Trauma-focused Therapies for Posttraumatic Stress In Psychosis

the RE.PROCESS randomised controlled trial

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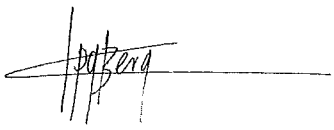
Dr. David van den Berg **Coordinating investigator/ project leader/ Principal investigator** **Vrije Universiteit/ Parnassia**		**18-02-2019**

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CR	**Cognitive Restructuring**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EMDR	**Eye Movement Desensitization and Reprocessing**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
PE	**Prolonged Exposure**
PTSD	**Posttraumatic stress disorder**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TFT	**Trauma-Focused Therapy**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Positive effects on PTSD, psychosis, adversities and revictimization were found in patients with psychosis for a small dose (8 sessions) of prolonged exposure (PE) or Eye Movement Desensitization and Reprocessing (EMDR). Replication is needed and there are many important issues that warrant further investigation, such as a test of a full treatment dose, improvement of the effects on psychosis symptoms, and an improvement of our understanding of mechanisms of change. Importantly, there is need for a head-to-head comparison of trauma-focused treatments with and without direct trauma memory processing in patients with psychosis.

Objective: The primary objective is to determine the effects of a full treatment dose of PE, EMDR, cognitive restructuring without direct trauma memory processing (CR), and Waiting List (WL) on researcher-rated severity of PTSD symptoms. The secondary objective is to investigate the effects of these treatments on researcher-rated presence of PTSD diagnosis, self-rated severity of PTSD and severity of complex PTSD symptoms, posttraumatic cognitions, dissociation, depression, paranoia, auditory verbal hallucinations, social functioning, disruption of social functioning by PTSD symptoms, resilience, personal recovery, sexual functioning, adversities, and revictimization. Third, with the 24-month follow-up we aim to test the long-term effects on all the outcomes for the first time. Fourth, we aim to explore how post-traumatic stress and psychosis interact dynamically, how the experimental treatments influence these interactions, and what factors significantly predict treatment response. Our fifth objective is to determine the cost-effectiveness of the interventions. Sixth, we will conduct a process evaluation of the therapy process by conducting interviews to examine how participants experienced receiving trauma-focused treatment.

Study design: A single-blind multicentre randomised controlled trial with four arms (PE, EMDR, CR, and WL), and assessments at baseline, mid-treatment (at 7 weeks), posttreatment (at 3 months), and at 6, 12, and 24-month follow-up. The WL group will only be assessed up to the 6-month follow-up, since they will then receive treatment of choice.

Study population: Adult patients (16+) meeting DSM-5 criteria for both a chronic posttraumatic stress disorder and a psychotic disorder in the schizophrenia spectrum.

Intervention: The PE, EMDR and CR groups will receive a maximum of 16 sessions of treatment. The third group will be a waiting list group up to the 6-month follow-up, after which they may choose to receive treatment. All groups receive treatment as usual for psychosis.

Main study parameters/endpoints: The main outcome is researcher-rated changes in severity of PTSD symptoms on the CAPS between baseline and 6-month follow-up.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants in the active treatment arms will be tested five times. The

participants will receive a maximum of 16 trauma-focused treatment sessions of maximally ninety minutes. Some patients may experience a short increase in symptoms during or following the sessions. Based on prior research, no major adverse events are expected. CR was found to be safe in patients with psychosis, and both PE and EMDR were actually found to reduce adversities in this group. Participants in the WL condition will have to wait for treatment for 6 months.

1. INTRODUCTION AND RATIONALE

Experiencing childhood trauma increases the chance of developing psychotic symptoms[1,2] and there are indications that trauma is associated with persistence of psychosis.[3] Traumas are highly prevalent in patients with psychotic disorders.[4] For example, one review found that 28.3% of the males and 47.7% of the females with a psychotic disorder have experienced sexual abuse in childhood;[5] later reviews also reported similar percentages.[6] For purposes of comparison, the worldwide prevalence rate of sexual abuse is reported to be 1.6%.[7] Moreover, individuals with psychotic disorders are at greatly increased risk of revictimization.[8] As a result, many individuals suffering from psychosis (12.4%-16.0%) have symptoms that meet the full diagnostic criteria for PTSD.[9,10]

Symptoms of PTSD and psychosis interact and overlap.[11-13] In psychosis, the presence of comorbid PTSD is associated with more severe psychiatric symptoms, lower levels of social functioning, and more suicide attempts.[14-16] Also, traumatized patients with psychotic disorders show more problems in service engagement and treatment adherence,[17] receive higher doses of psychotropic medications,[18] and respond less well to antipsychotics.[19] Both trauma and a comorbid PTSD aggravate symptoms of psychosis[20] and appear to function like 'accelerators' behind the psychosis via an array of 'vicious' interactions. Thus, many patients with a combination of trauma, psychosis and PTSD become stuck in a vicious cycle of 'stable instability', often for as long as the PTSD symptoms remain untreated.

Fortunately, the importance of both trauma and posttraumatic stress disorder (PTSD) in psychosis are increasingly acknowledged in both the scientific community and clinical practice. A large randomised controlled trial (RCT) found trauma-focused treatment (TFT) with direct trauma memory processing to be effective and safe in patients with both psychosis and PTSD.[21,22] TFT had neutral to positive effects on symptoms of psychosis, depression and social functioning.[23] In this RCT, the effects of two different TFTs, prolonged exposure therapy (PE) and eye movement desensitization and reprocessing therapy (EMDR), were compared with waiting list for TFT (WL) at baseline, posttreatment, and 6-month follow-up. Standard PE and EMDR protocols were used and participants received a dose of only 8 sessions of therapy. All participants received treatment as usual for psychosis. Compared to WL, both PE and EMDR significantly decreased clinician rated PTSD symptoms, self-rated PTSD symptoms, negative posttraumatic cognitions, and paranoid-referential thinking. In both TFT conditions, significantly more participants achieved remission from schizophrenia. Only PE was found to significantly reduce the severity of depression symptoms. In comparison to WL, there

were no significant effects for PE and EMDR on social functioning and voice hearing. Effects observed at posttreatment were generally maintained until 6-month follow-up. Replication of these findings is required and there are many important issues that warrant further investigation.

Most individuals with both PTSD and psychosis have suffered severe and multiple childhood trauma.[10,21] In our RCT we observed that participants with more severe PTSD symptoms at baseline exhibited higher posttreatment PTSD symptom severity end state, but also showed a greater reduction in PTSD symptoms.[24] This suggests that the severely traumatized patients with psychosis responded well, but derived insufficient benefit from only 8 sessions of trauma-focused treatment (i.e. the maximum treatment dosage in that study). Others found that adding extra treatment sessions enhanced treatment outcomes for patients who did not improve (sufficiently) after a standard dosage.[25] Therefore, the beneficial effects of a full treatment dose should be tested in this severely traumatized population.

Both PE and EMDR were found to positively affect symptoms of psychosis.[23] More fine-grained insight into these effects is however needed,[26] preferably by assessment of these symptoms in everyday life. Also, therapists were previously restricted to reprocessing PTSD related memories, although they also identified traumas that showed direct or indirect associations with symptoms of psychosis. And it has been reported in case studies that reprocessing psychosis related traumas may positively influence symptoms of psychosis.[27,28] It is important to test the effects of allowing therapists to also reprocess psychosis-related traumas.

Individuals with psychotic disorders are at substantially increased risk of revictimization.[8,29] PTSD symptoms are not only a consequence, but also a precursor of victimization and are reported to be a significant mediator in the relationship between childhood sexual abuse and revictimization, e.g.[30] TFT was found to reduce the odds of revictimization in patients with psychosis and this reduction was significantly associated with a reduction in PTSD symptoms during treatment.[22] It may be that effective TFT increases resilience in these vulnerable patients. Considering the great importance of preventing revictimization, more research into this important topic is needed.

Similarly, in our previous RCT we observed significant and long-term reductions in disruption of social functioning by PTSD symptoms, although positive effects on social functioning itself were absent.[31] This is in opposition to the fact that presence of PTSD symptoms in psychosis has repeatedly been found to be associated with lower levels of social functioning.[16] It suggests that in this severely traumatised sample, with severe and complex (and often neglected) symptom profiles, and problems in many domains of life, many other factors than PTSD influence social functioning. It must also be noted that we

used a very short and global assessment of social functioning, which might limit reliability and validity. Therefore, future studies should test the effects of trauma-focused treatment on social functioning in everyday life with more ecologically valid measures, e.g. weekly longitudinal assessments. Longer follow-up periods are also desirable.

People who experience sexual trauma are four times more likely to report sexual problems compared with non-sexual trauma.[32] Sexual dysfunction rates are higher in people with PTSD, compared with similarly exposed victims without PTSD, regardless of the nature of the trauma.[33-35] So even though sexual dysfunction has often been linked with exposure to sexual trauma rather than to the presence of PTSD, studies on trauma, sexual dysfunction and PTSD suggest that PTSD, rather than trauma exposure per se, might be the more proximal antecedent to sexual problems. As a result, it may be expected that trauma-focused treatment for PTSD may decrease sexual dysfunction.[36]

To date, TFTs with direct trauma memory processing (e.g. PE or EMDR) have never been compared head-to-head to treatments without this feature in patients with psychosis. The research group of Kim Mueser in the USA developed an adapted cognitive restructuring program without trauma memory processing.[37] This CR protocol was found to be effective in patients with severe mental illnesses,[38,39] but less so in a sample of patients with psychosis.[40] A head-to-head comparison of treatments with and without trauma memory processing within the same clinical context will answer the important question of whether direct trauma memory processing is a necessary feature of TFT in psychosis or not.[41]

Finally, in order to really progress mental healthcare, we need to enhance our understanding of how symptoms dynamically interact over time, e.g.[42,43] Similarly, although trauma-focused treatments are based on theory and are clearly effective in treating PTSD, experimental research into their working mechanisms is however scarce.[44]

In summary, we aim to set up a trial that answers important unanswered questions concerning the effects of trauma-focused treatments in patients with psychosis in routine clinical practice. This trial will experimentally test and greatly improve our understanding of the working mechanisms of three different trauma-focused treatments. It will also shed light on the longitudinal and dynamic associations between post-traumatic stress and psychosis.

2. OBJECTIVES

Primary Objective:

Our primary objective is to test the effects on researcher-rated severity of PTSD symptoms of a full dose of prolonged exposure therapy (PE), eye movement desensitization and reprocessing therapy (EMDR), cognitive restructuring therapy without direct trauma memory processing (CR), and waiting list (WL). We will compare all arms and are primarily interested in comparing the active treatments (PE, EMDR and CR) to WL, and in comparing the interventions with (PE and EMDR) to the intervention without (CR) direct memory processing.

Secondary Objectives:

Second, we aim to investigate the effects of PE, EMDR, CR, and WL on researcher-rated presence of PTSD diagnosis, self-rated severity of PTSD symptoms and severity of complex PTSD symptoms, posttraumatic cognitions, dissociation, depression symptoms, paranoia, auditory verbal hallucinations, social functioning, disruption of social functioning by PTSD symptoms, experienced resilience, personal recovery, sexual functioning, adversities, and revictimization. Third, with the long follow-up we aim to test the long-term effects on all the outcomes for the first time. Fourth, we aim to explore how post-traumatic stress and psychosis interact dynamically, how the experimental treatments influence these interactions, and what factors significantly predict treatment response. Our fifth aim is to determine the cost-effectiveness of the interventions. Sixth, we will conduct a process evaluation of the therapy process by conducting interviews in a subgroup of participants to examine how they experienced receiving trauma-focused treatment.

3. STUDY DESIGN

A single-blind multicentre randomised controlled trial with four arms: PE, EMDR, CR, and WL. All groups receive treatment as usual for psychosis. All the groups will be assessed at baseline (T0), mid-treatment (T1), posttreatment (T2), and at 6-month follow-up (T3). These assessments will take about 90 minutes to administer. Participants in the WL condition can choose to undergo treatment of choice after the 6-month follow-up assessment. The PE, EMDR and CR conditions will also be assessed at 12-month and 24-month follow-up. Up to the 6-month follow-up assessment, all groups weekly monitor the outcomes social functioning, adversities, and revictimization. Participants in the active treatment arms will receive two treatment sessions per week.

4. STUDY POPULATION

4.1 Population (base

Participants will be recruited from outpatient services of mental health organisations in the Netherlands that offer care to people with psychotic disorders. We previously found that 16% of these patients meet full PTSD diagnostic criteria.[10] Participating mental health organisations are: Antes, Arkin/Mentrum, GGZ Centraal, GGZ Eindhoven, GGZ Noord-Holland Noord, GGZ Oost-Brabant, Parnassia, en PsyQ.

4.2 Inclusion criteria

In order to be eligible to participate in this study, patients must meet all of the following criteria:

- age 16+ years
- a lifetime diagnosis of a psychotic disorder in the schizophrenia spectrum, confirmed by the Structured Clinical Interview for DSM-5 (SCID-5)
- full DSM-5 diagnostic criteria for chronic PTSD on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) with a minimum score ≥23
- willingness to undergo randomisation and a trauma-focused therapy

4.3 Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- changes in antipsychotic or antidepressant medication regimen within 4 weeks before the inclusion interview assessment (to control for medication effects)
- insufficient competence in the Dutch language

- severe intellectual impairment, defined as an estimated IQ of 70 or less
- not being able to travel (or be accompanied) to the outpatient service
- not willing or able to learn to use a smartphone

4.4 Sample size calculation

Sample size for longitudinal intention-to-treat (ITT) analyses with linear mixed models (LMM) was calculated according to the method presented by Liu and Liang (1997)[45] and based on data from previous RCTs.[21,40] Although an ITT analysis with LMM is robust against moderate attrition, we aim to include an additional 20% to compensate for dropout. With alpha = 0.05; beta = 0.2; rho = 0.45; 3 repeated follow-up assessments; we will need 50 participants in each arm to detect at least medium effects (0.5), which are expected based on previous research. Therefore, we aim to include 200 participants.

5. TREATMENT OF SUBJECTS

All therapists will deliver both PE, EMDR and CR and will be trained in all the protocols. All sessions are videotaped, a selection will be rated for treatment fidelity. The therapist is provided with the baseline assessment data concerning trauma, PTSD and psychosis to support the development of a case formulation and treatment plan. The case formulation and treatment plans will be reviewed by a supervisor. Monthly group supervisions will be organized. Supervision will be delivered by experts in the experimental treatments. Maximally 90-minute sessions will be held two times a week and will be provided within the mental health organization where the participant receives his or her usual care. Participants in the three treatment arms will receive a maximum of 16 sessions, delivered in two phases. All therapies are preceded and succeeded by one meeting with the therapist. The first meeting is an introductory meeting in which treatment and recovery goals are formulated. In this last meeting, the treatment is evaluated together with the case coordinator and recovery goals for the future are reformulated. The treatments will be delivered in a recovery and goal-oriented manner. The key message is that the aim of the treatment is to reclaim one's life, to reach one's goals, to improve social functioning, to enhance resilience, and increase feelings of safety. All treatments encompass elements of recognition of the trauma, the consequences of the trauma, attention and hope. As part of the treatment protocols in each active arm, post-traumatic stress and psychosis factors are assessed and reviewed weekly via smartphone on the RoQua web platform (see the instruments section). This weekly therapy assessment contains 49 items and takes about 4 minutes to administer. Factors that are assessed are: re-experiencing (5 items, 0 - 4 rating),[46] avoidance (2 items, 0 - 4 rating),[46] negative cognitions and mood (7 items, 0 - 4 rating),[46] hyper arousal (6 items, 0 - 4 rating),[46] beliefs about self/beliefs about others (9 items, 1-7 rating),[47] dissociation (4 items, 0 - 4 rating),[48] control (3 items, 1 - 7),[49] involuntary memory characteristics (7 items, 1 - 7 rating),[60] and hallucinations (3 items, 1 - 7 scale) and paranoia (3 items, 1 - 7).[50,51]

5.1 Investigational product/treatment

Prolonged exposure therapy (PE)

In the first session, the therapist delivers normalizing psycho-education and together with the participant develops a case formulation and treatment plan. The therapist informs the participant about trauma, PTSD and the many negative consequences that trauma can have on our lives, including symptoms of psychosis. In collaboration with the participant, the therapist develops a case formulation that contains the most important traumatic

experiences, a hierarchy of the most relevant trauma memories based on subjective units of distress scores (SUD) and frequencies of intrusions, the experience of psychosis and associated memories, the most important avoidance behaviours, the most important strengths of the person, and associations between these factors. The participants then receive 7 sessions in which re-experienced traumatic memories associated with PTSD symptoms are processed and in which exposure in vivo is done on trauma-related stimuli that are avoided. After the mid-treatment assessment (T1), participants will receive a maximum of 8 additional sessions in the second phase of treatment. The first session of the second phase starts with evaluating and updating the case conceptualisation, the treatment plan, and the treatment/recovery goals. The therapist also explains the rationale for the second phase of treatment. In this second phase additional trauma memories associated with PTSD will be processed. If PTSD comes into remission, therapists are allowed to process traumatic memories that are associated with psychosis symptoms in the absence of PTSD re-experiencing. The exact number of sessions that are delivered is based on predetermined completion criteria: i.e. symptoms of PTSD are in remission for at least two consecutive sessions (the participant scores 0 on sections B – reliving - and C – avoidance - of the PCL-5), there are no more traumas that are associated with PTSD on the hierarchy with a SUD > 0, and there are no more psychosis related memories or imagery with a SUD > 0) and a shared decision-making process between participant and therapist.

The PE therapy will be delivered conform the protocol of Foa, Hembree and Rothbaum (2007).[52] This protocol consists of imaginal exposure (whereby each session is audio recorded and participants listen to these recordings five times per week) and in vivo exposure (based on a list of avoided trauma-related stimuli).

Eye movement desensitization and reprocessing therapy (EMDR)

The procedures for EMDR are exactly the same as for PE. EMDR will be delivered according to the standard 8-phase protocol by Shapiro,[53] using the Dutch translation of the EMDR protocol.[54] Eye movements will be applied as the default dual attention stimulus.

Cognitive restructuring therapy (CR)

This adapted cognitive restructuring treatment was developed by Mueser et al.[37] and is based on cognitive models of PTSD that posit that appraisals of traumatic events, and subsequent attempts to cope with the associated negative affect, are the key factors in the development and maintenance of PTSD. Negative appraisals of traumatic events and their consequences for the self, others and the world can give rise to the sense of current

threat that characterizes PTSD. The most important adaptation of this CR protocol is the exclusion of direct memory processing since the developers expected that direct trauma memory processing would be too difficult to tolerate for patients with severe mental illnesses. The treatment methods and materials are also adapted to accommodate some of the unique challenges of people with severe mental illness, e.g. cognitive impairments. The first 3 sessions include learning breathing retraining for anxiety and education about trauma and PTSD, followed by 13 sessions of cognitive restructuring. Cognitive restructuring is taught as a self-management skill for dealing with negative feelings through the articulation of specific thoughts that underlie the distressing feeling, and the objective evaluation of evidence supporting those thoughts. Patients are taught how to challenge inaccurate thoughts that are not supported by the evidence (for example 'I am responsible for my sexual abuse'), and how to develop 'action plans' to address situations in which distressing thoughts are deemed to be accurate (for example 'My new boyfriend is becoming abusive and I am at risk of getting hurt'). People initially learn cognitive restructuring to cope with any distressing feelings, and as their skills develop they shift to addressing trauma-related thoughts and beliefs that underlie PTSD symptoms. Home assignments to practice breathing retraining and cognitive restructuring skills are collaboratively set each session.

Treatment-as-usual

Treatment as usual for psychosis consists of care in multidisciplinary assertive outreach teams, with care usually consisting of antipsychotic medication and treatment and/or supportive counselling by psychologists, caseworkers, nurses, or psychiatrists.

5.2 Escape medication (if applicable)

The participant and their treatment team are asked not to start any other form of trauma-focused treatment, to refrain from offering cognitive behaviour therapy for psychosis, and to keep medications unchanged up to the 6-month follow-up. However, in the case of adverse events or increases in symptoms of psychosis that demand intervention, antipsychotics, sedatives or CBT may be increased or provided.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

Researcher-rated changes in severity of PTSD symptoms on the CAPS between baseline and 6-month follow-up.

6.1.2 Secondary study parameters/endpoints (if applicable)

Changes in the number of participants fulfilling the diagnostic criteria of PTSD, self-rated severity of PTSD symptoms and severity of complex PTSD symptoms, posttraumatic cognitions, dissociation, depression symptoms, paranoia, auditory verbal hallucinations, social functioning, disruption of social functioning by PTSD symptoms, resilience, personal recovery, sexual functioning, adversities, and revictimization in the period between baseline and 6-month follow-up.

6.1.3 Other study parameters (if applicable)

12-month and 24-month follow-up outcomes for the primary and secondary study parameters in the PE, EMDR and CR conditions. Since the WL group is not assessed at 12 and 24-month follow-up, these comparisons are within group, i.e. 12 and 24-month follow-up outcomes are compared with the 6-month follow-up data for each arm. Cost-effectiveness of PE, EMDR and CR compared to WL between baseline and 6-month follow-up. Potential baseline predictors are PTSD, complex PTSD, paranoid ideation, negative impact of voices and social support. The baseline and post-treatment assessment will be augmented by daily monitoring to study how post-traumatic stress and psychosis symptoms dynamically interact and how treatment affects these dynamic interactions (see daily monitoring below).

6.2 Randomisation, blinding and treatment allocation

Randomization is conducted via a scientific randomization program on the Internet (http://www.randomizer.org) by the independent randomization bureau of Parnassia Psychiatric Institute. All trial therapists will provide all treatments. There will be 50 lots for each of the arms. These lots will be divided in proportion over the participating therapists. All research assistants are blind for treatment allocation. In case of incidental unblinding, another research assistant will perform the rest of the assessment.

6.3 Study procedures

Participating mental health organisations will refer eligible patients with a psychotic disorder in the schizophrenia spectrum (confirmed by the responsible clinician with the Structured Clinical Interview for DSM-5) and a suspicion of PTSD to the study. Trial therapists will inform patients with psychosis that they suspect to have comorbid PTSD about the study. If a patient is interested, the therapist asks for written permission to provide the (contact) details of the patient to the researchers. The patient will then be contacted by a researcher and informed about the study both verbally and in reading. Patients then receive at least one week to consider participation in the study. If patients decide to participate, they are invited for a face-to-face meeting in which they can ask additional questions about participation, informed consent is obtained and in which inclusion criteria and exclusion criteria are assessed. When patients meet all inclusion and no exclusion criteria, they will undergo the T0 baseline assessment and will then be randomised. They will be instructed how to perform the web-based assessments and are provided a smartphone and sim-card if they don't own one. All participants will be invited by their allocated trial therapist who will inform them about the allocated study arm, set up a schedule for the treatment sessions, and start with the therapy. Up to the 6-month follow-up assessment participants weekly monitor the outcomes social functioning, adversities, and revictimization, since these factors may be more difficult to estimate in hindsight and may be more susceptible to memory bias. Seven weeks after baseline, the mid-treatment assessment (T1) will be performed. Then the second treatment phase will start, after which participants will undergo the posttreatment assessment (T2) at week 13, and later the 6-month follow-up assessment (T3). All assessments are done by researchers from the VU/Parnassia. They travel to the institution where the participant receives treatment and collect the data through the online data-management program Castor. Participants in the WL condition can choose to undergo their TFT of choice after the latter assessment. The PE, EMDR and CR conditions will also be assessed at 12-month and 24-month follow-up.

All interviews and assessments take place at locations of the participating mental health organisation, ideally the location that the patient regularly attends for treatment.

Instruments

TABLE 1 presents an overview of the instruments used.

Demographic characteristics: to determine demographics at recruitment. These include age, sex, cultural identity, education, employment, living condition, relationship status, duration of PTSD, duration of psychosis, duration of being in mental healthcare. Substance use is assessed using the first two questions of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) that was developed for the World Health Organization (WHO).[55]

TALE: to assess traumatic childhood experiences at recruitment.
The Trauma and Life Event Checklist (TALE) is a 21-item checklist for traumatic experiences and shocking life events in people with psychotic disorders that was recently developed.[56] It covers all main categories of trauma (abuse and neglect) and also bullying, stressful psychotic experiences, experiences of loss, and stressful experiences in contact with mental health or criminal justice services.

CAPS-5: to assess diagnosis of chronic PTSD at inclusion and as an outcome.
The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) is a valid and reliable measure with high specificity and sensitivity and is the gold standard diagnostic interview for posttraumatic stress disorder.[57,58] The DSM-5 version has recently been validated and has good psychometric properties.[59] With the CAPS-5 all DSM-5 symptoms are assessed and scored on intensity and frequency. The enumeration of those scores lead to a continuous severity score which will be used as the primary outcome of the study. Every symptom with a severity score > 2 is regarded as a clinically significant symptom. Using this cut-off it can be determined whether the criteria for a PTSS diagnosis are met. The CAPS-5 provides a symptom severity score and also assesses the presence of a PTSD diagnosis. The CAPS-5 will be administered by psychologists with a Msc. degree and Bachelor and Master students. They will be trained and monitored by a clinical psychologist with extensive experience in administering the CAPS-5.

PSYRATS: to assess auditory verbal hallucinations and delusions at recruitment.
The psychotic symptoms rating scales (PSYRATS) is an 18-item clinical interview that assesses delusions (The Delusion Rating Scale) and Auditory Hallucinations (The Auditory Hallucination Rating Scale, AHRS) and will be assessed at baseline. The PSYRATS scales were found to have excellent inter-rater reliability and to have strong validity.[61] We slightly augmented the PSYRATS in that it also captures the type of delusions and hallucinations. At follow-ups we will assess only 3 items of the AHRS, i.e. frequency, duration, and disruption in order to capture intensity of voices.

ESSI: To assess social support at baseline (predictor).
The Enriched Social Support Instrument (ESSI) is a short 5-item measure of social support and was found to have good validity and reliability.[62]

PCL-5: to assess self-rated severity of PTSD symptoms.
The PTSD Checklist for the DSM-5 (PCL5) is the most commonly used PTSD self-report questionnaire and has been validated in many different types of samples.[63] The DSM-5 version was recently found to demonstrate strong validity and reliability.[46] PCL-5 item scores are summed to yield a continuous PTSD symptom severity score.

ITQ: to assess complex PTSD.
The International Trauma Questionnaire (ITQ) is an 18-item self-report questionnaire that assesses the presence of complex PTSD as defined in the ICD-11 and includes an assessment of disruption of social functioning by PTSD symptoms.[64] Psychometrics have been tested and will be published shortly.

TSDQ-s: to assess dissociation.
The Trait State Dissociation Questionnaire – short version (TSDQ-s) is a 15 item self-report questionnaire that assesses dissociation. It was developed from existing dissociation measures (including the Dissociative Experiences Scale, Bernstein & Putnam, 1986 and the Peritraumatic Dissociation Scale, Marmar et al, 1994) and also included new items measuring aspects of dissociation which were not sufficiently represented in existing scales, particularly emotional numbing. The TSDQ-s has been shown to be psychometrically robust.[48]

PTCI-9: to assess post-traumatic cognitions.
The Brief version of the Posttraumatic Cognitions Inventory (PTCI-9)[47] measures trauma-related cognitive distortions about the self, the world and about self-blame. This is a 9-item version is based on the original PTCI[65] and was found to have strong psychometrics.[47]

BDI-II: To assess severity of depression at inclusion and as an outcome.
The Beck Depression Inventory II (BDI-II) is a widely used 21-item self-report for depression. It provides a continuous score for the severity of depression symptoms. The BDI-II has excellent psychometric properties.[66,67]

GPTS: to assess paranoid ideation.
The Green et al. Paranoid Thought Scales (GPTS) assess ideas of persecution and social reference and were found to have good internal consistency. Validity was established for both scales. The scales were sensitive to clinical change. A hierarchical relationship between social reference and persecution was found.[68]

VIS: assess the impact of auditory verbal hallucinations.
The Voice Impact Scale (VIS) is a 24-item self-report questionnaire that assesses the impact of voices. It contains three subscales: negative Impact of voices, positive impact of voices, and living well with voices. The psychometric qualities of the VIS are good. A publication concerning the psychometrics is under way.

BRS: to assess resilience.
The Brief Resilience Scale (BRS) is a 6-item questionnaire of resilience that was found to have good psychometric properties.[69]

QPR: to assess personal recovery.
The 15-item questionnaire about the process of recovery (QPR) assesses personal recovery.[49] The QPR showed internal consistency, construct validity and Reliability.

ASEX and SAS: to assess sexual functioning.
The 5-item Arizona Sexual Experience Scale (ASEX) assesses sexual dysfunction. It measures the strength of sex drive, ease of sexual arousal, penile erection/vaginal lubrication, ability to reach orgasm and satisfaction with orgasm on a six-point scale, ranging from 1 (no impairment) to 6 (complete impairment). The ASEX total score ranges from 5–30, with higher scores representing greater sexual dysfunction. The ASEX scale is applicable with high validity and reliability to patients regardless of availability of a sexual partner and their sexual orientation.[70] The sexual autonomy scale (SAS) consists of three items measuring the extent to which participants feel their sexual behaviors are self-determined. Participants are asked to indicate the extent of agreement-disagreement on a seven-point Likert scale. The range for the total score is 3–21. Higher scores represent higher levels of sexual autonomy.[71]

TiC-P and EQ-5D: to assess cost-effectiveness and quality adjusted life years.

Care consumption list developed by Trimbos/iMTA for costs associated with psychiatric illness (TiC-P), short version.[72] Questions from the Productivity and Disease Questionnaire – PRODISQ. The EuroQol (EQ-5D) is the World Health Organisation measurement for health outcome that can be expressed in utilities. Utilities can be combined with cost-effectiveness data into Quality Adjusted Life Years (QALYs).[73]

Weekly monitoring: to assess the outcomes social functioning, adversities and revictimization in an ecologically valid way.

Once per week participants are prompted, at a standard day and time that they select themselves, to fill in a short assessment via smartphone. This type of monitoring is increasingly used to assess interventions, amongst others because it results in more ecologically valid results, is sensitive to change, and can be used to determine how variables relate to each other across time and contexts. Self-monitoring in psychosis has repeatedly been found to be feasible, with many studies using about 60 items (assessed in 2-3 minutes) that are presented 10 times per day for at least a 6-day period.[74] From baseline to 6-month follow-up all participants in this study assess social functioning, adversities and revictimization (17 items, 1,5 minutes) once per week. The RoQua web platform will be used for the smartphone assessments. RoQua is an online questionnaire application developed at the University Medical Center Groningen (UMCG) in cooperation with several large mental health care institutions from The Netherlands. The web application sends out a text message with a link. Via this link, participants can access the platform on which the assessment can then be conducted. The platform is only used for sending out questionnaires, collecting answers and data-storage. Participants do not receive any feedback on their answers. The outcomes of two of the questionnaires can be used by therapists to assess the progress of a participant in an intervention as part of the therapy protocol (see section 5 Treatment of subjects). RoQua is hosted in data centres of the University of Groningen (UG), and operates entirely in compliance with the NEN-ISO/IEC 27001 standard and the EU General Data Protection Regulation (GDPR). All sessions with the web application are secured with SSL. HL7 traffic is shielded with VPN between the users and the RoQua server clusters.

Outcomes that are assessed weekly from baseline to 6-month follow-up are:

- Social functioning: with 2 items adapted from time use survey,[75,76]
- Adversities: using the 7-item TTIP Adverse Events Questionnaire.[22]
- Revictimization: using the 8 interpersonal victimization items from the TALE.[56]

Daily monitoring: to assess how post-traumatic stress and psychosis dynamically interact at baseline and post-treatment.

As part of the baseline and post-treatment assessment participants are asked to monitor post-traumatic stress and psychosis symptoms once per day for the duration of two weeks (49 items, 4-minutes). This is optional and participants will be randomized regardless of whether they will do the daily monitoring. Factors that are assessed via the RoQua platform are: re-experiencing (5 items, 0 - 4 rating),[46] avoidance (2 items, 0 - 4 rating),[46] negative cognitions and mood (7 items, 0 - 4 rating),[46] hyper arousal (6 items, 0 - 4 rating),[46] beliefs about self/beliefs about others (9 items, 1-7 rating),[47] dissociation (4 items, 0 - 4 rating),[48] control (3 items, 1 - 7), [49] hallucinations (3 items, 1 - 7 scale), paranoia (3 items, 1 - 7),[50,51] and involuntary memory characteristics (7 items, 1 - 7 rating).[60]

TABLE 1 Overview of the instruments used at the different time-points.

Recruitment assessment

Demographic characteristics

Trauma and Life Event Checklist (TALE)

Clinician Administered PTSD Scale (CAPS-5)

Psychotic symptom rating scales (PSYRATS)

Enriched Social Support Instrument (ESSI)

Baseline and follow-up assessments

Clinician Administered PTSD Scale (CAPS-5)

PTSD Checklist for DSM-5 (PCL-5)

The International Trauma Questionnaire (ITQ)

Trait Dissociation Screening Questionnaire – short version (TDQ-s)

Brief version of the Posttraumatic Cognitions Inventory 9-item (PTCI-9)

Beck Depression Inventory II (BDI-II)

Green et al. Paranoid Thought Scales (GPTS)

The Voice Impact Scale (VIS)

Auditory Hallucination Rating Scale, 3-item frequency subscale (AHRS)

The Brief Resilience Scale (BRS)

The Questionnaire about the Process of Recovery (QPR)

Arizona Sexual Experience Scale and sexual autonomy scale (ASEX, SAS)

Cost-effectiveness (TiC-P and EQ-5D)

Other assessments

Weekly monitoring of social functioning, adversities and revictimization (baseline to 6-month follow-up)

Daily monitoring at baseline and post-treatment (optional)

Personal views on TFT and influence on recovery (in subgroup)

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.5 Replacement of individual subjects after withdrawal

None. We will run intention-to-treat analyses.

6.6 Follow-up of subjects withdrawn from treatment

Yes, if the participant is willing to do the assessments.

6.7 Premature termination of the study

The researchers did not identify criteria for premature termination. The interventions that are tested have been found to be feasible and safe in this population and the study is situated in routine clinical practice. Premature termination of the study is not probable.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the investigator will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The investigator will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

If a SAE occurs, the responsible clinician/ specialist is responsible for the treatment plan and resulting actions. The principle investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other

SAEs will be reported within a period of maximum 15 days after the investigator has first knowledge of the serious adverse events.

8. STATISTICAL ANALYSIS

The primary and secondary outcomes will all be analysed intention-to-treat. We will run completers (sensitivity) analyses to test the robustness of our findings. Both the primary and secondary continuous outcomes will be analysed with Linear Mixed Models (LMM) with baseline values added as covariates. Dichotomous primary and secondary outcomes will be analysed with Generalized Estimating Equations (GEE). The main outcome will be the effect over time. We will also compute the effects for the different time-points using interaction terms. The predictive value of the potential predictor variables will be tested with regression analyses. To test whether the effects of PE, EMDR and CR on the primary and secondary outcomes endure on the long term, we will test the changes between the 6-month follow-up and the 12-month and 24-month follow-up respectively. These within group changes will be analysed with paired samples t-tests (continuous outcomes) and McNemar's tests (dichotomous outcomes). We will also test for differences between PE, EMDR and CR at these time points with independent samples t-tests and Chi-square tests for independence.

We will apply explorative multilevel network models to study the dynamics of post-traumatic stress and psychosis factors using the daily assessments at baseline and post-treatment. The variables in these assessments will be standardized to enhance comparability of the coefficients.[77] We will estimate a multilevel vector-autoregressive model that produces three networks: a temporal within-person network (lagged associations), a contemporaneous networks (within-time-window associations), and a between-person network (variance-covariance structures of mean scores).[78-80] These analyses will shed light on how post-traumatic stress and psychosis factors interact over time and how active intervention influences these interactions. They will also identify factors with high 'out-strength' (factors that have the highest influence on variables at the next time-point) and high 'in-strength' (factors that are influenced the most by variables at the previous time-point).

If a treatment is found to be effective, cost-effectiveness analyses will be performed. The incremental cost-effectiveness ratios (ICERs) are considered to be a single-point estimate of an underlying continuum. Acceptability curves are produced with bootstrap simulations and confidence intervals. The outcome will be costs in Euro's per QALY and the costs in Euro's per day without PTSD gained. If none of the treatments are effective, which is not expected, a cost-minimization calculation will be performed. Inductive

Thematic Analysis will be used to analyse themes in the views of participants TFT and the process of recovery.[81,82]

The trial is deemed successful when we have included enough participants to carry out all above-mentioned analyses and answer all hypotheses.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Patients will be referred to the study by clinicians from the participating centres. After both oral and written presentation of information about the study, and at least one-week time to decide upon participation, the patient is asked to sign informed consent.

9.3 Objection by minors or incapacitated subjects (if applicable)

Subjects will be capacitated and competent adults. In the informed consent, it will be stated clearly that participation in the study and associated interventions is voluntary in any case.

9.4 Benefits and risks assessment, group relatedness

The participants will probably benefit from the given therapy. Worsening of symptoms or other adverse events as a result of the interventions are not expected, as previous research has shown that treatment actually significantly reduces the odds of adverse events.

9.5 Compensation for injury

Exemption of risk assurance is asked from the METC because no risks are associated with the present study. We will test evidence-based trauma-focused treatments that are delivered in routine clinical practice, have been found to be safe in patients with psychosis,[21,22,40] and which are recommended by the ‘zorgstandaard psychose’ (www.ggzstandaarden.nl).

9.6 Incentives (if applicable)

Each participant is compensated for traveling expenses with Euro 20 per assessment (total is Euro 120 since there are 6 assessments) plus 50 euros for the daily and weekly assessments. Of course, also participants that prematurely stop their participation will have their compensation for the assessments they attended.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

The handling of personal data will comply with the Dutch General Data Protection Regulation. Data will be handled confidentially and data files will be separated from the name, date of birth and address data. The name and data files contain a code for the patient. The code is a two-digit site number and a three-digit patient number (XX-YYY). The principal investigators are the only persons who have the key of this code and have access to the source data. The CASTOR trial management software will be used for this trial. Raw data will be kept for five years according to the NFU guidelines.

10.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. The METC will be informed about the start of the study (based on the data of inclusion of the first subject) within one month.

10.4 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.5 Public disclosure and publication policy

The trial will be registered at an international trial register. The results on all hypotheses will be published, unreservedly, in the way this document has described. The sponsor will have no influence on the publication of the results.

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12. APPENDICES

Appendix 1: Research Plan and Timeline

Item	Timeline
Recruiting therapists/ sites and PhD students	May – September 2018
Finalizing protocol	≤ September 2018
Training therapists	September 2018 – February 2019
Science committee APH	October – December 2018
Medical Ethics Review Board	December 2018 – February 2019
Online registry	February 2019
Team trainings	February – July 2019
Recruiting research assistants	October – December 2018
Start inclusion	1st of March 2019
End of inclusion	December 2021
Last post-treatment assessment	April 2022
Last 6-month follow-up assessment	October 2022
Last 24-month follow-up assessment	April 2023
Data analyses and writing manuscripts	≥ December 2021

Appendix 2: Personnel

All costs in personnel, except for drs. Burger, are in kind matching by the participating organizations and research institutes and for the entire research period.

Function	***Title***	***Name***	***Hours/ week***
Principal and coordinating investigator/ co-promotor	*dr.*	*David van den Berg*	*0.2 fte*
Promotors/ PhD supervisors	*prof. dr.*	*Mark van der Gaag*	*0.1 fte*
	prof. dr.	*Agnes van Minnen*	*0.1 fte*
Co-promotors/ dissertation co-supervisors	*dr.*	*Amy Hardy*	*0.1fte*
	dr.	*Machteld Marcelis*	*0.1 fte*
PhD students	*drs.*	*Tineke van der Linden (external)*	*0.2 fte*
	drs.	*Simone Burger (full)*	*1.0 fte*
Investigators	*prof. dr.*	*Ad de Jongh*	*0.1fte*
	dr.	*Tonnie Staring*	*0.1fte*
	drs.	*Berber van der Vleugel*	*0.1fte*
	drs.	*Paul de Bont*	*0.1fte*
	drs.	*Carlijn de Roos*	*0.1fte*
	BSc.	*Arjan van den Berg*	*0.03 fte*
Research manager	*BSc.*	*Marion Bruns*	*0.2 fte*
Research assistants (psychology students, who write their theses on data from the trial or previous studies)		*To be recruited*	tbd

Appendix 3: Budget

Costs	**Participating organizations (matching)**	**Funding body Stichting Tot Steun VCVGZ**
Coordination and management of the trial, principal investigator and data monitor: 5yrs*0.60fte*€80.000,-=	€240.000,-	
Supervising the PhD student by professor and co-promotor: 5yrs*0.11fte*€90.000,-=	€50.000,-	
Productivity loss therapists for training: 24therapists*8dys*€882,-	€169.334,-	
Productivity loss therapists for supervision: 24therapists*12sessions*3yrs*€441,-=	€381.024,-	
Supervising the therapists: 3yrs*12sessions*3supervisors*€441,-=	€47.628,-	
Per diem for expert by experience in trial management team: 20meetings*€300,-=		€4.800,-
Costs of training therapists in PE/EMDR and in CR (on average 8 days of training per therapist):		€18.000,-
Accommodation for the training of therapists (including travel and hotel UK trainer): 8dys*€1.200,-=€9.600,- 2days*€350,-return flight+2 nights hotel=€700,-		€10.300,-
Accommodation for supervising of therapists (including travel and hotel UK supervisor): 3yrs*12sessions*€446,-accomodation costs=€16.056,- 3yrs*12sessions*€250,-return flight+1 night hotel=€9.000,-		€31.500,-
Training teams in trauma-sensitive attitude and screening. The training is delivered by an expert in trauma and psychosis and an expert with lived experience of both trauma and psychosis: 8trainings*€2.000,-=		€16.000,-
Productivity loss for training teams in trauma-sensitive attitude and screening: 48teams*8participants per team*€882,-=	€338.688,-	
Treatment delivered: 180 participants*18treatments*€196,-=	€635.040,-	
0.80 fte PhD student, for assessments and supervising research assistants: 5yrs*€55.000,-*0.80fte=		€220.000,-
Internship fee for research assistants to do assessments: 3yrs*8ra's*€350,-=		€8.400,-
Compensation for expenses by participants/ incentives: (136participants*7assessments*€20,-)+(30part*5assess*€20,-)+(166part*€60,-)=		€34.800,-
Travel expenses:	€12.500,-	
Daily monitoring application:		€20.000,-
Smartphones for daily assessment: 80*€200,-=		€16.000,-
Diverse costs and unforeseen costs:		€15.000,-
Total costs over 5 years	**€1.874.214,-**	**€394.800,-**

Appendix 4: Planned publications

1) Protocol paper
2) Primary and secondary outcomes
3) Objective effects on symptom worsening, adversities, and revictimization
4) Subjective expectancies and experiences of participants (incl burden, harm, effects)
5) Cost-effectiveness (6, 12 and 24 mo fu)
6) Long-term primary and secondary outcomes (12 and 24 mo fu)
7) How do trauma-related psychological mechanisms interact with psychosis (before and after therapy)?
8) Does memory contextualization predict severity of re-experiencing symptoms and auditory hallucinations psychosis (baseline data)?
9) How do trauma-related psychological mechanisms and PTSD symptoms interact over the course of therapy?
10) Predictors/moderators of treatment response (symptoms) and recovery.
11) Qualitative analysis of experiencing TFT and the recovery process