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Trauma-focused psychodynamic therapy and STAIR Narrative Therapy of post-traumatic stress disorder related to childhood maltreatment: trial protocol of a multicentre randomised controlled trial assessing psychological, neurobiological and health economic outcomes (ENHANCE)

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ABSTRACT

Introduction Success rates of psychotherapy in post-traumatic stress disorder related to childhood maltreatment (PTSD-CM) are limited.

Methods and analysis Observer-blind multicentre randomised clinical trial (A-1) of 4-year duration comparing enhanced methods of STAIR Narrative Therapy (SNT) and of trauma-focused psychodynamic therapy (TF-PDT) each of up to 24 sessions with each other and a minimal attention waiting list in PTSD-CM. Primary outcome is severity of PTSD (Clinician-Administered PTSD Scale for DSM-5 total) assessed by masked raters. For SNT and TF-PDT, both superiority and non-inferiority will be tested. Intention-to-treat analysis (primary) and per-protocol analysis (secondary). Assessments at baseline, after 10 sessions, post-therapy/waiting period and at 6 and 12 months of follow-up. Adult patients of all sexes between 18 and 65 years with PTSD-CM will be included. Continuing stable medication is permitted. To be excluded: psychotic disorders, risk of suicide, ongoing abuse, acute substance related disorder, borderline personality disorder, dissociative identity disorder, organic mental disorder, severe medical conditions and concurrent psychotherapy. To be assessed for eligibility: n=600 patients, to be e randomly allocated to the study conditions: n=328. Data management, randomisation and monitoring will be performed by an independent European Clinical Research Infrastructure Network (ECRIN)-certified data coordinating centre for clinical trials (KKS Marburg). Report of AEs to a data monitoring and safety board. Complementing study A-1, four inter-related add-on projects, including subsamples of

Strengths and limitations of this study

► This is the first randomised controlled trial (RCT) to enhance and compare the efficacy of STAIR Narrative Therapy (SNT) and trauma-focused psychodynamic therapy (TF-PDT) in post-traumatic stress disorder (PTSD) related to childhood maltreatment, with 328 patients to be allocated to the trial.

► Refined methods of SNT and TF-PDT tailoring the treatments more specifically to the patients needs, which includes performing of up to eight additional more flexibly usable sessions, will be applied.

► Primary outcome will be the severity of PTSD (Clinician-Administered PTSD Scale for DSM-5 total).

► The RCT is complemented by add-on projects on treatment integrity, moderators, mediators, neuroimaging, biological parameters and cost-effectiveness.

► The inclusion of only short-term methods of psychotherapy may be a limitation of the study since for some of the severely disordered patients longer-term treatments may be required.

the treatment study A-1, will examine (1) treatment integrity (adherence and competence) and moderators and mediators of outcome (B-1); (2) biological parameters (B-2, eg, DNA damage, reactive oxygen species and telomere shortening); (3) structural and functional neural changes by neuroimaging (B-3) and (4) cost-effectiveness of the treatments (B-4, costs and utilities).

Ethics and dissemination Approval by the institutional review board of the University of Giessen (AZ 168/19). Following the Consolidated Standards of Reporting Trials statement for non-pharmacological trials, results will be reported in peer-reviewed scientific journals and disseminated to patient organisations and media.

Trial registration number DRKS 00021142.

INTRODUCTION

Child maltreatment (CM) has long-lasting effects on mental health, including the development of mental disorders such as post-traumatic stress disorder (PTSD).[1] Psychotherapy is recommended as first-line treatment for PTSD.[2] Several methods of psychotherapy, including cognitive–behavioural therapy (CBT), exposure and eye movement desensitisation and reprocessing proved to be efficacious in improving symptoms of PTSD, interpersonal relationships, affect dysregulation and negative self-concept, with effect sizes depending on the comparator.[3] Survivors of CM often show problems in affect regulation and interpersonal relationships, increasing the risk for non-response and dropouts.[4–6] For these reasons, trauma-focused methods of psychotherapy have been developed specifically addressing these patients' needs. In STAIR-Exposure, a method of CBT, a **s**kills **t**raining in **a**ffect and **i**nterpersonal **r**egulation (STAIR) is applied before using exposure to traumatic memories (STAIR–Exposure).[4] STAIR–Exposure, later modified and called STAIR Narrative Therapy (SNT),[7] proved to be superior to exposure alone and was associated with less dropouts.[5] Although many patients were PTSD-negative after treatment with SNT (61%), only a minority achieved full remission (27%).[5] Thus, there is a need to further improve treatments for post-traumatic stress disorder related to childhood maltreatment (PTSD-CM). As a consequence, SNT has been even more specifically tailored to PTSD-CM.[7] From a psychodynamic perspective, this is true for trauma-focused psychodynamic therapy (TF-PDT) as well by focusing on ego functions,[8–10] specifically addressing internal resources, affect regulation and interpersonal relations.[8 9] Evidence for TF-PDT comes from randomised controlled trials (RCTs)[9 11] and quasi-experimental studies.[12 13] TF-PDT, however, has not yet been tested specifically in PTSD-CM and TF-PDT and trauma-focused CBT will be compared for the first time.

Aims and objectives

The main purpose of the study was to examine the efficacy of SNT and TF-PDT in PTSD-CM, both in relation to each other and to a minimal attention waiting list (MA-WL). In addition, by tailoring the treatments more specifically to the patients' needs by, for example, performing of up to eight additional more flexibly usable sessions,[7] which is a difference to the studies by Cloitre et al,[4 5] the efficacy compared with previous RCTs is expected to be enhanced.[4 5] The treatment procedures are described in refined treatment manuals.[7 8 14] Another aim of the study is to improve the psychological and biological understanding of PTSD-CM and to examine the

cost-effectiveness of the treatments. This study protocol follows the SPIRIT guidelines (online supplemental file 1).

METHODS AND ANALYSIS

Study design

A research network (Enhancing Understanding and Treatment of PTSD related to Childhood Maltreatment - ENHANCE) has been established encompassing an inter-related group of studies on PTSD-CM (figure 1, www.gesundheitsforschung-bmbf.de/de/enhance-posttraumatische-belastungsstorung-bei-erwachsenen-verbunden-mit-gewalt-und-8889.php). In a central randomised clinical multicentre trial (A-1), SNT and TF-PDT will be compared. As an additional control, a MA-WL will be included.[4] To control for researcher allegiance, both experts in CBT and PDT will be included on an equal basis as well as the senior authors of the treatment manuals (adversarial collaboration).[15] Four add-on studies (B-1, B-2, B-3 and B-4) are closely related to A-1 and with each other by including subsamples of A-1 (figure 1). Study duration encompasses 4 years in total.

Study setting

Five university cities in Germany will participate in the RCT, with one institution in each city representing SNT and another TF-PDT; each institution will also establish a MA-WL (figures 2 and 3).

Inclusion criteria

Inclusion criteria include outpatients of all sexes with a primary diagnosis of PTSD-CM by a caretaker or person in authority over them before the age of 18 years (age 18–65 years).

Exclusion criteria

Exclusion criteria for A-1 include current psychotic disorders, ongoing abuse, acute suicidality in the previous 3 months requiring referral to an emergency room or hospitalisation (implying that suicidality is serious and cannot be handled on an outpatient basis, and the patient cannot form credible contract), substance dependence, not in remission for at least 3 months, borderline personality disorder, dissociative identity disorder, organic mental disorder, severe medical conditions incompatible with psychotherapy and concurrent psychotherapy. Borderline personality disorder will be excluded since long-term therapy is required to offer these patients an adequate treatment[16–19] Thus, our sample will be representative of patients with PTSD-CM without a borderline personality disorder. While continuation of pharmacotherapy is permitted as long as it has been ongoing for at least 3 months prior to study entry, neither (newly applied) additional pharmacotherapy nor (concurrent) psychotherapy is permitted.

Treatments

STAIR Narrative Therapy

SNT is a manual-guided modular and sequential form of CBT. In the first eight sessions, patients are trained
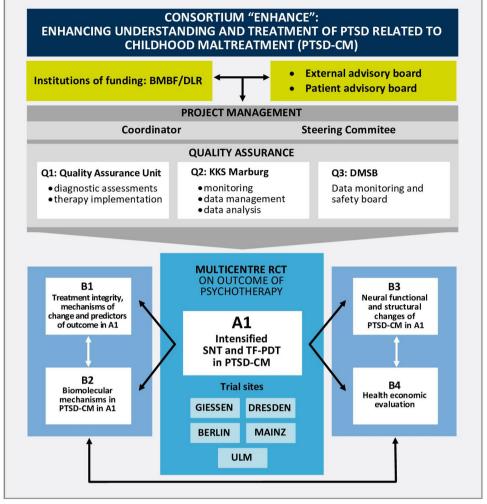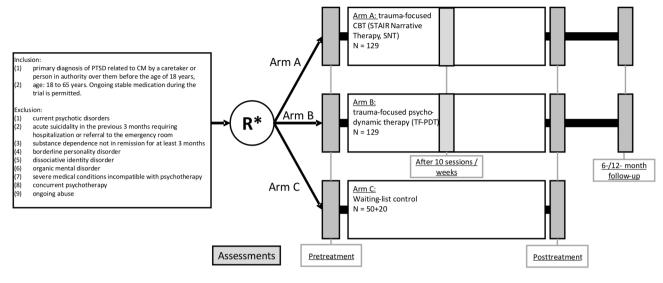
Figure 1 Structure of the ENHANCE network. BMBF, German Federal Ministry of Education and Research; DLR, Deutsches Zentrum für Luft- und Raumfahrt e.V.; DMSB, data monitoring and safety and board; PTSD-CM, post-traumatic stress disorder related to childhood maltreatment; RCT, randomised controlled trial; TF-PDT, trauma-focused psychodynamic therapy; SNT, STAIR Narrative Therapy.

in emotional and interpersonal skills, followed by eight further sessions of modified narrative prolonged exposure.[4 5] Two interventions have been added to standard prolonged exposure, that is, grounding exercises immediately after exposure and cognitive reappraisal of the trauma focusing on interpersonal schemes.[7] Between sessions, repeated practice of interpersonal skills is performed.[7] The existing RCTs of SNT encompassed 16 sessions.[4 5] In order to further improve the efficacy of the treatment, a more flexible application of SNT has recently been presented.[7] This flexible protocol allows for (1) skipping protocol sessions, (2) repeating sessions and (3) having non-protocol sessions.[7] There are three constraints, that is, three sessions of skills training in emotion regulation, four sessions of skills training in interpersonal functioning, five sessions of narrative work and two sessions that bookend the treatment (14 sessions) are mandatory. Between 2 and 10 additional sessions may be carried out for a maximum of 24 sessions (16+8).[7]

Manual-guided TF-PDT

Following a psychodynamic approach,[20] manual-guided TF-PDT puts a specific focus on ego functions, specifically on affect regulation, resources and interpersonal relationships.[8–10] Specific treatment techniques are used to stabilise the patients, such as establishing a secure alliance and strengthening the patients feeling of control (eg, by informing the patient about the disorder and the treatment). In addition, imaginative techniques, inner child work,[8] and techniques to manage dissociative states and to improve mentalisation are applied on a psychodynamic basis.[8] In order to foster working through from a psychodynamic perspective,[21 22] patients are encouraged to also apply these techniques between sessions.[8 21 22] The interventional style is more active and supportive and less neutral than in classical psychoanalysis.[8] Regressive transferences are avoided. Repairing ruptures in the alliance may be necessary.[23] After achieving control over emotional responses, traumatic memories may be processed.[8] Instead of working through traumatic

Figure 2 Design of the randomised clinical trial A-1. CBT, cognitive–behavioural therapy; CM, child maltreatment; PTSD, post-traumatic stress disorder; TF-PDT, trauma-focused psychodynamic therapy.

experiences in the 'here and now' of the transference, techniques are used for working them through in the 'there and then', for example, by the screen technique.[8] As SNT, TF-PDT will encompass up to 24 sessions. Finally, conscious and unconscious conflicts may be addressed by the psychodynamic techniques of confrontation, clarification and interpretation.[8]

As major differences between SNT and TF-PDT, exposure is not mandatory and less intensively applied in TF-PDT; TF-PDT is less strictly structured; and role plays, diaries and assertiveness training are not included. Instead, TF-PDT emphasises positive self-representations and imaginations, the therapeutic alliance, mentalisation, and the handling of transference and countertransference; in addressing conflicts confrontation, clarification and interpretation may be used.

Therapists

Psychotherapists are required to have completed their training in psychotherapy according to the German guidelines or must be in advanced psychotherapeutic training, implying that they are allowed to treat patients under supervision. For the trial, they have been specifically trained in workshops by experts of each approach in either SNT or TF-PDT. Dr Cloitre and Dr Wöller, who developed the SNT/TF-PDT manual, have been involved by supervising the main SNT/TF-PDT trainers and supervisors. In each centre, experienced supervisors attended the workshops and will closely supervise the therapists of the respective treatment during the trial. Supervision will take place weekly during the first 6 months of the study and fortnightly for the final 18 months. Before inclusion in the study, each therapist will have to competently treat one training case under supervision. No therapist will apply both SNT and TF-PDT. All patients will be treated in an outpatient setting.

MA-WL group

In the MA-WL group, patients will wait for treatment for 24 weeks, corresponding to the duration of SNT and TF-PDT. Minimal attention includes regular phone calls every 4 weeks to check the patients' status,[4] a measure also carried out for ethical reasons. In order to maintain masking, telephone calls will be carried out by a person involved neither in outcome assessment nor in treatment. After the waiting period, participants may choose either SNT or TF-PDT. The post-treatment data of the MA-WL will not be included in the main data analysis.
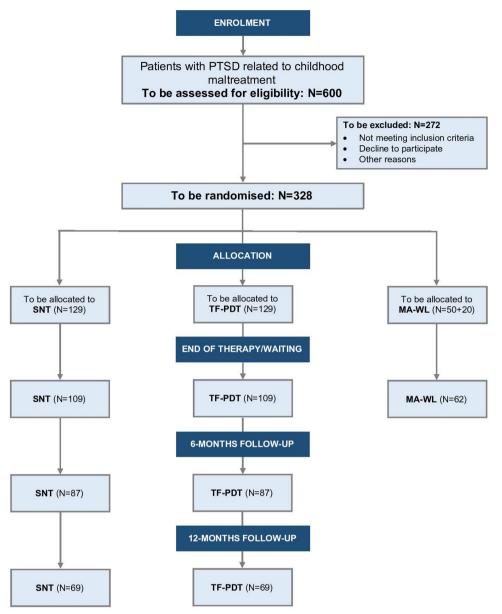
Stopping rules

For the individual patient, treatment may be terminated in case of adverse events (AEs), serious adverse events (SAEs) or non-compliance and must be terminated in case of patient withdrawing consent or investigator terminating treatment. A single centre may be excluded in case of unsatisfactory enrolment or data collection, accumulated (S)AEs or major failures to adhere to the study protocol. The study as a whole may be terminated in case of accumulated (S)AEs or change of risk–benefit considerations.

Monitoring and treatment fidelity

All treatment sessions will be audio-taped and checked for treatment integrity during supervisory sessions by specifically trained and experienced supervisors in each centre. In addition, treatment integrity will be empirically examined in a specific project (B-1; see further for details, figure 1).

Primary outcome

Primary outcome will be the total score of the Clinician Administered PTSD scale for DSM-5 (CAPS-5),[24] assessed by masked raters (table 1). From a patient's perspective,

Figure 3 Participant flow. MA-WL, minimal attention waiting list; PTSD, post-traumatic stress disorder; TF-PDT, trauma-focused psychodynamic therapy; SNT, STAIR Narrative Therapy.

severity of PTSD symptoms is highly relevant. A lower CAPS-5 value signifies less symptoms.

To assess traumatic events, the Life Event Checklist will be used.[25]

Secondary outcomes

Secondary outcomes include remission (CAPS-5 total score<20), response (50%-reduction of CAPS-5 total score),[24] complex PTSD,[26] dissociative symptoms,[27] depression,[28] Clinical Global Impression rating for improvement,[29] mentalisation,[30] attachment,[31] personality organisation[32] and number of treatment dropouts.

Participant timeline

Both SNT and TF-PDT encompass up to 24 weekly sessions (figure 2). Follow-up examinations will be carried out post-therapy (waiting list: after 24 weeks), 6 and 12 months after treatment termination.

Hypotheses

SNT is empirically well supported and among the most efficacious treatments for PTSD-CM.[4 5] On the other hand, research has emerged suggesting that methods of psychotherapy focusing on interpersonal relationships without emphasising trauma exposure may be as efficacious as methods emphasising exposure.[33 34] We expect this to be true for manualised TF-PDT, too. For this reason, we will examine both superiority of any of the two therapies over the other and non-inferiority of TF-PDT compared with SNT. First evidence suggests that PDT may be superior to CBT (SNT) in measures of mentalisation.[35]

Table 1 Assessment instruments and time of assessment of study A-1

Purpose	Domain	Instrument	Perspective	Pretreatment	After 10 sessions/week	Post-treatment	6/12 months of follow-up
Screening and diagnostic classification	Inclusion criteria, exclusion criteria	SCID-5-CV[60] SCID-5-PD[61]	Trained interviewers	x			
		CAPS-5[24]	Masked raters	x	x	x	x
		LEC[25]	Masked raters	x			
Primary outcome	Severity of PTSD	CAPS-5 total score[24]	Masked raters	x	x	x	x
Secondary outcomes	Remission	CAPS-5 total<20[24]	Masked raters			x	x
	Response	50% reduction of CAPS-5 total score[24]	Masked raters			x	x
	Complex PTSD	ITQ[26]	Patient	x	x	x	x
	Dissociative symptoms	DES[27]	Patient	x	x	x	x
	Clinical global impression-improvement	CGI-I[29]	Trained interviewers	x		x	x
	Depression	BDI-II[28]	Patient	x		x	x
	Mentalisation	MZQ[30]	Patient	x	x	x	x
	Attachment	ECR-RD[31]	Patient	x	x	x	x
	Level of personality identity integration and object relations	BPI[32]	Patient	x	x	x	x
	Costs	CSSRI[57]	Patient	x		x	x
	Utilities/quality of life	EQ-5D[58]	Patient	x		x	x
Moderators and mediators	Helping alliance	HAQ[47]	Patient		x	x	
	Therapy expectancies	PATHEV[46]	Patient	x			
	Negative mood regulation	Negative Mood Regulation Scale[48]	Patient	x	x	x	x
	Trauma history	CTQ[62]	Patient	x			
	Treatment adherence and competence	CPPS[45] Treatment-specific checklist	Independent raters		Randomly selected sessions		
Dropout	Reasons for dropping out	Drop-Out Inventory (KU Eichstätt, ProGrid study, 2017)	Patient		Time of dropping out		

BDI-II, Beck Depression Inventory II[28]; BPI, Borderline Personality Inventory[32]; CAPS-5, Clinician Administered PTSD Scale for DSM-5[24]; CGI-I, Clinical Gobal Impression Scale—Improvement[29]; CPPS, Comparative Psychotherapy Process Scale[45]; CSSRI, Client Sociodemographic and Service Receipt Inventory[57 63]; CTQ, Childhood Trauma Questionnaire[62]; ECR-RD, Experiences in Close Relationships—Revised[31]; EQ-5D, EuroQol Questionnaire[64–66]; HAQ, Helping Alliance Questionnaire[47]; ITQ, International Trauma Questionnaire[26]; Mentalization Questionnaire[30]; NMRS, Negative Mood Regulation Scale[48]; PATHEV, Therapy Expectancies Scale[46]; SCID-5-CV: Structured Clinical Interview for DSM-5 Disorders, Clinician Version[60]; SCID-5-PD, Structured Clinical Interview for DSM-5 Personality Disorder.[61]

To directly examine the efficacy of both SNT and TF-PDT (assay sensitivity), they will be tested against a MA-WL.[36 37]

Statistical analysis
Analysis populations
The primary non-inferiority analysis will be performed in the intention-to-treat (ITT) population of all randomised patients, and according to the randomisation, a secondary analysis will be performed in the per-protocol population (PP).[38] PP is a subset of the ITT population for whom no major protocol violations (eg, attending less than 10 sessions) were reported. All tests of superiority will be performed in the ITT population. Multiple imputation and direct likelihood methods will be used to handle missing data in the primary endpoint.

Multiple testing procedure
To control for the familywise error rate (FWER), we apply both sequential testing and alpha splitting. We denote by μ_X the mean of CAPS-5 total post-therapy in study group X=SNT, TF-PDT, MA-WL.
1. The null hypotheses H01: $\mu\_SNT=\mu\_TF\text{-}PDT=\mu\_MA\text{-}WL$ will be tested with an analysis of variance at an alpha level of 0.05.
2. If H01 can be rejected, H02: $\mu\_SNT\geq\mu\_MA\text{-}WL$ and H03: $\mu\_TF\text{-}PDT\geq\mu\_MA\text{-}WL$ will be tested by t-tests at a one-sided alpha level of 0.025. Due to the closed testing principle, this controls for the FWER. Only if both H02 and H03 can be rejected, the following comparisons between SNT and TF-PDT will be performed.
3. If H01, H02 and H03 can be rejected, we can keep testing at alpha=0.05 due to sequential testing. Alpha=0.05 will be split in two equal parts (0.025) to allow simultaneous testing of non-inferiority of TF-PDT to SNT and superiority of SNT over TF-PDT.
    a. The non-inferiority null hypotheses H04: $\mu\_TF\text{-}PDT>\mu\_SNT+\delta$ (δ=non-inferiority margin, see further) will be tested at a one-sided alpha-level of 0.0125.
        i. Furthermore, if H04 can be rejected in the ITT population, the superiority null hypothesis H05: $\mu\_TF\text{-}PDT\geq\mu\_SNT$ will be tested at a one-sided alpha-level of 0.0125. By the closed testing principle, this procedure (H05 only after H04) controls for the FWER.
    b. The superiority null hypothesis H06: $\mu\_SNT\geq\mu\_TF\text{-}PDT$ will be tested at a one-sided alpha-level of 0.0125. If H06 can be rejected, SNT will be declared superior to TF-PDT. The case where both H04 and H06 are rejected (ie, both non-inferiority of TF-PDT and superiority of SNT) signifies that, although there is a statistically significant difference in favour of SNT, the difference is regarded as below the margin of clinical relevance.

Choice of non-inferiority margin δ
We set the non-inferiority margin for the acceptable difference between TF-PDT and SNT post-therapy in the CAPS-5 total to 8 points. This is consistent with recent recommendations to regard a difference of 10 points as a minimal clinically important difference (MCID) in CAPS-5[39 40] and to use one-half of an SD of baseline scores as an MICD[41] (19/2=9.5).[5] The MCID can be used as an estimate of what is a clinically meaningful difference between TF-PDT and SNT, allowing for sample size calculation.[42]

Sample size and power calculation
We aimed at a total power of 80% to either demonstrate non-inferiority of TF-PDT or superiority of SNT. This total power is estimated as the power of rejecting H01, H02 and H03 in steps 1 and 2 multiplied by the power to reject one of the null hypotheses H04, H05 and H06 in steps 3a and 3b. For a power of 80% in testing H04 at one-sided alpha-level of 0.0125 with $\delta=8$, 109 patients are required in each TF-PDT and SNT. Assuming an actual difference of 8 between μ_SNT and $\mu\_TF\text{-}PDT$, a power of 80% in the superiority test of either H05 (in step 3ai) or H06 (in step 3b) at one-sided alpha-level of 0.0125 will be achieved by this sample size.

Cloitre *et al* reported a difference in CAPS total between μ_SNT and μ_WL of 31.[4] With 2×109 patients and an additional 50 patients in the MA-WL group, we expect a power above 99.9% for rejection of H01, H02 and H03, assuming differences of 30 (this even holds for a difference of 22=30 – δ).

To account for a dropout rate of 15% in the treatment groups and of 11% in the waiting list group,[4 5] 129 patients in each treatment group plus 56 in the WL group are required. As 20 additional waiting list patients are required for the projects B2 and B3, the dropouts in the MA-WL are well compensated for. In total, 328 patients are required (2×129+50+20). If attrition rates are higher than expected, more participants may be included to achieve the planned power.

Recruitment
The participating institutions provide established outpatient clinics for recruiting, screening and treating patients. Cloitre *et al* recruited a mean of 2.5 PTSD-CM patients per month using one centre.[4 43] Thus, with 10 recruiting centres in five cities, the necessary sample size will be realistically achieved within 18 months. For this purpose, additional measures will be applied, such as informing about the study in mass media (eg, newspapers, radio and social media), in psychotherapeutic and psychiatric clinics, in practitioners' private practices, and by using flyers and a homepage informing about the study.

Assignment
Only eligible patients are randomly assigned with a fixed unbalanced ratio (SNT vs TF-PDT vs MA-WL) of 3:3:1 (with the exception of one centre where, due to the need of additional patients in the MA-WL for subproject B3, the ratio will be 5:5:6). The randomisation will be stratified by centre, gender and severity of PTSD (CAPS-5 total<60 vs CAPS-5 total≥60) applying list randomisation

with randomly permuted block sizes. The lists are generated using an R script developed by KKS. KKS will use a central email-based randomisation service to inform about the randomisation result (figure 2). The masked assessors and the therapists treating patients will not be involved in the randomisation or allocation process.

Masking
Trained interviewers assessing the primary outcome (CAPS-5) will be masked with regard to study condition. Information about the condition the participant was allocated to will not be disclosed to the interviewers. In addition, patients are instructed not to talk about their treatment during assessment.

Data collection methods
Only measures with established reliability and validity will be used (table 1). Interviewers will be trained and inter-rater reliability will be determined. All study findings will be documented in a case report form (CRF). In each centre, the local investigator is responsible for ensuring that the CRFs are completed correctly and that entries can be verified against source data.

Data management
An electronic case report form (e-CRF/EDC System) for data collection and documentation, hosted by KKS Marburg will be used. Data will be entered directly via web browser into the e-CRF and are transferred via encryption (HTTPS (TSL/SSL)) to the central database. After completion of data entry checks for plausibility, consistency and completeness of the data will be performed. Based on these checks, queries will be produced combined with the queries generated by visual control. All missing data or inconsistencies will be reported to the centre(s) and clarified by the responsible local investigator. All data management activities will be performed according to the current standard operating procedures (SOPs) of the KKS. Each local investigator will be provided with an investigator site file (ISF) by KKS Marburg before the start of the study. This file contains all relevant documents necessary to conduct the study. This file and associated study-related documents will be safely archived after termination of the study for at least 10 years. All original patient files will be stored for the longest possible time permitted by the regulations at the respective hospital or research institute.

The coordinating investigator will oversee the intra-study data sharing process, with input from the trial steering committee. All local heads of the centres will be given access to the cleaned data sets after publication of the results. Trial data sets will be housed on a secure file exchange cloud (SFX-Cloud) system created for the study. The access to the SFX-Cloud will be password protected. Local heads of the centres will have direct access to their own site's data sets on request access to the cloud system. Access to other sites data will be granted after request and approval by the coordinating investigator. To ensure confidentiality, data dispersed to project team members will contain only the pseudonymised patient ID of the trial subjects as unique identifier.

Plans to promote participant retention
In an introductory interview before treatment starts, patients will be informed about the disorder and the treatment to reduce the risk of dropout.[44] Patients in MA-WL will be regularly contacted via phone.[4] A similar approach will be applied for patients during the follow-up period, following a standardised protocol (no therapy provided, interview only). In addition, patient representatives will be included in a patient advisory board during the study to be consulted in questions of recruiting, informing patients and minimising dropouts (figure 1). Reasons for dropping out will be assessed by the Drop-Out Inventory (KU Eichstätt, ProGrid Study, 2017).

Data monitoring
Monitoring will be carried out by KKS Marburg, including an initiation visit and one close-out visit. Trial centres which successfully recruited patients will be monitored once a year according to the SOPs from the KKS Marburg. Monitoring, quality assurance and data management will be continuously conducted by the KKS Marburg staff who are both independent of the investigators and the funder. A risk-based approach will be used, implying that data monitoring will be continuously performed via quality reports of the data management, combined with central and on-site monitoring.

Safety and harms
An independent data monitoring and safety and board (DMSB) has been established, consisting of a patient representative, a representative of CBT and a representative of psychodynamic therapy. AE (any untoward medical occurrence) and SAE (eg, self-harm, suicide, hospitalisation and death) will be documented and reported to the DMSB. The safety analysis will be based on the as-treated sample; that is, patients having received at least one treatment session or who have been randomised to the MA-WL will be evaluated for safety data.

Ancillary and post-trial care
The participating centres will offer ancillary and post-trial care if required.

Patient involvement
Representatives of patient organisations were involved in developing the trial.

ADD-ON PROJECTS
Project B-1 (treatment integrity, moderators and mediators)
To empirically examine treatment integrity, three sessions will be randomly selected from each treated patient, one from the early, one from the middle and one from the late phase of treatment (3×125 for each treatment). These sessions will be rated by masked and trained raters

with regard to treatment integrity by use of the Comparative Psychotherapy Process Scale[45] and by treatment-specific checklists that include core interventions. In addition to treatment integrity, B-1 will study moderators (eg, type and duration of CM, personality organisation[32] and therapy expectancies[46]) and mediators of outcome (eg, therapeutic alliance,[47] mood regulation,[48] mentalisation[30] and attachment[31]). To examine whether the latter variables represent mediators of outcome, they will be additionally assessed after session 10 (table 1) to see if they show changes prior to changes in outcome.[49]

Project B-2 (biological parameters)

In a subgroup of patients from A-1 (60 from each TF-PDT, SNT and MA-WL), B-2 will examine biological parameters of PTSD-CM before therapy, after therapy and 6 and 12 months post-therapy. Biomaterials will include cellular (peripheral blood mononuclear cells (PBMC)) and fluid peripheral blood components (serum and plasma), hair-follicle cells, cell-free hair samples and buccal cells. The primary outcomes will be DNA integrity of genomic DNA in PBMC.[50] Secondary outcomes include serum levels of the neuroplasticity marker brain-derived neurotrophic factor (BDNF) protein and the epigenetic regulation of the BDNF gene, biomarkers of oxidative stress in blood serum and telomere length in PBMC-derived lymphocytes.[51–53]

Project B-3 (neuroimaging)

In B-3, structural and functional neural changes will be examined in 87 patients of the treatment study and in 29 healthy controls by functional MRI, including several experimental tasks (behavioural pattern separation task,[54] cognitive and emotional stroop task,[55] cognitive emotion regulation task and fear conditioning task).[56] In addition, brain structural measures will be applied (grey matter volume and structural integrity of white matter tracts).

Project B-4 (health economic analysis)

Direct and indirect costs will be measured by the Client Sociodemographic and Service Receipt Inventory,[57] utilities by the EuroQol Questionnaire (EQ-5D).[58] Healthcare use will be monetarily valued by unit costs. Economic outcomes include the incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability curves (CEACs) based on net-benefit regression to adjust for potential confounding.[59]

The subprojects B-1–B-4 will allow, for example, relating specific treatment elements or biological parameters of PTSD-CM to treatment effects and cost-effectiveness.

ETHICS AND DISSEMINATION

The trial was approved by the institutional review board (IRB) of the University of Giessen (AZ 168/19). Patients will be informed of procedures, are required to give informed consent and may withdraw at any point with no disadvantage (online supplemental file 2). Dissemination of results will be ensured by (1) publishing both treatment manuals and study results, (2) including patient representatives, and (3) informing patients and the general public about the results.

AMENDMENTS

Any modifications to the protocol which may have an impact on the execution of the study, potential benefit of the patient or may affect patient safety including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol and will be submitted to the IRB.

CONFIDENTIALITY

The 'Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)' will be noted by all parties involved. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with restricted access.

CURRENT STUDY STATUS

Trial preparation started in February 2019 (eg, administrative issues, recruiting and training of interviewers and therapists). Recruiting is scheduled to begin in October 2020.

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