BMJ Open

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)

Falk Leichsenring,1,2 Christiane Steinert,2,3 Manfred E. Beutel,4 Lila Feix,2 Harald Gündel,2 Andrea Hermann,1,6,7 Alexander Karabatsiakis,6,9 Christine Knaevelsrud,10 Hans-Helmout König,11 Iris T. Kolassa,16 Johannes Kruse,2,12 Helen Niemeyer,10 Fatima Nöske,2 Sebastian Palmer,6 Eva Peters,13,14 Jens-Peter Reese,15,16 Alexander Reuss,16 Simone Salzer,3,17 Carmen Schade-Brittinger,16 Patrick Schuster,2 Rudolf Stark,1,6,7 Kerstin Weidner,18 Jörn von Wietersheim,5 Michael Witthöft,19 Wolfgang Wöller,20 Jürgen Hoyer21

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 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 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).

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.
INTRODUCTION
Child maltreatment (CM) has long-lasting effects on mental health, including the development of mental disorders such as post-traumatic stress disorder (PTSD). Psychotherapy is recommended as first-line treatment for PTSD. 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. Survivors of CM often show problems in affect regulation and interpersonal relationships, increasing the risk for non-response and dropouts. For these reasons, trauma-focused methods of psychotherapy have been developed specifically addressing these patients’ needs. In STAIR-Exposure, a method of CBT, a skills training in affect and interpersonal regulation (STAIR) is applied before using exposure to traumatic memories (STAIR-Exposure). STAIR-Exposure, later modified and called STAIR Narrative Therapy (SNT), proved to be superior to exposure alone and was associated with less dropouts. Although many patients were PTSD-negative after treatment with SNT (61%), only a minority achieved full remission (27%). 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. From a psychodynamic perspective, this is true for trauma-focused psychodynamic therapy (TF-PDT) as well by focusing on ego functions, specifically addressing internal resources, affect regulation and interpersonal relations. Evidence for TF-PDT comes from randomised controlled trials (RCTs) and quasi-experimental studies. 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, which is a difference to the studies by Cloitre et al., the efficacy compared with previous RCTs is expected to be enhanced. The treatment procedures are described in refined treatment manuals. 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-belastungsstoring-bei-erwachsenen-verbindungsmit-gewalt-und-8889.php). In a central randomised clinical multicentre trial (A-1), SNT and TF-PDT will be included. As an additional control, a MA-WL will be included. 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). 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. 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...
in emotional and interpersonal skills, followed by eight further sessions of modified narrative prolonged exposure. 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. Between sessions, repeated practice of interpersonal skills is performed. The existing RCTs of SNT encompassed 16 sessions. In order to further improve the efficacy of the treatment, a more flexible application of SNT has recently been presented. This flexible protocol allows for (1) skipping protocol sessions, (2) repeating sessions and (3) having non-protocol sessions. 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).

Manual-guided TF-PDT

Following a psychodynamic approach, manual-guided TF-PDT puts a specific focus on ego functions, specifically on affect regulation, resources and interpersonal relationships. 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, and techniques to manage dissociative states and to improve mentalisation are applied on a psychodynamic basis. In order to foster working through from a psychodynamic perspective, patients are encouraged to also apply these techniques between sessions. The interventional style is more active and supportive and less neutral than in classical psychoanalysis. Regressive transferences are avoided. Repairing ruptures in the alliance may be necessary. After achieving control over emotional responses, traumatic memories may be processed. Instead of working through traumatic
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. 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.

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, 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), assessed by masked raters (table 1). From a patient’s perspective,
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 organisation32 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

---

**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.
| 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<sup>60</sup>         | Trained interviewers | x            |                        |                |                          |
|                                       |                                     | SCID-5-PD<sup>61</sup>               |                  |              |                        |                |                          |
|                                       |                                     | CAPS-5<sup>24</sup>               |                  |              |                        |                |                          |
|                                       |                                     | LEC<sup>25</sup>                  |                  |              |                        |                |                          |
| Primary outcome                       | Severity of PTSD                    | CAPS-5 total score<sup>24</sup> | Masked raters    | x            | x                      | x              | x                        |
|                                       |                                     |                                 |                  |              |                        |                |                          |
| Secondary outcomes                    | Remission                           | CAPS-5 total score<sup>24</sup> | Masked raters    | x            | x                      | x              | x                        |
|                                       |                                     | 50% reduction of CAPS-5 total score<sup>24</sup> | Masked raters | x            |                        |                |                          |
|                                       | Complex PTSD                        | ITQ<sup>26</sup>                 | Patient          | x            | x                      | x              | x                        |
|                                       | Dissociative symptoms               | DES<sup>27</sup>                 | Patient          | x            | x                      | x              | x                        |
|                                       | Clinical global impression-improvement | CGH<sup>28</sup>             | Trained interviewers | x            |                        |                |                          |
|                                       | Depression                          | BDI-II<sup>28</sup>             | Patient          | x            | x                      | x              | x                        |
|                                       | Mentalisation                       | MZO<sup>30</sup>                | Patient          | x            | x                      | x              | x                        |
|                                       | Attachment                          | ECR-RD<sup>31</sup>             | Patient          | x            | x                      | x              | x                        |
|                                       | Level of personality identity integration and object relations | BPI<sup>32</sup>            | Patient          | x            | x                      | x              | x                        |
|                                       | Costs                               | CSSRI<sup>57</sup>             | Patient          | x            | x                      | x              |                          |
|                                       | Utilities/quality of life           | EQ-5D<sup>58</sup>              | Patient          | x            | x                      | x              |                          |
| Moderators and mediators              | Helping alliance                     | HAQ<sup>47</sup>                | Patient          | x            | x                      |                |                          |
|                                       | Therapy expectancies                | PATHEV<sup>46</sup>            | Patient          | x            |                        |                |                          |
|                                       | Negative mood regulation            | Negative Mood Regulation Scale<sup>48</sup> | Patient | x            | x                      | x              | x                        |
|                                       | Trauma history                      | CTQ<sup>52</sup>                | Patient          | x            |                        |                |                          |
|                                       | Treatment adherence and competence  | CPPS<sup>55</sup>              | Independent raters | Randomly selected sessions |                  |                |                          |
|                                       |                                     | Treatment-specific checklist     |                  |              |                        |                |                          |
| Dropout                               | Reasons for dropping out            | Drop-Out Inventory              | Patient          | x            | x                      |                |                          |
|                                       | (KU Eichstätt, ProGrid study, 2017) |                                 |                  |              |                        |                |                          |

BDI-II, Beck Depression Inventory II<sup>38</sup>; BPI, Borderline Personality Inventory;<sup>32</sup> CAPS-5, Clinician Administered PTSD Scale for DSM-5<sup>24</sup>; CGH-I, Clinical Global Impression Scale—Improvement<sup>29</sup>; CPPS, Comparative Psychotherapy Process Scale;<sup>46</sup> CSSRI, Client Sociodemographic and Service Receipt Inventory<sup>27</sup>;<sup>63</sup> CTQ, Childhood Trauma Questionnaire<sup>64</sup>; ECR-RD, Experiences in Close Relationships—Revised<sup>31</sup>; EQ-5D, EuroQol Questionnaire<sup>64–66</sup>; HAQ, Helping Alliance Questionnaire<sup>37</sup>; ITQ, International Trauma Questionnaire<sup>26</sup>; MZQ, Mentalization Questionnaire<sup>30</sup>; NMRS, Negative Mood Regulation Scale<sup>48</sup>; PATHEV, Therapy Expectancies Scale<sup>46</sup>; SCID-5-CV, Structured Clinical Interview for DSM-5 Disorders, Clinician Version<sup>60</sup>; SCID-5-PD, Structured Clinical Interview for DSM-5 Personality Disorder<sup>61</sup>.
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). 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: µ_SNT=µ_TF-PDT=µ_MA-WL will be tested with an analysis of variance at an alpha level of 0.05.
2. If H01 can be rejected, H02: µ_SNT≥µ_MA-WL and H03: µ_TF-PDT≥µ_MA-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: µ_TF-PDT≥µ_SNT+δ (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: µ_TF-PDT≥µ_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: µ_SNT≥µ_TF-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 and to use one-half of an SD of baseline scores as an MCID (19/2=9.5). 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 δ=8, 109 patients are required in each TF-PDT and SNT. Assuming an actual difference of 8 between µ_SNT and µ_TF-PDT, a power of 80% in the superiority test of either H05 (in step 3ai) or H06 (in step 3bi) 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=30–8).

To account for a dropout rate of 15% in the treatment groups and of 11% in the waiting list group,43 129 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 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 (TLS/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. Patients in MA-WL will be regularly contacted via phone. 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 (3x125 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 and by treatment-specific checklists that include core interventions. In addition to treatment integrity, B-1 will study moderators (e.g., type and duration of CM, personality organisation and therapy expectancies) and mediators of outcome (e.g., therapeutic alliance, mood regulation, mentalisation and attachment). 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.

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. 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.

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, cognitive and emotional stroop task, cognitive emotion regulation task and fear conditioning task). 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, utilities by the EuroQol Questionnaire (EQ-5D). 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.

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.

Author affiliations
1. Justus Liebig University Giessen and Philipps University Marburg, Center for Mind, Brain and Behavior (CMBB), Giessen and Marburg, Germany
2. Department of Psychotherapy and Psychosomatics, Justus Liebig University Giessen, Giessen, Germany
3. International Psychoanalytic University Berlin gGmbH, Berlin, Germany
4. Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Mainz, Mainz, Germany
5. Department of Psychosomatic Medicine and Psychotherapy, University Ulm Medical Centre, Ulm, Germany
6. Department of Psychotherapy and Systems Neuroscience, Justus Liebig Universität Giessen, Giessen, Germany
7. Justus Liebig University Giessen Bender Institute of Neuroimaging, Giessen, Germany
8. Clinical Psychology II, University of Innsbruck, Innsbruck, Tyrol, Austria
9. Institute for Psychology and Education, Clinical & Biological Psychology, Ulm University, Ulm, Germany
10. Division of Clinical Psychological Intervention, Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany
11. Department of Psychotherapy and Psychosomatics, Philipps University Marburg, Marburg, Germany
12. German Centre for Neurodegenerative Diseases (DZNE), Marburg, Germany
13. Charité University Medicine Berlin and Charité Institute of Psychosomatic Medicine and Psychotherapy, Berlin, Germany
Contributors FL, CS, JK, JH and CW conceived of the study. MEB, LF, HG, AH, CK, HI-HK, AK, IK, EP, J-PR, SS, CS-B, PS, RS, KW, JW and MW reviewed the study design and contributed to study implementation. HM, FN and SP contributed significantly to the implementation of diagnostic and therapeutic procedures. CS-B and AR provided statistical expertise and will conduct the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

Funding The study was funded by the German Federal Ministry of Education and Research (01KR1801A).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any errors and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Falk Leichsenring http://orcid.org/0000-0002-3808-0072

REFERENCES
1 Gilbert R, Wridom CS, Browne K, et al. Burden and consequences of child maltreatment in high-income countries. Lancet 2009;373:68–81.
2 National Institute for Health and Care Excellence. Post-traumatic stress disorder - NICE guideline, 2018. Available: www.nice.org.uk/guidance/ng116.
3 Karatzias T, Murphy P, Cloitre M, et al. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. Psychol Med 2019;49:1761–75.
4 Cloitre M, Koenen KC, Cohen LR, et al. Skills training in affective and interpersonal regulation followed by exposure: a phase-based treatment for PTSD related to childhood abuse. J Consult Clin Psychol 2002;70:706–74.
5 Cloitre M, Stovall-McClough KC, Noonier K, et al. Treatment for PTSD related to childhood abuse: a randomized controlled trial. Am J Psychiatry 2010;167:915–24.
6 Dorr SE, Thomaes K, Hoogendoorn AW, et al. Evidence-Based treatment for adult women with child abuse-related complex PTSD: a quantitative review. Eur J Psychotraumatol 2014;5:23613.
7 Cloitre M, Henn-Haase C, Herman JL, et al. A multi-site single-blind clinical study to compare the effects of STAIR narrative therapy to treatment as usual among women with PTSD in public sector mental health settings: study protocol for a randomized controlled trial. Trials 2014;15:197.
8 Wölter W, Leichsenring F, Leweke F, et al. Psychodynamic psychotherapy for posttraumatic stress disorder related to childhood abuse—Principles for a treatment manual. Bull Menninger Clin 2012;76:69–93.
9 Stoewert C, Bumke PJ, Hollekkamp RL, et al. Resource activation for treating post-traumatic stress disorder, co-morbid symptoms and impaired functioning: a randomized controlled trial in Cambodia. Psychol Med 2017;47:553–64.
10 Bellia L, Hurvich M, Gediman H. Ego functions in schizophroneics, neurotics, and normals. New York: Wiley, 1973.
11 Brom D, Kiebler RB, Defares PB. Brief psychotherapy for posttraumatic stress disorders. J Consult Clin Psychol 1986;54:607–12.
12 Sachsse U, Vogel C, Leichsenring F. Results of psychodynamically oriented trauma-focused inpatient treatment for women with complex posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD). Bull Menninger Clin 2006;70:125–44.
13 Levi O, Bar-Haim Y, Kreiss Y, et al. Cognitive-Behavioural therapy and Psychodynamic psychotherapy in the treatment of combat-related post-traumatic stress disorder: a comparative effectiveness study. Clin Psychol Psychother 2016;23:298–307.
14 Levitt JT, Malta LS, Martin A, et al. The flexible application of a manualized treatment for PTSD symptoms and functional impairment related to the 9/11 world Trade Center attack. Behav Res Ther 2007;45:1419–33.
15 Mellers B, Hertwig R, Kahneman D. Do frequency representations eliminate conjunction effects? An exercise in adversarial collaboration. Psychol Sci 2001;12:269–75.
16 Kopita SM, Howard KI, Lowry JL, et al. Patterns of symptomatic recovery in psychotherapy. J Consult Clin Psychol 1994;62:1009–16.
17 Linehan MM, Comtois KA, Murray AM, et al. Two-Year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry 2006;63:757–66.
18 Bateman A, Fonagy P. Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. Am J Psychiatry 2009;166:1355–64.
19 Clarkin JT, Levy KN, Lenzenweger MF, et al. Evaluating three treatments for borderline personality disorder: a multiwave study. Am J Psychiatry 2007;164:922–8.
20 Gabbard GO. Psychodynamic psychiatry in clinical practice. Washington, DC: American Psychiatric Press, 2000.
21 Stricker G. Using homework in psychodynamic psychotherapy. J Psychother Integr 2005;15:219–37.
22 Freud S. Remembering, repeating and working through. In: Strachey J, ed. The standard edition of the complete psychological works of Sigmund Freud. London: Hogarth, 1914: 12: 147–56.
23 Muran JC, Safran JD, Sarantow L, et al. Evaluating an alliance-focused treatment for personality disorders. Psychotherapy: Theory, Research, Practice, Training 2005;42:532–45.
24 Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD scale. J Trauma Stress 1995;8:75–90.
25 Gray MJ, Litz BT, Hsu J, et al. Psychometric properties of the life events checklist. Assessment 2004;11:330–41.
26 Cloitre M, Shevlin M, Brewin CR, et al. The International trauma questionnaire: development of a self-report measure of ICD-11 PTSD and complex PTSD. Acta Psychiatr Scand 2018;138:536–46.
27 Spitzer C, Stiegitz RD, Freyberger H. Fragebogen zu dissoziativen Symptomen (PDS) - German adaptation of the Dissociative Experience Scale (E. Bernstein-Carlson und F. W. Putnam. Göttingen: Hogrefe, 2005.
28 Beck AT, Bahr SS, Steer RA, et al. Manual for the Beck depression Inventory-II. 2nd, 1996.
29 Guy W. ECDEU assessment manual for psychopathology. US dept health, education, and welfare publication (ADM). Rockville, Md: National Institute of Mental Health, 1976.
30 Hausberg MC, Schulz H, Piegerl T, et al. Is a self-rated instrument appropriate to assess mentalization in patients with mental disorder? development and first validation of the mentalization questionnaire (MZQ). Psychother Res 2012;22:699–709.
31 Ehrenthal JC, Dinger U, Lamla A, et al. [Evaluation of the German version of the attachment questionnaire “Experiences in Close Relationships—Revised” (ECR-RD)]. Psychother Psychosom Med Psychoth 2009:59:215–23.
32 Leichsenring F. Development and first results of the borderline personality inventory: a self-report instrument for assessing borderline personality organization. J Pers Assess 1999;73:45–63.
33 Markowitz JC, Petkovska E, Neria Y, et al. Is exposure necessary? A randomized clinical trial of interpersonal psychotherapy for PTSD. Am J Psychiatry 2015;172:430–40.

Leichsenring F, et al. BMJ Open 2020;10:e040123. doi:10.1136/bmjopen-2020-040123
