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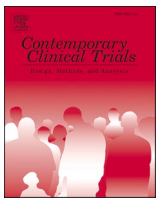

Comparative effectiveness of trauma-focused and non-trauma-focused psychotherapy for PTSD among veterans with comorbid substance use disorders: Protocol & rationale for a randomized clinical trial

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ABSTRACT

Background: Co-occurrence of posttraumatic stress disorder (PTSD) and substance use disorders (SUDs) is common and concurrent treatment is recommended. Relatively little is known about which evidence-based psychotherapies for PTSD are most effective for patients with varying substance use profiles. We aim to examine the comparative effectiveness of trauma-focused therapy (TFT) and non-trauma-focused therapy (NTFT) among Veterans with PTSD and SUD. TFT has been found to be effective among those with PTSD/SUD, though effects are smaller and rates of treatment non-completion are higher than in those without SUD. NTFTs suggested for the treatment of PTSD, such as Present Centered Therapy, (PCT) have not been examined among those with co-occurring SUD, despite lower rates of treatment dropout. We will also examine the comparative effectiveness of TFT and NTFT for patients with varying SUD severity, type of substances used, and patient treatment preference.

Method: 420 Veterans with PTSD and SUD will be randomized in a prospective, pragmatic comparative effectiveness trial at 14 Veterans Health Administration facilities. Participants will receive either TFT (Prolonged Exposure or Cognitive Processing Therapy) or NTFT (PCT) after enrolling in concurrent SUD treatment-as-usual. Assessments will occur at baseline, posttreatment, 3- and 6 -months posttreatment. Main outcomes are PTSD symptom severity and PTSD treatment dropout. Clinician, patient, and leadership stakeholder panels advise study activities, and a process evaluation will identify strategies to enhance the implementation of evidence-based PTSD treatments in SUD care settings.

Conclusions: Results will provide critical information to guide clinicians when recommending PTSD treatments to patients with comorbid SUD.

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1. Introduction

Posttraumatic stress disorder (PTSD) and substance use disorder (SUD) comorbidity is widespread and associated with greater clinical complexity than either disorder alone. About one-third of patients receiving outpatient SUD care from the Department of Veterans Affairs (VA) have PTSD [1]. Those with PTSD/SUD have more severe PTSD symptoms and are more likely to experience comorbid mental health diagnoses, suicidal ideation and behavior, poor vocational and social functioning, and physical health complaints, than those without SUD [2–7]. Attrition rates from PTSD treatment are also higher [8]. Among patients with SUD, the presence of PTSD is associated with shorter duration of abstinence and worse treatment outcomes [9,10].

Despite the high rate of comorbidity and increased complexity among patients with SUD/PTSD, evidence regarding treatment of PTSD in the presence of SUD is lacking. A systematic review found that 75% of randomized clinical trials (RCTs) of PTSD treatment had SUD-related exclusion criteria; this review concluded that findings from these studies may not be fully applicable to people who have both disorders [11].

Trauma-focused therapies (TFTs), including Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT), are the first-line recommended treatments for PTSD across all published clinical practice guidelines (CPGs) [12]. Accumulating evidence suggests that TFTs are safe and effective for patients with PTSD/SUD, and do not increase substance use or craving [13,14]. These emerging data led to recommendations in the Department of Veterans Affairs/Department of Defense CPG for PTSD that guideline-consistent treatments for PTSD be delivered alongside evidence-based SUD care [15].

However, the only guideline-recommended treatments for PTSD that have been tested in adequately powered RCTs among those with PTSD/SUD are trauma-focused. Given the smaller effect sizes and considerably higher dropout rates from TFTs among those with this comorbidity, evaluations offering alternatives to TFTs are warranted [14,15]. Present Centered Therapy (PCT), a second-line, non-trauma-focused therapy (NTFT), may be uniquely beneficial for this population, given its robust treatment effects and lower treatment dropout than TFT [16].

2. Research aims and hypotheses

The Comparative Effectiveness of Trauma-Focused and Non-Trauma-Focused Treatment Strategies for PTSD among those with Co-Occurring SUD (COMPASS) study adds to knowledge about treatments for PTSD in patients with comorbid SUD by comparing the first-line TFT approach to PCT, a second-line NTFT approach. Our first aim is to determine the comparative effectiveness of TFT (CPT and PE) and NTFT (PCT) on posttreatment PTSD symptom severity among Veterans with PTSD who have recently initiated SUD treatment-as-usual. We hypothesize that TFT will lead to greater reductions in PTSD severity than NTFT. The second aim is to evaluate our hypothesis that patients with co-occurring PTSD and SUD randomized to TFT drop out of PTSD treatment more often than those randomized to NTFT. Additionally, patients with varying SUD profiles (severity and substance type) and treatment preferences may respond differentially to these competing approaches. Thus, our third aim is to examine whether TFT differs from NTFT in the effect on PTSD severity and number of PTSD therapy sessions attended in patients with varying (a) levels of baseline SUD severity, (b) classes of misused substances, and (c) treatment preferences. Given the lack of published data to inform Aim 3, we have no prespecified hypotheses for the direction of variation in effects by subgroups. Finally, we will examine the comparative effectiveness of TFT and NTFT for PTSD symptom severity at 3- and 6-months posttreatment and for a range of secondary outcomes, including (a) patient-centered PTSD and SUD-related outcomes, functioning, and quality of life at posttreatment, 3-, and 6-month follow-up, (b) posttreatment treatment satisfaction, and (c) self-reported PTSD and SUD symptom exacerbation during treatment. Finally, we explore the impact of gender, participation in varying SUD treatments, baseline PTSD severity, trauma type and load, and relative onset of PTSD and SUD on Aim 1 & 2 findings.

3. Materials and methods

3.1. Overview

COMPASS is a two-arm pragmatic RCT in which 420 patients at 14 VA facilities will be randomized to receive either TFT or NTFT for PTSD alongside SUD treatment-as-usual (Fig. 1). All patients will be assessed prior to treatment initiation, immediately following treatment completion or drop out, and again 3- and 6-months after posttreatment assessment. The primary outcomes will be PTSD symptom severity assessed using the Clinician-Administered PTSD Scale DSM-5 (CAPS-5) [17] posttreatment and PTSD treatment completion. COMPASS also includes clinician, patient, and leadership stakeholder panels to provide consultation on study activities throughout the project and a qualitative process evaluation to inform future implementation efforts.

3.2. Participants, inclusion, and exclusion criteria

Participants are adult male and female Veterans with a PTSD diagnosis initiating outpatient SUD treatment with no SUD treatment in the 90 days prior to the current episode at one of the participating VA facilities. Participants must meet Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5) [18] criteria for SUD (mild, moderate or severe) as determined by the Structured Clinical Interview for DSM-5 (SCID-5) [19]; excluding those whose only SUD is tobacco use disorder, and report substance use in the 30 days prior to screening (Table 1). They must also meet DSM-5 criteria for PTSD (determined by the CAPS-5). We will exclude patients with severe cognitive impairment, current suicidal or homicidal intent with a specific plan, and uncontrolled psychotic or manic symptoms not attributable to SUD that are severe enough to interfere with the participant's ability to participate in an outpatient treatment program.

3.3. Recruitment, screening, and randomization

The primary recruitment method will use referrals from outpatient SUD providers at participating VA facilities. Providers in other clinics (PTSD and general mental health clinics) will be asked to refer potentially eligible patients to a SUD specialist before recruitment. We will also use the electronic medical record (EMR) to identify patients starting new episodes of SUD treatment at participating VA facilities. All potential participants will be telephone screened for eligibility then consented and scheduled for the baseline assessment. If the patient is deemed eligible, they will be assigned to a study therapist and randomized to a treatment condition (TF or NTFT) using a within therapist computer-generated 1:1 randomization schedule.

3.4. Interventions

Eligible patients will be randomized to receive individually delivered outpatient TFT or NTFT concurrent with outpatient SUD treatment as usual at their VA facility.

3.4.1. Trauma-Focused Therapy (TFT)

The TFT arm includes PE and CPT; both therapies are highly recommended in all published PTSD treatment guidelines [12]. About 40% of Veterans with PTSD no longer meet criteria for PTSD following treatment with PE or CPT [20]. We chose to include both PE and CPT based on feedback from clinician stakeholders during project development suggesting that in treatment planning the primary determination was whether a specific Veteran would be likely to tolerate and benefit from a trauma-focused intervention, not which TFT was best. Overall,

effects of CPT are similar to PE in reducing PTSD symptoms. A comparative effectiveness trial of PE and CPT among Veterans found that while PE had slightly better PTSD outcomes, the difference in CAPS-5 severity scores was not clinically meaningful [21]. Although the comparative effectiveness of PE and CPT has not been examined among those with co-occurring SUD, these findings increase our confidence in including both treatments in the TFT arm. As in clinical care, patients randomized to TFT will receive the TFT therapy that the assigned therapist is verified to provide. If the therapist is verified in both TFTs, the provider will decide which treatment to deliver. That decision may be based on logistical factors (e.g., availability for 90-min sessions), therapist preference, or clinical judgement about which treatment may be the best fit given the veteran's PTSD symptom profile from the baseline CAPS-5.

PE includes psychoeducation, breathing retraining, in-vivo exposure, and imaginal exposure and is delivered weekly in 90-min sessions [22]. During in-vivo exposure, patients systematically approach trauma-related reminders that have been avoided because they cause distressing emotional and physical reactions. In-vivo exposures are conducted as out-of-session homework. Imaginal exposure involves purposefully and repeatedly recounting the traumatic memory aloud and in detail. Imaginal exposure occurs during session and is audio-recorded for daily listening between sessions.

CPT is a cognitive therapy that focuses on challenging and modifying maladaptive beliefs related to the trauma during weekly 60-min sessions [23]. Sessions are largely spent helping patients identify and challenge trauma-related beliefs, and later in therapy, overgeneralized beliefs about oneself and the world. Patients continue to identify and challenge such thoughts daily between sessions using treatment worksheets. Patients write an impact statement that details the way in which their trauma has impacted their lives at the beginning and end of therapy.

Table 1
Inclusion/exclusion criteria.

Inclusion criteria
• DSM-5 diagnosed PTSD as assessed by baseline CAPS-5
• DSM-5 diagnosed current SUD, not in early remission, as assessed by baseline SCID-5 (tobacco use alone not sufficient for inclusion)
• Initiation of a new treatment episode (i.e., no outpatient treatment in past 90 days) of outpatient SUD treatment at a participating VA, operationalized as attending a treatment planning appointment with a designated SUD provider & agreeing to a treatment plan*
• Substance used in the prior 30 days (or in 30 days prior to being in a controlled environment)
• Agree not to received active psychotherapy for PTSD during treatment period (case management and supportive therapy allowed)
• Willing to provide consent and be randomized to treatment condition
Exclusion criteria
• Severe cognitive impairment
• Suicidal or homicidal ideation at baseline that needs to be the immediate focus of treatment
• Current unstable psychotic or manic symptoms not attributable to SUD
• To ensure concurrent PTSD & SUD treatment, >30 days between initiating SUD care and consent or >90 days between initiating SUD care and PTSD treatment start

* Participants remain eligible if they do not adhere to/drop out of their agreed to SUD treatment plan.

Finally, CPT includes an optional written trauma account that patients write and read to themselves and therapists early in treatment.

3.4.2. Non-Trauma-Focused Therapy (NTFT)

Patients randomized to NTFT will receive PCT. PCT focuses on "current life problems as manifestations of PTSD" in weekly 60-min sessions; it includes psychoeducation and normalization of responses

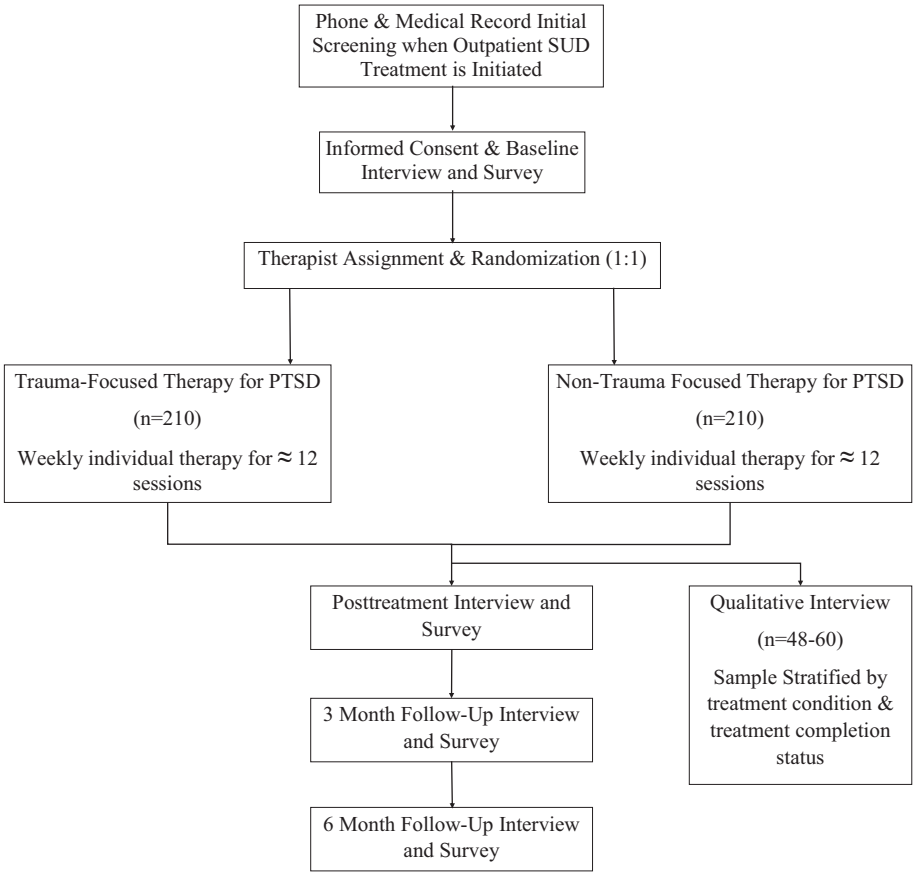

Fig. 1. Study overview.

to trauma, problem-solving related to current life difficulties and stress identified by patients, and emotional support and validation [24]. PCT is hypothesized to work through improved insight, increased mastery over current life difficulties, and enhanced interpersonal connectedness. Originally designed as a strong comparator for psychotherapy, PCT is now a bonafide treatment suggested as the second-tier treatment in multiple guidelines [12]. PCT is slightly less effective than TFTs but has significantly higher rates of treatment completion [16].

3.4.3. PTSD treatment delivery

To reflect clinical practice and meet patient need, TFT and NTFT will be delivered flexibly. Two recent RCTs conducted by the study team employed similar flexibility parameters [21,25]. The standard treatment length will be 12 sessions; however, patients and providers can collaboratively agree to early completion or extension. As in other recent PTSD comparative effectiveness trials [21], early completion can occur following stable remission (two sessions with Posttraumatic Checklist [PCL-5] [26] scores below 19). Conversely, participants can receive up to 4 additional treatment sessions (for a maximum total of 16 sessions) if their PCL-5 score remains above 33 at session 12. Neither early completion nor extension will be determined solely by PCL-5 score; rather, the score will trigger a collaborative conversation between the patient and therapist about treatment length. All sessions must be completed within 22 weeks of randomization. Further, up to two stressor sessions will be allowed during the active treatment phase as needed (decided collaboratively by patients and providers) to address psychosocial stressors or other cooccurring issues impacting PTSD treatment, and may be used to address SUD as needed (e.g., facilitate greater engagement in SUD services). Stressor sessions do not follow the TFT or NTFT protocols and may include any treatment strategies deemed appropriate by the provider (e.g., supportive therapy, motivational interviewing). Stressor sessions do not count towards the total number of allowable therapy sessions. Mirroring VA clinical practice, treatment can be delivered either in person or via videoconferencing. In both treatment arms, the relationship between SUD and PTSD will be emphasized during psychoeducation, goals for SUD treatment will be elicited, substance use and craving since last session will be queried weekly, and improvements in both PTSD and SUD will be highlighted in the final session.

3.4.4. SUD treatment as usual

SUD treatment received by study participants will be selected by a SUD specialist from an array of evidence-based treatments offered on an outpatient basis by their VA facility and individualized to the patient's needs and agreement. Outpatient treatment options can include SUD treatment through an intensive outpatient program; motivational enhancement therapy or cognitive behavioral therapy for relapse prevention; 12-step facilitation counseling, contingency management, SUD-focused behavioral couples counseling or family therapy; and evidence-based pharmacotherapy for alcohol or opioid use disorder. The intensity of SUD therapy and interventions offered will vary by participant. Both abstinence and harm-reduction goals will be allowed.

3.5. Treatment fidelity and monitoring

Participating study therapists, all of whom will be existing VA clinicians, will have verified training and proficiency in delivery of TFT (PE and/or CPT) and NTFT (PCT) and will provide both TFT and NTFT to study participants. Participating therapists will complete VA (or VA-equivalent) training in PE or CPT and will have their competence confirmed by experts in the treatment delivery. All therapists will participate in eight hours of PCT training, including a 6-h didactic workshop delivered by the therapy developer, M. Tracie Shea, PhD, and have skillful PCT delivery verified by trained raters. To ensure treatment fidelity, study therapists will participate in weekly supervision meetings. At the end of each session, therapists will complete a brief checklist indicating delivered treatment elements and planned/unplanned protocol deviations. In addition, four sessions (two TFT and two NTFT) per therapist randomly selected from all study sessions delivered by the therapist will be rated by experts in the treatment of PTSD.

3.6. Assessment

Participants will be assessed at baseline, immediately after treatment completion or drop out, and 3-months and 6-months posttreatment. There will be three sources of data: 1) independent evaluator (IE)-administered interviews, 2) self-report surveys (web-based or paper and pencil), and 3) medical record data. IEs will be collecting the primary endpoint outcomes and will be blinded to treatment condition throughout the study. Table 2 lists each assessment, timing of administration, and data source. In addition, data will be collected from the EMR to determine the participants' SUD treatment plan, number and type of sessions attended, any pharmacotherapy prescribed, and the length of SUD treatment retention. SUD retention is defined as starting at treatment intake and ending at the last documented SUD treatment appointment, prior to 30 days with no new appointments. Non-VA and self-help service use will be collected from participant self-report.

Our primary outcome is PTSD symptom severity posttreatment, as measured by CAPS-5 (Table 2) [17]. This semi-structured diagnostic interview is the gold standard for assessing PTSD symptom severity. To ensure valid administration of the CAPS-5, IEs will participate in 3 stages of training: readings, expert-led instruction, and mock interviews. After training, IEs will engage in weekly to biweekly CAPS-5 fidelity oversight meetings which will include discussions of difficult scoring and administration. Additionally, a minimum of 10% of randomly selected CAPS-5 interviews per assessor will be reviewed by an expert throughout the study to prevent drift. Our second main outcome is PTSD treatment dropout. Dropout, extracted from the EMR, will be a dichotomous variable representing patient completion of all sessions of the PTSD treatment protocol. Patients will be categorized as dropouts if they attend fewer than 12 protocol sessions (stressor/emergency sessions not included) and are not early completers (two weekly PCL scores below 19 and therapist report of early completion). All manually extracted EMR data will be coded by two independent coders.

Secondary outcomes are detailed in Table 2. Weekly measures of self-reported PTSD symptoms and SUD craving and use will be used to examine symptom exacerbation during treatment and inform therapy.

3.7. Analytic plan

3.7.1. Primary aim analyses

We will fit a linear mixed model for CAPS-5 severity using intervention, assessment (posttreatment, 3 months, and 6-months posttreatment), baseline CAPS-5, and interactions of assessment with intervention and baseline CAPS-5 as fixed effects. The model will include random effects for participant, clinician, and study site. We will use a model-based Wald test of the assessment by intervention interaction to examine variation in effects over time; our primary assessment of an intervention effect will use a model-based Wald test of an effect posttreatment. To address missing data, we will use all observed CAPS-5 scores along with participant demographics, trauma type, SUD history, therapy received, and therapy retention measures, in a sequence of chained regression models, implemented separately within each intervention arm, to generate 50 imputed data sets with complete data [27]. We will use these imputed data sets to fit the model described above and aggregate results across imputed datasets using the standard methods for combining results [28]. For the second aim, we will fit a random effects logistic regression of therapy completion on intervention and baseline CAPS-5 severity score, incorporating random effects for clinician and study site. We will compare treatment retention rates using a model-based likelihood ratio test. A significance level of 0.05 will be used for assessing significance of effects in both analyses.

Table 2
Assessment schedule.

Assessment schedule			
Construct (Purpose)	Measure	Timeline*	Source
PTSD symptom severity (1° outcome) PTSD diagnosis (2° outcome)[a] PTSD remission (2° outcome)[b]	Clinician Administered PTSD Scale-5 (CAPS-5) [17]	Pre, Post, FUs	Interview
PTSD treatment dropout (1° Outcome)	Fewer than 12 protocol sessions without evidence of early completion	Post	EMR
% Days with heavy drinking and/or illicit drug use (2° outcome)	Timeline Follow-Back Interview [32]	Pre, Post, FUs	Interview
Consequences of drinking/drug use (2° outcome)	Short Inventory of Problems – Revised [33]	Pre, Post, FUs	Self-report
PTSD-related functioning (2° outcome)	Brief Inventory of Psychosocial Functioning [34]	Pre, Post, FUs	Self-report
Sleep (2° outcome)	Insomnia Severity Index [35]	Pre, Post, FUs	Self-report
Anger (2° outcome)	Dimensions of Anger Reactions – 5 [36]	Pre, Post, FUs	Self-report
Quality of life (2° outcome)	World Health Organization - Quality of Life, Brief [37]	Pre, Post, FUs	Self-report
Depression (2° outcome)	Patient Health Questionnaire-9 (PHQ-9) [38]	Pre, Post, FUs	Self-report
Treatment satisfaction (2° outcome)	Client Satisfaction Questionnaire [39]	Post	Self-report
Self-reported PTSD symptoms (2° outcome)	PTSD Checklist –DSM-5 (PCL5) [26]	Pre, Post, FUs & Weekly**	Self-report
SUD use & craving (2° outcome)	Brief Addition Monitor (use subscale & craving item) [40]	Weekly**	Self-report
Trauma type & load (subgroup analyses)	Life Events Checklist for DSM-5 [41]	Pre	Interview
SUD diagnoses (subgroup analyses)	Structured Clinical Interview for DSM-5 (AUD/SUD modules) [19]	Pre	Interview
Treatment preference (subgroup analyses)	Likert item assessing desire for TFT vs. NTFT	Pre	Interview
SUD treatment participation (subgroup analyses)	Number and type of treatment services, pharmacotherapy prescribed and length of continuous medication possession, length of treatment retention.	Post	EMR
	Non-VA self-reported treatment measure	Post	Survey

[a] No longer meeting DSM-5 symptom criteria on the CAPS.
[b] No longer meeting DSM-5 symptom criteria and a severity score under 12 on the CAPS.
* Pre = prior to randomization, Post ≤1 month posttreatment, FUs = 3 & 6-month follow-ups.
** Weekly during treatment only (immediately prior to session).

3.7.2. Prespecified subgroup analyses

We will examine variation of intervention effects on CAPS-5 severity scores and treatment completion, here measured using the number of PTSD therapy sessions attended, between subgroups defined by three variables; SUD severity as defined by DSM-5 [mild/moderate SUD severity or severe SUD severity], substance type [alcohol use only, use of non-alcohol drugs only, or both alcohol and other drug use], and treatment preference [preference for TFT or preference for NTFT]. We will expand the posttreatment CAPS-5 regression analysis described above to include an interaction between intervention and the subgroups defining variable. For number of sessions attended, we will fit a generalized linear mixed model using intervention, baseline CAPS-5, the subgroup variable and its interaction with intervention as fixed effects and random effects for clinician and site.

3.7.3. Power and sample size

Assuming an 85% posttreatment follow-up rate and a 0.05 two-sided significance, comparing posttreatment CAPS-5 scores will have at least 80% power for an underlying 0.30 standard deviation (*SD*) difference and 90% power for a 0.35 *SD* difference. Using a 0.05 significance level, we will have over 80% power to detect differences in completion rates assuming a 15% increase in completion with NTFT and a TFT completion rate around 50%. Subgroup analyses will assess intervention effects within seven subgroups. We anticipate subgroup prevalence rates of 25% or more. For two-sided 0.05 significance levels and subgroup prevalence of 25%, the study will have 80% power for 0.60 *SD* differences between interventions and 90% power for 0.70 *SD* differences. For subgroup prevalence of 33%, the study will have 80% power for underlying 0.55 *SD* differences in CAPS-5 scores and 90% power for 0.60 *SD* differences. Assuming a linear regression is appropriate, similar power will be available for sessions attended.

3.8. Process evaluation

The process evaluation goals are to 1) ensure trial findings are relevant to patients, clinicians, and health care decision-makers; 2) allow for rapid translation of study findings into clinical practice, and 3) better interpret trial findings. The qualitative process evaluation will consist of semi-structured interviews with study participants (n = 48–60), clinicians (2 per site, $n = 28$) and leaders (1 per site, $n = 14$). The Process Evaluation Team will also observe and document implementation processes by taking field notes during regularly scheduled meetings and calls with study sites.

We will interview participants post-intervention from both treatment arms, including PTSD treatment completers and non-completers. Participants will be sampled across study sites and include those diverse in age, gender, race, or ethnicity. Questions will address their experience with treatment, the integration of PTSD treatment into SUD treatment, their recommendations for improving this integration, and the aspects of the intervention that were most or least influential in their outcomes. All interviews will be recorded and transcribed.

Site clinicians and leaders will be interviewed using interview guides based on the RE-AIM and Consolidated Framework for Implementation Research (CFIR) frameworks [29,30]. Questions will include leaders' and clinicians' perceptions of TFT and NTFT and how the interventions were integrated into the existing SUD treatment processes. We will also assess the potential for long-term sustainability and further implementation. Field notes from study meetings will be summarized and coded in real-time using CFIR constructs, then coding will be discussed and agreed upon by the Process Evaluation Team. These notes will provide a description of the implementation process at each site and will be used to inform future implementation efforts.

3.9. Stakeholder engagement

The COMPASS study will include three stakeholder panels to advise the research team and ensure the study is relevant to clinicians, patients, and health care systems. The Study Advisory Panel includes healthcare leaders, from within the VA and from outside healthcare systems, to provide guidance on how our findings might be operationalized in their setting. Our Clinician Engagement Panel includes COMPASS study therapists to provide their unique perspectives on integrating PTSD treatment into the SUD clinics at their local facilities. The Veteran Consultant Panel is composed of Veterans with lived experience with PTSD and SUD. They guide development of our patient-facing materials and give voice to the patient perspective. All three panels will be

involved through study start-up, implementation, data interpretation, and dissemination of findings.

4. Discussion

This paper describes the methods and importance of a stakeholder-informed, mixed-method study using RCT methodology to examine whether TFT or NTFT are most effective in treating Veterans with PTSD/SUD and whether SUD characteristics and patient preference may moderate that effect. Despite the challenges of effectively treating PTSD among those with comorbid SUD, treatment options remain limited and information regarding who is likely to benefit from first-line treatments is lacking. This is the first study to compare effectiveness of TFT with a guideline-recommended NTFT among patients with PTSD/SUD comorbidities. The study is also unique in its inclusion of both PE and CPT in the TFT arm. As discussed above, this design better reflects the decisional dilemma as framed by our stakeholders: Which patients with co-occurring SUD can tolerate and benefit from trauma-focused PTSD treatments? It also closely aligns with VA policy and actions, which have focused on the implementation of TFT, without prioritization of PE or CPT.

Our approach to comparing the effectiveness of these two treatment modalities has several strengths. First, we are employing methodologically strong best practices for psychotherapy research such as using blinded assessments, monitoring treatment fidelity, assessing Veterans who discontinue treatment, conducting opinion interviews at the end of the treatments, and assessing outcomes at 3- and 6-months posttreatment. Multiple elements of pragmatic clinical trials are incorporated including broad inclusion criteria, use of field-based providers, flexibility in intervention delivery, and utilizing intent-to-treat analyses [31]. These elements ensure our sample represents the diverse set of patients treated in clinical settings and findings can be easily translated beyond the trial. Study therapists are providing both TFTs and NTFTs to participants to eliminate confounding therapist characteristics with therapy type and to mirror non-study treatment delivery. Finally, to promote effective collaboration among partners and researchers throughout the study and ensure relevance of study findings, we have assembled three engagement panels. Our engagement model encourages active participation of the project advisory groups by engaging them in planning study processes, monitoring progress, problem-solving identified issues, and aiding in disseminating the results.

There are also limitations of our design. Since the SUD treatment is treatment as usual rather than prescribed, participants will receive a variety of types and intensities of SUD treatment. We attempt to limit the variation in SUD treatment by requiring that each SUD treatment clinic provides a range of evidence-based SUD treatment modalities. Through the participants' VA EMRs, we will identify the type, intensity, and length of SUD treatment that participants engaged in to explore the impact of SUD treatment variation on outcomes. Another potential limitation is the low minimum threshold of 63 female Veterans (~15%) we aim to recruit. This low percentage could prevent investigators from detecting potential differences related to gender, which could limit generalizability. However, given that this is a minimum goal, our recruitment numbers could be more heterogeneous than what we aspire for. Because allocation to PE and CPT is not randomized within the TFT arm, any analyses examining the comparative effectiveness of those treatments among those with SUD will be preliminary. Project findings may not generalize outside of VA or to civilian populations. Finally, due to clinic and study adjustments in response to the COVID-19 pandemic (see below), patients without access to technology for virtual care may not be represented in the study. While VA provides such technology to Veterans in need, access to broadband or a private space to participate in treatment may exclude some of the most vulnerable Veterans. Conversely, some patients who otherwise may not have been able to participate will be enrolled.

COMPASS's study launch (May 2020) was simultaneous with the start of the COVID-19 pandemic. This required rapid changes to the study protocol prior to beginning recruitment. While the original study protocol allowed for delivery of the PTSD treatment either virtually or in person, research study procedures were shifted for fully virtual participation (e.g., consent obtained remotely). Perhaps of greatest significance to the project was the shift in recruitment strategies. Initial recruitment strategies relied on maintaining an in-person presence within the SUD clinics. The study team worked with each facility to develop individualized recruitment plans that identified the most efficient ways for study staff to maintain consistent contact with SUD clinic providers whom they were relying on for study referrals. The study team also worked with each facility to identify ways to simulate a "warm handoff" from referring providers to study coordinators in a virtual environment.

We anticipate that COMPASS, which we believe to be the largest treatment study of patients with PTSD/SUD, will provide data to help patients and clinicians make better informed treatment decisions for which therapy may be the best option for an individual patient. Further, the inclusion of stakeholder engagement and the qualitative process evaluation is likely to deepen our understanding of the challenging clinical comorbidity and speed implementation of study findings into regular clinical practice.

Author note

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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