our findings.

7. Confidence intervals and p-values

Two-sided 95% confidence intervals will be reported for all estimated effects.

A two-sided p-value of <0.05 will be considered statistically significant for outcomes.

8. Analysis populations

Intention-to-treat (ITT) population

All randomised participants will be included in the ITT analysis, which will be conducted according to their assigned groups, regardless of their adherence to the intervention.

Per-protocol (PP) population

The PP analysis will include participants who fulfil completer criteria as per protocol. Completer criteria include attending five MD sessions, 10 psychologist sessions, and, additionally, two intersectoral collaborative meetings for the intervention group.

9. Outcome measures

Outcome measures are collected pre- and post-treatment and are divided into primary, secondary, and explorative outcomes. Explorative outcomes are scales that are not yet validated in the study population. We also conduct a follow-up at 8 months after treatment, but the follow-up study is not included in this SAP (follow-up data will be analysed in a separate study).

Abbreviation	Scale Name	Type	Measuring	Score reporting	Better score
Primary outcome					
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0 (12-item)	Interview	Functioning	Total score 0-48	Lower
Secondary outcomes					
HDRS	Hamilton Depression Rating Scale (17-items)	Observer	Depression symptoms	Total score 0-52	Lower
HARS	Hamilton Anxiety Rating Scale	Observer	Anxiety symptoms	Total score 0-56	Lower
GAF-S	Global Assessment of Functioning - Symptoms	Observer	Global symptoms	Score 0-100	Higher
GAF-F	Global Assessment of Functioning - Functioning	Observer	Global functioning	Score 0-100	Higher
HTQ	Harvard Trauma Questionnaire (Part IV, 16 items)	Self-rating	PTSD Symptoms	Mean score 1-4	Lower
HSCL-25	Hopkins Symptom Checklist 25	Self-rating	Anxiety and depression symptoms	Mean score 1-4	Lower
WHO-5	World Health Organization Five Well-Being Index	Self-rating	Quality of life	Transformed scores 0-100	Higher
SDS	Sheehan Disability Scale	Self-rating	Functioning	Total score 0-30	Lower
Exploratory outcomes					
PMLD	Post-Migration Living Difficulties Check List	Self-rating	Post-migration Stressors	Total count 0-17*	Lower
EQ-5D-5L	European Quality of Life (5 Dimensions, 5 Levels)	Self-rating	Quality of Life	Utility score -0.757 to 1** EQ-VAS score 0-100	Higher
CHAI	Consumer Health Activation Index	Self-rating	Patient activation	Transformed score 0-100	Higher

*Total count is calculated on number of positive items, defined as a minimum score of “serious”.
**Based in the Danish value set[3]

10. Statistical analyses

Baseline Characteristics

Descriptive statistics will summarise baseline demographic and clinical characteristics by group. Continuous variables will be presented as means and standard deviations, while categorical variables will be presented as frequencies and percentages. We will describe and compare the means and differences between the two intervention groups.

Primary Analysis

The primary analysis will compare the change in functioning scores (WHODAS 2.0) from pre- to post-treatment between the TAU and intervention group with adjustment for the corresponding baseline measures by ANCOVA/linear regression and with multiple imputations to handle missing data. The analysis will follow the ITT principle, including all randomised participants with available data.

Secondary and explorative analyses

Secondary outcomes will be analysed similarly using ANCOVA/linear regression.

11. Interim analyses

No interim analyses are performed.

12. Handling of missing data

The proportion and amount of missing data will be reported. Missing data will be addressed using multiple imputations, under the assumption that data is missing at random. Sensitivity analyses will be conducted to assess the robustness of the findings in relation to different missing data mechanisms (*see 14. Sensitivity analyses*).

13. Covariate adjustment

Analyses will be adjusted for the stratification variable and no other, complying with RCT analysis guidelines from the European Medicines Agency. For outcome variables, we will adjust for their corresponding baseline measure.

14. Sensitivity analyses

Sensitivity analyses will be conducted to assess the robustness of the primary results and will be reported as supplementary to the main analyses.

Baseline covariates found to be imbalanced between the intervention and TAU groups will be identified based on group comparisons and included as covariates in adjusted outcome analyses.

We will examine whether participants with missing post-treatment outcome data differ systematically from those with complete data by comparing baseline characteristics.

To explore the potential impact of missing data, outcomes will be calculated with all missing outcome data replaced with a value equalling the mean of the outcome variable ± 2 standard deviations.

We will conduct observed case analyses.

Additionally, we will conduct a PP analysis to evaluate the influence of adherence to the intervention. Results from the PP analysis will be compared with the ITT analysis to assess whether non-adherence may have affected the study outcomes.

15. Assumptions

To ensure the validity of the statistical models used in this study, the following assumptions will be tested:

a) *Normality of residuals*
   Assumption: Model residuals should be approximately normally distributed.
   Control: Visual inspection using histograms and Q-Q plots of residuals.
   Formal test: Shapiro-Wilk test (if required).

b) Homogeneity of variance (Homoscedasticity)
   Assumption: The variance of residuals should be consistent across groups.
   Control: Levene's test or Bartlett's test for equality of variance.
   Breusch-Pagan test to check for heteroscedasticity.

c) Outliers and influential cases
   Assumption: No extreme outliers that unduly influence results.
   Control: Cook's distance and standardised residual plots to detect influential cases.

If statistical assumption checks indicate violations of normality or homoscedasticity, we will apply analyses of log transformation of outcome and Mann-Whitney U-test.

17. Software

All statistical analyses will be conducted using STATA version 18.

References

1. Bruhn, M. *et al.* The effect of an integrated care intervention of multidisciplinary mental health treatment and employment services for trauma-affected refugees: study protocol for a randomised controlled trial. *Trials* **23**, (2022).

2. Danish Health Authority. Focused clinical question regarding National Clinical Recommendation on the use of mild tranquilizers. (2022).

3. Jensen, C. E. *et al.* The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl Health Econ Health Policy* **19**, 579 (2021).