Trauma-focused Therapies for Post-Traumatic Stress in Psychosis: the RE.PROCESS Randomized Controlled Trial

Statistical Analysis Plan

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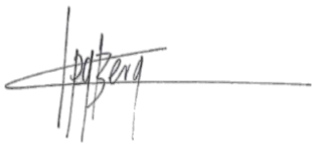
Author: drs. Inez Verdaasdonk

Reviewers: dr. Amy Hardy, dr. Catherine van Zelst, drs. Simone Burger

Approved by:

	Name	Signature	Date
Principle Investigator	Prof. dr. David van den Berg		May 28th 2025

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Study Overview

Introduction

This Statistical Analysis Plan (SAP) outlines the statistical methodologies and procedures for analysing data from the RE.PROCESS study, a four-armed randomized controlled trial. Three trauma-focused therapies (Prolonged Exposure [PE], Eye Movement Desensitization and Reprocessing [EMDR], and Cognitive Restructuring [CR]) are compared to a waitlist control group (WL) in individuals with co-occurring posttraumatic stress disorder (PTSD) and lifetime psychotic disorder. Primary and secondary outcomes are measured at baseline (T0), mid-treatment (T2) at 7 weeks, posttreatment (T3) at 3 months, and 6-month follow-up (T6). An extensive study protocol, including information on rationale, participants, and interventions, is published elsewhere.[1]

Study Design

This study is a pragmatic, single-blind multicentre superiority randomized controlled trial with four arms: CR, PE, EMDR, and WL. Therapy in all three active arms will be delivered over 16 sessions by trained therapists working in routine mental health services. All groups receive TAU for psychosis and will be assessed at T0, T2, T3, T6. Participants in the WL condition receive therapy of choice after T6.

Study Objectives

Primary objective

The primary objective is to compare the effects of CR, PE, and EMDR to WL on researcher-rated severity of PTSD symptoms (CAPS-5 total score) over time from baseline to 6-month follow-up.

Secondary objective

Secondary objectives are to compare the effects of CR, PE, EMDR, to WL for researcher-rated severity of PTSD symptoms at the separate time-points (i.e. mid-treatment, post-treatment, and at 6-month follow-up) and to test the effects (over time and at each time-point) for clinician-rated presence of PTSD diagnosis according to the DSM-5 criteria, and self-reported severity of complex PTSD symptoms.

Tertiary objectives

In addition, we will explore the effects of the treatments on disruption of social functioning by PTSD symptoms, post-traumatic cognitions, dissociation, depression symptoms, paranoid ideation, presence and impact of voice-hearing, social functioning, personal recovery, adversities, experienced resilience, and revictimization over time and at each time-point.

An overview of each outcome variable, corresponding measure, and outcome type is provided in Table 1.

Table 1. Outcome variables and corresponding measures for primary, secondary, and tertiary objectives

Outcome variables	Measure	Type (continuous or dichotomous)
PTSD symptoms		
Researcher-rated PTSD symptom severity	CAPS-5[2]	C
PTSD diagnosis	CAPS-5 [2]	D
Self-reported PTSD symptom severity	PCL-5 [3]	C
Self-reported complex PTSD symptom severity	ITQ [4]	C
Post-traumatic cognitions	PTCI-9 [5]	C
Disruption of social functioning by PTSD symptoms	ITQ [4]	C
Dissociation	TSDQ-s [6]	C
Psychosis symptoms		
Frequency of voice-hearing	PSYRATS-AHRS-FRQ [7]	C
Impact of voice-hearing	VIS [8]	C
Paranoid thoughts	R-GPTS [9]	C
Depression symptoms	BDI-II [10]	C
Social functioning	Adapted TUS [11]	C
Personal recovery	QPR [12]	C
Adversities	TAEQ [13]	C
Revictimisation	Interpersonal victimisation items of the TALE [14]	C
Resilience	BRS [15]	C

Note: CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; PCL-5 = PTSD Checklist for DSM-5; ITQ = International Trauma Questionnaire; PTCI-9 = Brief version of the Posttraumatic Cognitions Inventory; TDSQ-s = Trait State Dissociation Questionnaire – short version; PSYRATS = Psychosis Symptom Rating Scale – Auditory Verbal Hallucinations Scale; VIS = Voice Impact Scale; R-GPTS = Revised version of the Green et al Paranoid Thoughts Scale; BDI-II = Beck Depression Inventory II; Adapted TUS = Adapted Time Use Survey; QPR = Questionnaire about the Process of Recovery; TAEQ = TTIP Adverse Events Questionnaire; TALE = Trauma and Life Events; BRS = Brief Resilience Scale .

Randomisation and Blinding

Participants are randomized by an independent researcher using a randomization programme (http://www.randomizer.org) with a 1:1:1:1 allocation ratio, stratified by trial therapist. The allocation sequence is saved in a protected folder to which the research team has no access. The independent researcher informs the therapist of the allocation who in turn informs the participant.

Sample Size Calculation

A formal power analysis was conducted to determine the required sample size for the planned longitudinal intention-to-treat (ITT) analyses using linear mixed models (LMM).

Based on data from previous randomized controlled trials in this field [16,17], the calculation used the following parameters: significance level (α) of 0.05 (two-sided), power (1-β) of 0.80, expected correlation between repeated measures (ρ) of 0.45, and 3 repeated follow-up assessments. The minimum detectable effect size was set at 0.5 (medium effect, compared to waiting list control), while accounting for an anticipated attrition rate of 20%. These calculations indicated that 50 participants would be needed in each study arm. Therefore, our aim will be to randomize a total of 200 participants.

Statistical Methods

General principles

This Statistical Analysis Plan describes the methods for analysis of the effect of trauma-focused therapies for individuals with PTSD and psychosis on primary, secondary, and adverse outcomes. Other analyses outlined in the published protocol, such as cost-effectiveness analysis, will be described and published separately.

All analyses will be completed in R (version 4.4.2) unless stated otherwise. All tests are two-sided and a significance level of α=0.05 is adopted.

Data will be analysed following the intention-to-treat principle, ensuring all randomized participants are analysed in their assigned groups, regardless of adherence or missing data. Missing data will be treated as missing at random.

Statistical analyses will be carried out by Inez Verdaasdonk, under supervision of dr. Simone Burger, dr. Catherine van Zelst, dr. Amy Hardy, and prof. dr. David van den Berg. An independent statistician will be consulted throughout the analysis process.

Primary Outcome Analysis

To evaluate changes in researcher-rated PTSD symptom severity over time and treatment differences, a LMM will be fitted using restricted maximum likelihood (REML) estimation. The primary model includes baseline scores as covariate, treatment condition as fixed effect, time as categorical variable, an interaction term between treatment condition and time, and a random intercept for each participant to account for within-subject correlations. An interaction effect between treatment condition and time variables would indicate differential treatment effects over time. To appropriately model the within-subject correlation of repeated outcome measures across unequally spaced timepoints, an unstructured covariance matrix will be applied to the residuals in the LMM. This results in the following model equation:

$$Y_{ij} = \beta_0 + \beta_1 \cdot Baseline_i + \sum_{k=1}^{3} \beta_{2k} \cdot Group_{ik} + \sum_{l=1}^{3} \beta_{3l} \cdot Time_{jl} + \sum_{k=1}^{3}\sum_{l=1}^{3} \beta_{4kl} \cdot (Group_{ik} \times Time_{jl}) + u_i + \varepsilon_{ij}$$

Where:

- Y_{ij}: Outcome for participant i at timepoint j
- $Baseline_i$: Baseline outcome value for participant i
- $Group_{ik}$: Dummy-coded treatment condition indicators (3 dummies: CR, PE, EMDR; WL = reference)
- $Time_{jl}$: Dummy-coded time indicators (3 dummies: midtreatment, posttreatment, 6-month follow-up; baseline = reference)
- $Group_{ik} \times Time_{jl}$: Group-by-time interaction terms
- u_i: Random intercept for participant i
- ε_{ij}: Residual error
- Fixed effects:
    - Intercept β_0: Mean outcome at baseline for WL
    - β_1: Effect of individual baseline outcome value (covariate)
    - β_{2k}: Group main effects at baseline, compared to WL
    - β_{3l}: Time effects for WL (how outcomes change over time within WL)
    - β_{4kl}: Additional group-specific changes over time relative to WL

To quantify the magnitude of treatment effects, effect sizes will be estimated for timepoints T3 and T6 based on the mean pre-post change (i.e. baseline scores vs. follow-up scores) of the treatment condition minus the mean pre-post change of WL, divided by the pooled pretest standard deviation [18]

Secondary and Tertiary Outcome Analyses

For continuous outcomes, LMMs with similar methodology as the primary outcome analysis will be applied. For dichotomous outcomes (e.g., clinician-rated presence of PTSD diagnosis) generalized linear mixed models (GLMMs) with a logit link function will be used, in line with the following model equation:

$$\log\left(\frac{\Pr(Y_{ij}=1)}{1-\Pr(Y_{ij}=1)}\right) = \beta_0 + \beta_1 \cdot Baseline_i + \sum_{k=1}^{3} \beta_{2k} \cdot Group_{ik} + \sum_{l=1}^{3} \beta_{3l} \cdot Time_{jl} + \sum_{k=1}^{3}\sum_{l=1}^{3} \beta_{4kl} \cdot (Group_{ik} \times Time_{jl}) + u_i + \varepsilon_{ij}$$

Here, the left-hand side of the model equation indicates the log-odds of the outcome being 1 (e.g., no longer meeting PTSD diagnosis criteria).

The trial protocol specified Generalised Estimating Equations (GEE) would be used to analyse dichotomous outcomes.[1] This plan has been updated to employ GLMMs, as they allow explicit modeling of random effects and individual-level variability, while offering more robust performance when handling missing data under missing at random (MAR) assumptions, which better suits our study's anticipated data structure.[19]

Similar to the primary analysis, effect size of continuous outcomes will be estimated with d_{ppc2}. For dichotomous outcomes, odds ratios (ORs) will be calculated from the fitted GLMM. Here, exponentiated model coefficients will be interpreted as odds ratios comparing the odds of the outcome between treatment arms and timepoints.

In addition to testing treatment effect on primary and secondary outcomes over time, post-hoc pairwise comparisons between treatment groups and the waitlist control group will be conducted at each timepoint using estimated marginal means with Bonferroni correction to adjust for multiple comparisons.

Sensitivity Analyses

To evaluate the robustness of the findings of the primary outcome analysis, the following sensitivity analyses will be performed:

- Per-protocol analysis: estimating treatment effects among participants who completed their allocated therapy (i.e., participants who completed all 16 therapy sessions or participants who met criteria for early completion[a]).
- Multiple imputation sensitivity analysis: compare primary model with only assessment completers to model with missing outcome data imputed to examine if data is missing at random (MAR). Missing data in the outcome variable will be handled using multiple imputation via chained equations.

Safety Analysis

During study participation, trial therapists were asked to monitor and report any severe adverse events (e.g., death, life threatening situations) and their possible study-relatedness. Severe adverse events will be summarized over the full study period (i.e., baseline up until 6-month follow-up) and reported by treatment arm.

In addition, all participants were asked to monitor adversities and revictimization weekly using smartphone questionnaires up to the 6-month assessment timepoint to enhance ecological validity. To assess group differences on these tertiary outcomes, events reported in the weekly online questionnaires will be aggregated between assessment timepoints and averaged to generate a single composite score corresponding to each formal assessment timepoint (i.e. baseline, T2, T3, and T6) for LMM-analysis.

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[a] Early completion of EMDR or PE therapy was permitted only after consultation with the therapist and supervisor, and required that all trauma memories on the case conceptualization achieved Subjective Units of Distress (SUDs) scores of 0, participants scored 0 on both the re-experiencing (section B) and avoidance (section C) sections of the PCL-5, all psychosis targets achieved SUD scores of 0, and psychosis symptoms were in remission.

Data Management and Quality Assurance

Data will be collected using Castor, an electronic data capture system, and managed in accordance with Good Clinical Practice guidelines. Regular data monitoring and validation checks will ensure data quality.

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