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Design of VA Cooperative Study #591: CERV-PTSD, Comparative Effectiveness Research in Veterans with PTSD ☆

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ABSTRACT

CERV-PTSD is a randomized controlled trial of two of the most effective treatments for PTSD, Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT). Despite solid evidence that both treatments are effective, there is limited evidence about their effectiveness relative to one another. The primary objective is to compare the effectiveness of PE and CPT for reducing PTSD symptom severity in a healthcare system that offers both treatments. The secondary objective is to compare the effectiveness of PE and CPT for reducing the severity of comorbid mental health problems and service utilization as well as improving functioning and quality of life. The tertiary objective is to examine whether discrepancy between patient preferences and treatment assignment reduces the effectiveness of each treatment. Exploratory analyses will examine whether demographic and clinical characteristics predict differential response to PE and CPT. The study is designed to randomize 900 male and female veterans with PTSD due to any traumatic military event to receive PE or CPT. The standard dose of treatment is 12 weekly sessions but veterans who improve more rapidly may finish in fewer sessions and veterans who improve more slowly may have additional sessions. The primary outcome is improvement in PTSD symptoms, measured during and after treatment and then 3 and 6 months later. As a large multi-site trial with men and women, CERV-PTSD is designed to advance the delivery of care for PTSD by providing conclusive information about whether one treatment is better than the other, overall, and for different types of patients.

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1. Introduction

Posttraumatic stress disorder (PTSD) is a serious mental health problem in veteran and non-veteran populations and can develop following exposure to a traumatic event such as combat, assault, disaster, and accidents [1]. Lifetime prevalence in US adults is higher in women (11.7%) than in men (4.0%) [2] and is especially high among military veterans. For example, a report by the RAND Corporation estimated that current

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prevalence was 13.9% in military personnel who served in the Iraq and Afghanistan Wars [3].

The symptoms of PTSD include intrusive thoughts and memories of the traumatic event, avoidance of stimuli associated with the event, alterations of cognition and mood, and increased arousal [1]. However, PTSD has much broader effects on the lives of individuals who develop it. PTSD is associated with a range of comorbid conditions and functional difficulties, including depression, substance abuse, anxiety disorders, psychosocial impairment, poor physical health, and greater service utilization [e.g., 4,5]. Without adequate treatment, PTSD can become chronic [6], lasting even into old age [2,7,8]. Unfortunately, individuals with PTSD are less likely than those with other common psychiatric disorders to seek treatment [9].

Practice guidelines for PTSD recommend cognitive behavioral therapy (CBT), Eye Movement Desensitization and Reprocessing, selective serotonin reuptake inhibitors, and the serotonin norepinephrine reuptake inhibitor venlafaxine as primary treatments [10–12]. CBT is a type of psychotherapy based on learning theory and cognitive psychology that uses systematic techniques such as exposure and cognitive restructuring to help patients identify and change dysfunctional thoughts, behaviors, and emotions. Evidence demonstrating the effectiveness of two types of CBT, Prolonged Exposure (PE) [13] and Cognitive Processing Therapy (CPT) [14], is particularly strong [15,16]. PE and CPT are being disseminated nationally in Department of Veterans Affairs (VA) healthcare facilities [17].

There have been very few comparative effectiveness studies of treatments for PTSD, and none have been sufficiently large to have adequate power to compare the relative efficacy of active treatments. A report by the Agency for Healthcare Research and Quality (AHRQ) [15] on PTSD treatment called for studies that compare psychological treatments with the best evidence of efficacy, following a similar recommendation by the Institute of Medicine (IOM) [16] that specifically mentioned the need for more research on the treatment of PTSD in military veterans.

In contrast to the amount of evidence indicating the effectiveness of PE and CPT, there is almost no direct evidence about their effectiveness relative to one another. The only study to compare the treatments was a single-site trial in civilian female rape survivors [18]. Both PE and CPT were highly effective but the effect size (d) of the posttreatment difference between them, the ratio of the mean difference between treatments over the pooled standard deviation, was neither clinically nor statistically significant ($d = .14$). Follow-up assessment an average of 6 years later found a between-treatment effect size of $d < 0.01$ [19]. However, with 62 participants per group, the study was not powered to detect an effect smaller than medium ($d = 0.50$) [20], which is unlikely for two highly effective treatments. Thus, the lack of difference between the treatments is inconclusive.

2. Materials and methods

2.1. Overview

CERV-PTSD is a prospective randomized clinical trial with blinded assessment. Participants will be male and female veterans with PTSD due to any traumatic military event. Veterans who are eligible and agree to participate in the study will be randomly assigned to receive PE or CPT. The primary outcome is improvement in PTSD symptom severity as measured by change on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [21], which will be administered before, during, and after treatment and then 3 and 6 months later.

2.1.1. Specific objectives

The primary objective is to compare the effectiveness of PE and CPT for reducing the severity of PTSD symptoms within a healthcare system that offers both treatments. The secondary objective is to compare the effectiveness of PE and CPT for reducing the severity of comorbid mental health problems and service utilization and improving functioning and quality of life. The tertiary objective is to examine whether discrepancy between patient preferences and treatment assignment reduces the effectiveness of each treatment. Exploratory analyses will examine whether demographic characteristics (e.g., gender, age, cohort, race, ethnicity) and clinical characteristics (e.g., PTSD severity, comorbidity, trauma type) predict differential response to PE and CPT. Although data are insufficient to justify a much larger study to address the question of which treatment works for which patients, these exploratory analyses can generate findings to inform future hypothesis-driven research. Exploratory analyses also will characterize amount and quality of treatment and examine how these factors relate to outcomes.

2.1.2. Design considerations

The study is designed to provide information for patients, clinicians, administrators, and policymakers about the comparative effectiveness of treatments for PTSD. When designing the study, we considered the option of proposing an equivalence design given the limited evidence suggesting that the treatments differ. We also considered proposing a traditional superiority design, hypothesizing that CPT is superior to PE given suggestive findings in the 2012 AHRQ report [15] and a recent meta-analysis [22]. However, because methodological factors may account for the apparent difference between PE and CPT, we decided to propose a traditional superiority design with a nondirectional hypothesis. We believe the question this design allows us to ask – *is one treatment more effective than the other?* – is the most important and most appropriate given the available evidence. In addition, we considered whether to include a control group, but ultimately decided that it was not necessary to demonstrate the effectiveness of PE and CPT (vs. control) given the strength of the evidence about the effectiveness of both treatments [15,16,22].

We plan to enroll 900 participants to achieve 90% power to detect a mean difference of 5 points in the primary outcome, which corresponds to an effect size of 0.25. By designing a study large enough to detect a small difference, we are willing to risk the possibility that the true difference between PE and CPT is smaller. If so – for example, if the true difference is $d = .15$ (as in [18]) – the difference would have little scientific or practical value. In contrast, finding that one treatment is more effective would enhance understanding of both etiology and treatment and yield information that has practical clinical significance. Regardless of outcome, patients would have more information to help them make an informed decision about which

treatment to choose and VA would have stronger evidence to help drive veteran-centered care.

Because the majority of veterans who use the VA healthcare system are male, we will need special efforts to enroll female veterans for study generalizability and subgroup analysis. Although an enrichment design and stratified randomization is a way to assure the proper enrollment of women and balance of treatment assignments, it is not practical in a trial of this size. Instead, we carefully selected our study sites in partnership with the VA Women's Health Practice Based Research Network [23] to improve outreach and enhance the enrollment of female veterans. We also focused on VA Medical Centers with a large volume of veterans who served in the wars in Iraq and Afghanistan. Gender variations and different war experiences are important subgroups to explore possible treatment interactions for personalized treatment choices.

2.2. Participants

Each of 17 sites is projected to enroll 64 participants over 30 months of active recruitment. Participants are male and female veterans with PTSD due to any military event. Inclusion criteria are: Current PTSD and symptom severity of 25 or higher on the CAPS-5 [21]; agreement to not receive psychotherapy for PTSD during study treatment and to allow digital recording of phone interviews and therapy; and regular access to a telephone (or agreement to come to the VA for centrally conducted telephone interviews for participants who do not have telephone access). Medications for PTSD and other mental or physical conditions, psychotherapy for other problems, brief visits with an existing therapist, and self-help groups will be allowed. Individuals who are taking medication must be on a stable regimen for 2 months prior to study entry. Exclusion criteria are: substance dependence not in remission for at least 1 month; current psychotic symptoms, mania, or bipolar disorder; significant current suicidal or homicidal intent that includes a specific plan; or moderate to severe cognitive impairment.

Selection criteria follow those used in prior VA Cooperative Studies on the treatment of PTSD [24,25], other trials of PE and CPT [18,26,27], and the National VA rollouts of PE and CPT [17] in order to ensure feasibility and patient safety. Inclusion and exclusion criteria were designed to yield a maximally generalizable sample of patients for comparative effectiveness, replicating insofar as possible the actual patients with whom these treatments could be used. The aim of the criteria is to promote participants' safety and their ability to engage in treatment.

2.3. Assessment

Like the inclusion and exclusion criteria, the measurement protocol follows closely the protocols used in prior VA Cooperative Studies of PTSD treatment [24,25]. The aim is to measure a range of relevant outcomes while minimizing participant burden. We will attempt to follow participants for assessment regardless of treatment completion. The measures and schedule of assessments are listed in Table 1.

The primary outcome is PTSD severity on the CAPS-5 [21], a clinician-administered interview that has excellent reliability and validity and is the gold standard for PTSD treatment research [28]. The CAPS-5 includes a lifetime trauma checklist (the Life Events Checklist, or LEC). We will use the CAPS-5 to compute additional measures of clinical outcomes: response (defined as at least 10-point improvement in severity), loss of diagnosis (response plus no longer meeting DSM-5 symptom criteria), and remission (loss of diagnosis plus a score <20).

Both PE and CPT incorporate measurement-based care with PTSD and depression measures administered weekly or biweekly during treatment; in the VA, therapists use the PTSD Checklist 5 (PCL-5) [29] to assess PTSD and Patient Health Questionnaire (PHQ-9) [30] to assess depression. These measures will be administered prior to each session. However, because the unblinded therapists will administer the PCL-5 and PHQ-9 as part of treatment, we will use different measures of

Table 1
Schedule of assessment measures.

Measure	Baseline	During treatment	Post-treatment	3-months	6-months
Clinician-Administered PTSD Scale – 5 [21]	X	X (week 6)	X	X	X
Posttraumatic Diagnostic Scale [31]	X		X	X	X
Beck Depression Inventory-II [32]	X		X	X	X
Spielberger State Anger Inventory [33]	X		X	X	X
Brief Addiction Monitor (2 items) [34]	X		X	X	X
Short Inventory of Problems-Revised [35]	X		X	X	X
World Health Organization Disability Adjustment Scale-II [36]	X		X	X	X
World Health Organization Quality of Life-BREF [37]	X		X	X	X
Client Satisfaction Questionnaire [38]			X		
Treatment preference	X				
Expectancy of Therapeutic Outcome [39]	X				
Utilization	X		X		X
Structured Clinical Interview for DSM-5 [40]	X				
Montreal Cognitive Assessment [41]	X				
Demographic information	X				
VA traumatic brain injury screen	X				
VA military sexual trauma screen	X				
Suicide screening questions	X		X	X	X
Life Events Checklist [21]	X				
PTSD Checklist - 5 [29]		X (weekly)			
Patient Health Questionnaire-9 [30]		X (weekly)			

PTSD and depression symptoms as outcomes: the PTSD Diagnostic Scale [31] (updated for DSM-5) and the Beck Depression Inventory-II [32]. Other measures used for screening, sample description and outcome measurement are listed in Table 1.

2.3.1. Centralized telephone assessment

Independent Doctoral-level Assessors located at a single site will perform all diagnostic and outcome assessments (CAPS-5) [21] and the Structured Clinical Interview for DSM-5 (SCID) [40] by telephone. Although we considered conducting in-person interviews, we elected to conduct telephone interviews for several reasons. First, being able to complete the interviews by phone is convenient for patients because it prevents them from having to make an additional trip to the VA in order to be interviewed. Second, centralized assessment enhances quality control by reducing site-level variation in interview fidelity and quality. Third, the psychometric quality and acceptability to research participants of psychiatric phone interviews are now well-established in veteran [8,42,43] and non-veteran [44–46] samples. Fourth, because we are using separate therapists to administer CPT and PE, centralized phone assessment assures that the person who is collecting the primary outcome (the CAPS-5) will not see the therapist and patient together, inadvertently breaking the blind. In summary, the phone interviews will provide a valid method of assessing mental disorder constructs, yet be considerably more cost-effective and more convenient for participants than in-person interviews.

2.3.2. Blinding

Using the standard double-blinding procedures employed in medication research is not feasible or desirable in psychotherapy research. Therapists need to be aware of which treatment they are delivering, and patients need to know as well. Blinded assessment is the gold standard in psychotherapy trials. Using centralized phone assessment for the primary outcome in this trial enhances blinding because assessors are not physically located where patients are receiving treatment, which offers an additional layer of protection from accidental unblinding. For secondary outcomes, the Site Coordinator collects patient self-report questionnaires by providing folders containing the questionnaire measures to participants and then collecting these folders from participants after completion.

2.3.3. Reliability monitoring

All diagnostic interviews will be digitally recorded. One hundred SCID-5 [40] and 200 CAPS-5 [21] interviews (sampled equally from each of the 5 assessment periods) will be randomly selected in an ongoing way in order to monitor the reliability of the interview process. An Assessment Adherence Monitor, a licensed clinical psychologist, will conduct reliability assessment. In order to maintain reliability, the Monitor will provide feedback to Assessors during biweekly supervision sessions that will continue throughout the study period.

2.4. Enrollment

Participants will be recruited from specialty and general mental health clinics, primary care, deployment health clinics, Vet Centers, and the community. The sites will be encouraged to use a variety of recruitment strategies: presentations by the Site Principal Investigator or Site Coordinator to clinical personnel at the referral programs to remind them about the study; attendance at clinical team meetings; follow-up with individual clinicians; networking with veterans groups likely to yield potential participants; and advertising. Study staff also will work with the Site Lead at VA Women's Health Practice Based Research Network [23] sites to facilitate enrollment of female veterans. Additionally, the study seeks to take advantage of recent innovations in recruitment strategies using the Network of Dedicated Enrollment Sites [47] to take a more site-based, patient-centric approach to recruitment.

Participants will be enrolled using a 3-phase screening process structured so as to minimize both participant burden and cost to the study due to extensive assessment of ineligible participants [24,25]. All participants will enter the study through a clinician at the participating site; self-referrals will undergo standard clinical intake procedures at sites in order to enter the study. In the first phase of screening, the Site Coordinator consults the referral source in order to establish a provisional PTSD diagnosis and other inclusion and exclusion criteria. In prior studies, this strategy resulted in a highly efficient screening process. For example, in Schnurr et al. [25], 43 of the 396 patients who were discussed with a referral source were ruled out at this phase. Of the 353 patients who met with study staff, 320 were screened and 284 were randomized – 71.7% of those discussed and 88.8% of those screened.

During the second phase of screening, the Site Coordinator will obtain consent and administer screening and questionnaire assessments. In order to enhance participants' understanding of the treatments, the Site Coordinator will also read a brief standardized description of each treatment and will provide a written description of each treatment for participants to take home. Potential participants who are eligible and who agree to continue will then be scheduled for a telephone interview with one of the centralized Assessors in Phase 3, during which the Assessors will assess PTSD and other psychiatric diagnoses. The phone interview also will include measures of treatment preference and expectancy.

2.5. Randomization

After verifying that the participant has signed the informed consent form, met all the enrollment criteria, and completed the baseline assessments, the Site Coordinator will use the randomization procedures established by the study coordinating center. Participants will be randomly assigned in a 1:1 ratio to receiving PE or CPT. Randomization will be based on permuted blocks within each site. After a participant is randomized, the site coordinator will obtain the treatment assignment and then communicate the information to the participant.

2.6. Treatment

Treatment will be delivered in an outpatient setting. PE and CPT will be administered weekly. The standard protocol for CPT is 12 sessions, whereas the standard protocol for PE is 8–15; 10 sessions were used for PE in CSP #494. Given the flexibility in the number of sessions allowed according to the protocols in

the VA rollouts, it would be difficult to constrain the total number of sessions to 10 in PE and 12 in CPT. Therefore, we propose to administer 12 sessions of each treatment as a standard "dose" but to allow participants who improve more rapidly to finish in 10 or 11 sessions and participants who have not attained adequate improvement by session 12 to have up to 2 additional sessions.

We standardized the number of sessions at 12 in both treatments based on evidence showing that number of sessions is related to improvement in psychotherapy (up to a point, at which a longer number of sessions reflects treatment nonresponse) [e.g., 48–50]. Almost none of the literature on the dose-response relationship in psychotherapy discusses session length. In fact, session length is hardly ever reported nor is it treated as a potentially influential variable. We found no discussions or evidence relevant to our decision to equate number of sessions and not total amount of treatment. We did find a small naturalistic study in which investigators were required to shorten exposure sessions from 90 minutes to 60 minutes during the course of a PTSD trial [51]. The results suggested that total amount of treatment did not matter. The 60 and 90 minutes groups did not differ in PTSD and other outcomes. Although the study was not designed to examine session length and was not powered to detect anything other than large differences, the similarity of findings in both groups was striking. However, we did not feel that this evidence was sufficient to support changing the PE protocol from 90 to 60 minutes. Therefore, PE sessions are 90 minutes and CPT sessions are 60 minutes.

Our approach is an attempt to optimally balance standardization (to ensure internal validity) and flexibility (to enhance generalizability). Although there are inherent differences in duration of sessions in each treatment, we believe it is important to administer them in an ecologically valid way, that is, to not artificially equate the duration of sessions. Because this is a comparative effectiveness trial and not an efficacy study, we believe it is important to administer the treatments as they would be used in practice. We will perform sensitivity analyses to examine whether amount of treatment is differentially related to outcome.

2.6.1. Prolonged Exposure

Prolonged Exposure is based on the Emotional Processing Theory of anxiety disorders and their treatment [52] and its expansion to explain the natural recovery after a traumatic experience, the maintenance of chronic PTSD, and treatment of the disorder [53]. According to the theory, to reduce PTSD symptoms, trauma memory must be activated and information that is incompatible with the basic erroneous perceptions must be incorporated in the trauma memory. This is accomplished by confronting the trauma through revisiting the traumatic memory in imagination and recounting it and processing it (to enhance organization of the traumatic memory and correct erroneous perceptions about it), as well as in vivo exposure to distressing (but actually safe) stimuli that disconfirm the erroneous perception that the world is entirely dangerous. Both kinds of exposure help disconfirm the perception of oneself as incompetent and unable to cope with stress.

The central components of PE [13] are in vivo and imaginal exposure. In vivo exposure consists of gradually and systematically having patients approach trauma-related situations, places, and people that elicit distress and have been avoided. Between-session homework of in vivo exposure consists of systematically confronting trauma-related situations that are avoided and to remain in the situation until distress reduces by half. Imaginal exposure involves repeated revisiting of the memory in imagination and recounting aloud the traumatic event(s) in detail, while vividly imagining the event(s) and paying specific attention to emotions and thoughts that occurred *at* the time of the event. Treatment sessions are audio-recorded and patients are asked to listen to their recounting of the trauma daily. Psychoeducation and controlled breathing exercises are also included in PE.

2.6.2. Cognitive Processing Therapy

According to the model of Cognitive Processing Therapy [14], PTSD develops because trauma survivors distort their beliefs about themselves and the world in an attempt to protect themselves from future trauma. They also tend to blame themselves or non-perpetrating others in order to maintain a belief in a just world ("I must have done something wrong, for this outcome to have occurred"). Treatment begins by focusing on distorted beliefs such as denial and self-blame and then shifts to distorted beliefs about oneself and the world ("No one can be trusted"). During treatment, patients are taught through Socratic questioning and daily worksheets to challenge their beliefs and assumptions. As beliefs become less distorted, patients generate more balanced self-statements for practice and PTSD symptoms lessen. Patients also write detailed accounts of the most traumatic incident(s) that they read to themselves and to the therapists in order to experience their natural emotions emanating from the event rather that those generated by erroneous beliefs. The accounts are also used to assist the therapist and patient in challenging the discrepancies between what actually happened and the patients' erroneous beliefs.

CPT [14] consists of cognitive therapy and a written-trauma narrative. Patients briefly process their trauma directly by writing a narrative of their traumatic event(s) that they read to themselves and to therapists after sessions 3 and 4. The majority of the sessions are focused on helping patients challenge their beliefs through Socratic questioning and the use of progressive daily worksheets. The initial focus is on beliefs such as hindsight bias, just world violations, and self-blame or erroneous other-blame, and then shifts to overgeneralized beliefs about self and the world. Statements on the impact of the trauma are written at the beginning and end of therapy to allow the patients to see concretely the changes in their thinking.

2.6.3. Procedures for early completion and additional sessions

The standard number of sessions of PE and CPT will be 12. However, participants may complete treatment with more or fewer sessions depending on their response to treatment. The criteria for flexing the number of sessions are based on experience in the rollouts as well as studies that have used flexible dosing of manualized protocols for treating PTSD [26,54,55]. Our aim is to optimize standardization and flexibility by ensuring that participants achieve substantial and stable gains before terminating early and at the same time not requiring extra sessions unless participants have failed to achieve an adequate response. In addition to reporting number

of sessions attended in each condition, we will also examine variability in early versus late completion in PE and CPT and explore how the variables relate to outcomes.

Participants who have experienced stable remission before completing 12 sessions may terminate early. Stable remission is defined as 2 consecutive sessions in which the participant reports a PCL-5 score below 19. Beginning at session 8, participants who have a PCL-5 below 19 for 2 consecutive sessions may terminate treatment early and receive the final session content at the subsequent session if they prefer to not complete all 12 sessions (i.e., in session 10 for someone remitted in sessions 8 and 9 and session 11 for someone remitted in sessions 9 and 10). Participants whose PCL-5 scores have not dropped below 33 by session 12 may receive up to 2 additional sessions depending on their preference for more treatment.

2.6.4. Stressor sessions

We will add a maximum of 2 additional sessions in the event of significant patient crises or emergencies that present obstacles to study participation. These sessions will be allocated according to a procedure described by Galovski et al. [54]. If after a collaborative discussion with a participant a study therapist judges that a stressor session is necessary, the therapist will offer the participant the option of postponing one session of treatment in order to discuss and consider solutions for this stressor. Participants will be informed that a maximum of two such special sessions will be available to them as part of the study and that they can decide whether they need to use one of these extra sessions to discuss the stressor or continue with the PE or CPT protocol as usual. The stressor session will focus on providing support, problem-solving the stressor situation, and/or applying PE- or CPT-related intervention components to the issue at hand. If more than 2 sessions are needed to attend to a crisis, the patient will be removed from treatment but allowed to resume therapy outside of the study when ready.

2.6.5. Additional treatment

Participants may receive some additional types of non-study treatment while receiving study therapy: medication, self-help groups, and treatment for mental health problems other than PTSD. Participants who have a usual therapist also are allowed to see the therapist for brief supportive sessions if necessary. In addition, participants who develop problems requiring additional inpatient or outpatient treatment will be allowed to receive the additional treatment. They may remain in study treatment if this would be clinically appropriate. After completing study treatment, participants are allowed to resume any PTSD treatment that was discontinued or to seek additional treatment for PTSD. We will use a specifically detailed measure to assess medication use during treatment [25], expanding the measure to capture psychotherapy.

Based on our prior experience, the majority of patients will be on some kind of medication and the clinicians prescribing the medication may wish to change drugs or dose while the participant is receiving study treatment. Our approach in prior studies [24,25] was to discourage unnecessary medication changes but to respect patient preferences. In this study, we will offer consultation by a Medication Monitor to study therapists or prescribing clinicians on best practices in medication management. The goal is not to prevent clinicians from doing what they feel is in the best interests of their patients, but rather, to standardize insofar as possible the use of medications across patients and sites and discourage ineffective or potentially harmful prescribing practices.

2.6.6. Discontinuation of study treatment

Experience with PE and CPT in the rollouts indicates that some patients will have temporary disruptions of study treatment due to other comorbid problems or life events, but that patients typically can come back into treatment after being stabilized. However, participants will be discontinued from treatment if they show substantial worsening of PTSD, other symptoms, or functioning requiring lengthy hospitalization of if the worsening is due to treatment. For intent-to-treat purposes, all participants, including those who are terminated from treatment early, will be followed at posttreatment and at 3 and 6 months.

2.6.7. Therapist training and supervision

There are 4 PE and 4 CPT therapists at each of the 17 sites, chosen from among those who have completed the full VA training for either PE or CPT and are registered on VA rosters as providers of one of those therapies. Study-specific training, aside from instruction regarding the protocol and documentation, consists of completion in 8-9 hours of online training courses. To establish therapist proficiency, therapists are asked to submit two audio-recorded treatment sessions prior to selection. Senior clinicians in each treatment will review the tapes in order to establish adherence and competence with the treatments.

Supervisors will provide case consultation in weekly group conference calls with no more than 8 therapists per call. Review of audio recordings of therapy sessions will not be necessary for supervision because therapists will be required to have completed all VA-provider training elements and review of audio recordings will be used to confirm therapists' proficiency before entry into the trial. However, all sessions will be audio-recorded for quality control.

2.6.8. Therapy fidelity monitoring

Monitoring of therapist behavior in both treatment conditions is necessary to ensure treatment fidelity, i.e., that therapists are delivering the interventions specified in the manual and not using interventions that are not part of the treatment. Independent monitoring will provide a detailed assessment of manual adherence and therapist competence. Using procedures developed in our prior studies [24,25], two independent Fidelity Monitors, senior clinicians who are not involved in training or consultation in the study, will rate audio recordings of 512 randomly-selected sessions (4 per therapist; 32 per site) for adherence and competence.

2.7. Statistical methods

The primary outcome is the change of CAPS-5 total score from baseline (pretreatment) to the average in the 6 months post-treatment (measured at immediate posttreatment, and 3- and 6- month follow-up visits). We chose to use the average in the 6 months posttreatment to define the primary outcome (vs. using a single posttreatment time point) because we anticipate

based on prior findings about the durability of effects in PE and CPT that improvement established during treatment will be sustained in the 6 months after treatment [18,19,24–27] and incorporating multiple measurements from the same participant will reduce the required sample size.

2.7.1. Sample size and power considerations

We considered an effect size of $d = \Delta\mu/\eta = 0.25$ to be a clinically meaningful difference, where $\Delta\mu$ is the mean difference in the primary outcome between PE and CPT, and η is the standard deviation of the change of CAPS-5 total score from baseline to a specific posttreatment time point. By using Schnurr et al.'s [25] estimated $\eta = 19.6$, the effect size of 0.25 translates to a $\Delta\mu = 4.9$ point difference in the primary outcome. For simplicity, the sample size for this study is aimed to have 90% power to detect $\Delta\mu = 5$ in the primary outcome.

Cohen [20] defined 0.20 as a small effect. We have powered the study to detect a difference of 0.25 because both PE and CPT are effective treatments. It is implausible based on existing data to think that the true difference between them is much larger. Conversely, if we did not have adequate power to detect a difference as small as 0.25, then any failure to find a difference between treatments could be seen as inconclusive, which was the problem with the only study that directly compared the treatments [18]. If the true difference between the effects of PE and CPT is less than 0.25, this would be clinically insignificant.

For an individual participant with a CAPS-5 total score measured at pretreatment and at t posttreatment time points, the variance of the primary outcome under a linear mixed effects model is

$$\tau^2 = \sigma_P^2 + \frac{\sigma_{WS}^2}{t} + \sigma_{WS}^2,$$

where σ_P^2 is the variance of the therapist random effect and σ_{WS}^2 is the within-subject variation of the CAPS-5 total score. If each participant were treated by a different study therapist, a total of 452 participants (226 per group) would be needed in order to have 90% power to detect a difference of $\Delta\mu = 5$ between CPT and PE in the primary outcome. However, each therapist will deliver either PE or CPT to a number of study participants. Although the treatment will be delivered on an individual basis, observations from the participants treated by the same therapist are likely to be correlated. Assuming each therapist treats m study participants, the sample size needs to be inflated by the following inflation factor f to retain the same power [56,57]: $f = 1 + (m - 1)\rho$, where ρ is the intraclass correlation due to therapist, or equivalently, the correlation between the primary outcomes from two individuals receiving treatment from the therapist. When each of these two individuals has t post-treatment measurements, ρ can be expressed as

$$\rho = \frac{\sigma_P^2}{\tau^2} = \frac{\sigma_P^2}{\sigma_P^2 + \frac{\sigma_{WS}^2}{t} + \sigma_{WS}^2}.$$

Using the variance estimates from Schnurr et al. [24], $\rho = 0.134$ when $t = 3$. The Planning Committee determined that it is reasonable to assume each therapist will deliver either PE or CPT to 8 participants over the course of the study ($m = 8$). It follows that $f = 1 + (8\text{-}1)^*0.134 = 1.94$. Hence, a total of 878 participants (439 per group) is needed to provide 90% power to detect $\Delta\mu = 5$ in the primary outcome (assuming each participant has baseline CAPS-5 total score and complete follow-up CAPS-5 total score at immediate post-treatment and at 3 and 6 months post treatment). If each participant has $t = 2$ follow-up CAPS-5 (instead of 3), then $\rho = 0.121$, $f = 1.85$, and it requires a total of 920 participants (460 per group) to provide 90% power to detect $\Delta\mu = 5$ in the primary outcome, using the same values of variance components as above. To protect against missing CAPS-5 total scores, potential deviations of the various variances from the assumed values and possible deviation that some therapists will treat more than 8 participants, we plan to enroll 900 participants in this study (450 per group).

2.7.2. Planned primary analysis for the primary outcome

Analyses will be performed according to the intention-to-treat principle. Linear mixed effects models (SAS PROC MIXED) will be used to compare the primary outcome between the two treatment groups. The mixed effects model will include time, treatment, the treatment by time interaction, and site as fixed effects, and participant and therapist as random effects. We will allow the improvement in CAPS-5 total score to vary at these three posttreatment time points in the mixed effects model; the contrast or estimate statement in SAS will be used to estimate and compare the primary outcome between PE and CPT. Although we anticipate the improvement in CAPS-5 total score established in the treatment course will sustain for 6 months for both PE and CPT, this more flexible model allows the possibility of worsening PTSD symptoms after study treatment is discontinued and the possibility of continued improvement of PSTD symptoms or initiating other PTSD treatments after completing study treatment. We will also use other covariance structures to assess robustness of results.

It is expected that there will be some missing data. Imputation techniques, such as linear interpolation and multiple imputation methods, will be examined to assess the robustness on the results. Completer analyses will also be done based on participants who remained in the study throughout the 6-month follow-up period. When large fractions of information are missing, we will perform sensitivity analyses under weaker assumptions (e.g., non-ignorable missingness). We will attempt to collect outcome data from all participants at all time points regardless of whether they continue or complete the study treatment. We will also collect reasons for missing data when possible. Also, the telephone CAPS-5 assessment can facilitate completeness by enhancing the convenience for participants, who will not have to travel for assessment sessions.

2.7.3. Interim analysis

The study does not plan to conduct interim analyses to allow early stopping of the study for efficacy (when there is sufficient evidence that one treatment is superior to the other treatment) or for futility (when it is futile to establish a statistical significant difference at the end of the trial). Both PE and CPT are effective treatments for PTSD, so there are no ethical concerns in continuing the study even when it is unlikely to establish a statistical significant difference at the end of the trial. Also, even if there are treatment differences between PE and CPT, the differences are not likely to alter the VA policy to make all evidence-based treatments available to

PTSD patients based on interim analysis results. It is important from public health, policy, and scientific perspectives to collect sufficient data on the secondary outcomes to support findings in the primary outcome, in the hope that the totality of the evidence will be able to provide guidance to or change clinical practice.

3. Conclusions

AHRQ [15] has recommended comparative effectiveness trials of effective PTSD treatments and the IOM [16] specifically noted the need for research on veterans. Despite solid evidence that PE and CPT are effective treatments for PTSD in veterans and non-veterans, there is insufficient evidence about the relative effectiveness of these treatments. The available evidence is suggestive but not conclusive. With only one head-to-head comparison that was conducted in a relatively small and select sample of female non-veteran trauma survivors [18], it is not possible to draw reliable conclusions about the comparative effectiveness of PE and CPT. Although there is no specific reason to indicate that Resick et al.'s [18] results would not generalize to men and to other types of trauma survivors, determination of the applicability of the findings beyond female civilian rape survivors will be enabled by a comparison in a more heterogeneous sample. A large multi-site trial with men and women also will substantially strengthen the inferences that can be drawn from the study and the study's impact on the field.

CERV-PTSD aims to address the gap in information about comparative effectiveness of PTSD treatments by directly responding to recommendations from AHRQ [15] and the IOM [16] for studies that compare treatments with the best evidence of efficacy. By comparing PE and CPT, the study will determine whether two of the most effective treatments differ. By using a large sample of male and female veterans from all eras, the study will be address the question of what works for which patients, which is a key goal of comparative effectiveness research. The study incorporates procedures used successfully in other large multisite trials of psychotherapy for PTSD in veteran populations [24,25], including a 3-phase screening process to enhance efficiency and remote supervision of therapists to enhance treatment fidelity. The study also incorporates a centralized assessment procedure to enhance the reliability and validity of the primary outcome and the efficiency of data collection.

VA's integration of a clinical research infrastructure within its healthcare delivery system uniquely positions it to conduct a study that would be extremely difficult to do in the civilian sector. Additionally, VA's tradition of answering comparative effective questions [58] enhances its ability to address the critical methodological and pragmatic elements for a definitive trial. The national rollouts of PE and CPT [17] have enhanced the ability to do large-scale psychotherapy research on these treatments. As of August, 2014, over 6,000 therapists nationwide have been trained in one or both of the therapies. By using therapists who have already been trained in PE and/or CPT, we were able to avoid the delay required by training, which is often 6 months or more to ensure that a therapist is proficient in a new psychotherapy technique. Furthermore, training the large number of therapists needed – 136 – would be cost-prohibitive for a typical research study. Another unique advantage for this study is that there are administrative structures led by members of the study team – the Evidence-Based Psychotherapy Program [17] and the PTSD Mentoring Program, a VA initiative that provides administrative guidance to directors of specialized PTSD treatment programs [59] – that exist to facilitate implementation of study findings. The findings will inform clinical practice outside VA as well.

A comparison of PE and CPT has significant scientific relevance because each treatment reflects a different theoretical model of the etiology of PTSD: emotional processing of trauma memories in PE [13] and maladaptive cognitions in CPT [14]. If one treatment is found to be more effective, this can further the understanding of the etiology of PTSD and lead to enhanced prevention efforts, as well as refinement of existing treatments. There are also practical considerations. The standard CPT protocol consists of 12 1-hr sessions, whereas the standard PE protocol consists of 9-12 1.5-hour sessions. More sessions can be added to either treatment to achieve desired outcomes. However, the length of CPT sessions is easier to accommodate in VA, where mental health treatment sessions last 1 hour or less. CPT can also be implemented in group settings. In contrast, an important advantage of PE is that exposure therapy can be used to treat other anxiety disorders such as phobias, panic disorder, and obsessive-compulsive disorder.

In addition to knowing how PE and CPT compare overall, there is a similar need for information about the relative benefits for subgroups of patients [16]. The study that compared PE and CPT [18] offers little guidance. The homogeneity of the sample in terms of gender and trauma type prevented the investigators from looking at the potential differences related to these variables. Subsequent analyses from this study [60] examined age, education, intelligence, depression, anger, and general (non-trauma) guilt as predictors of treatment outcome in PE and CPT. Among younger women, those who received CPT had greater improvements in PTSD than those who received PE, whereas among older women, those who received PE had greater improvements. The investigators also looked at dropout and found that higher baseline anger was related to dropout from PE, but not from CPT. There was not enough evidence about predictors of differential treatment response in PTSD to justify powering a study to perform subgroup analyses, e.g., to examine whether men and women differ in response to PE and CPT. However, the study will permit exploratory analyses of predictors of response to PE and CPT.

A report by the IOM in 2009 [61] set out a national agenda for comparative effectiveness research, in response to a Congressional allocation of over $1 billion to facilitate optimal decisions about healthcare. There have been very few comparative effectiveness studies of treatments for PTSD, and none have been sufficiently large to have adequate power to compare active treatments. CERV-PTSD is designed to address this gap by providing much-needed information about the comparative effectiveness of treatments that can help to improve the lives of veterans and non-veterans with PTSD. The study also can guide future research about what works for whom, a key goal of comparative effectiveness research and a necessary ingredient in delivering optimal, patient-centered care.

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Update

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Corrigendum

Corrigendum to "Design of VA Cooperative Study #591: CERV-PTSD, Comparative Effectiveness Research in Veterans with PTSD" [Contemp. Clin. Trials 41 (2015) 75–84]☆

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The authors regret reporting on p. 77 that remission of PTSD would be defined as a score < 20 on the Clinician-Administered PTSD Scale for 5th Edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5). The text should have indicated that remission will be defined as loss of diagnosis plus the DSM-5 score t corresponds to a score < 20 on the 4th Edition of Clinic Administered PTSD Scale for DSM-IV. The authors would like to a ogise for any inconvenience caused.

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