An efficient, exposure-based treatment for PTSD compared to Prolonged Exposure: A non-inferiority randomized trial

Principal Investigator: Denise Sloan, Ph.D.
Phone: 857-364-6333
E-mail: denise.sloan@va.gov

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1. Protocol Summary/Abstract

Objectives:	The goal of this study is to investigate whether written exposure therapy (WET) is non-inferior compared to Prolonged Exposure (PE) in the treatment of PTSD in a sample of veterans diagnosed with PTSD. Treatment dropout rates and moderators of treatment outcome will also be examined.
Research Design:	The study is a randomized, non-inferiority design.
Methodology	Men and women veterans diagnosed with PTSD will be randomly assigned to either WET (*n* = 90) or PE (*n* = 90). There will be three VA recruitment sites; Boston, Charleston, SC and Madison, WI. PTSD symptom severity will serve as the primary outcome. Assessments will be conducted by independent evaluators at baseline, 10-, 20-, and 30-week post first treatment session.
Clinical Implications:	If WET is found to be non-inferior to the more time intensive PE treatment then the VA will have evidence to support the use of a brief PTSD treatment, which will assist in addressing the high demand for PTSD clinical services.

2. Aims/Objectives

The proposed study will examine the extent to which WET is non-inferior in reducing PTSD symptom severity among veterans with PTSD relative to the widely used but more time intensive, PE.

We propose the following aims and hypotheses:

Aim 1: Determine if WET is non-inferior relative to PE in terms of PTSD symptom severity.

> **Hypothesis 1a.** WET will be non-inferior to PE at both 10- and 20-weeks after initiating treatment. PTSD symptom severity will be assessed using the Clinician Administered PTSD Scale for DSM-5.
>
> **Hypothesis 1b.** Non-inferiority will be maintained 30 weeks after initiating treatment.

Aim 2. Determine if WET has better treatment retention than PE.

> **Hypothesis 2a.** WET will have significant fewer treatment dropouts compared with the first 5 sessions of PE.

Aim 3: We will explore potential moderators of treatment effects for both WET and PE. Given that prior studies of PTSD treatment moderators have shown mixed results, this aim is exploratory. Our exploratory analyses will include variables that have been tested in other studies (e.g., age, sex, combat era, pre-treatment depression, social support, and estimated IQ).

Aim 4: Functioning will be examined as a secondary outcome.

Hypothesis: We expect that participants assigned to both PE and WET will display significant improvements in functioning as measures by the WHOQOL-BREF, however, we do not expect to find between condition differences.

3. Background Information

PTSD is a highly prevalent condition for which veterans frequently seek treatment in the VA healthcare system (Fulton et al., 2015). Several evidence-based psychotherapies are available, with Prolonged Exposure (PE; Foa et al., 2007) and Cognitive Processing Therapy (CPT; Resick et al., 2007) having the strongest evidence (Cusack et al., 2016). VA has devoted considerable resources to ensure that its mental healthcare providers are trained in these two gold standard PTSD treatments (Karlin et al., 2010). Unfortunately, implementation data indicate that trained VA providers are not consistently using these treatments, citing high clinic demands in combination with limited staff resources as a barrier (Finley et al., 2015; Watts et al., 2014). Moreover, many veterans are either unwilling or unable to engage in these treatments, with attrition as high as 50% in some clinics and studies (Kehle-Forbes et al., 2016; Steenkamp et al., 2015). These circumstances suggest that there is a critical need to identify alternative evidence-based PTSD treatments that are brief, well-tolerated, and do not place heavy burdens upon clinicians and veteran patients alike.

4. Rationale and Purpose

Written Exposure Therapy (WET) is a promising alternative that fulfills these requirements. WET is brief (i.e., 5 sessions with no between session assignments) and is the result of careful, systematic research on the components necessary for successful PTSD treatment. Prior studies on WET have demonstrated its efficacy in reducing PTSD symptoms, with extremely low attrition among those who received the treatment (e.g., less than 10%). Although the accumulated evidence for WET is sufficiently strong that it is now included as a recommended PTSD treatment in the VA/DoD Clinical Practice Guidelines for managing PTSD (2017), there have been no randomized clinical trials (RCTs) of WET focusing solely on veterans. Such a study is crucial as PE and CPT are not as effective with veterans as they are with non-veteran trauma survivors and dropout rates tend to be higher with veterans as well (Steenkamp et al., 2015). Before WET is used throughout the VA to treat veterans with PTSD, it is necessary to conduct a rigorous RCT on WET with a veteran sample to demonstrate the efficacy of WET with veterans. We are directly comparing WET with Prolonged Exposure, to investigate if WET is just as effective as a greater time and resource intensive, exposure-based approach.

5. Relevance to Veterans Health

PTSD is a prevalent condition for which veterans frequently seek treatment in the VA healthcare system. There are a number of first-line PTSD treatment approaches available, such as Prolonged Exposure and Cognitive Processing Therapy. However, the efficacy rates of these treatments is not as high as what has been observed with civilian populations (e.g., Hoge, 2016; Steenkamp et

al., 2015) and approximately 36% of individuals drop out of these treatments prematurely (Imel et al., 2013). In addition to these efficacy and treatment dropout concerns, implementation barriers have been noted among VA mental health providers (e.g., Finley et al., 2015), with clinical care demands in combination with limited staff resources cited as a barrier to implementation. Taken together, these issues underscore the need to identify alternative treatment approaches that address the barriers cited by both patients and providers. Written Exposure Therapy (WET) is one potential alternative treatment approach that addresses these barriers. WET is a five session treatment that has demonstrated efficacy and is associated with low treatment dropout rates (e.g., 5-10%). If WET is found to be non-inferior relative to the more time intensive Prolonged Exposure in the treatment of veterans with PTSD, then VA would be able to recommend its use for the veteran population.

6. Study Design

The proposed study will use a non-inferiority design to examine whether WET is non-inferior to Prolonged Exposure (PE), a first-line treatment for PTSD that is frequently used by VA treatment providers and is more time intensive.

The study will take place at three sites: VA Boston Healthcare System (VABHS), which has two PTSD clinic (PTC) clinics (Jamaica Plain and Brockton campuses), Ralph H Johnson (RHJ) VAMC PTC clinic, in Charleston, South Carolina, and William S. Middleton Memorial Veterans Hospital, Madison, WI. Veterans will be randomly assigned to either WET (*n* = 90) or PE (*n* = 90). Assessments will be conducted at baseline, and 10-, 20-, and 30- weeks post first treatment session. PTSD symptom severity, acquired through the use of a clinician-administered structured interview, will serve as the primary outcome variable.

Randomization and Blinding

After eligibility is determined, the project statistician, who is not involved in evaluations, will randomize participants using a computerized block (gender) randomization procedure with a 1:1 allocation ratio for WET and PE conditions. The project coordinator, who will be responsible for final determination of study eligibility, will be blinded to the randomization sequence. Participants will be unaware of study hypotheses and will be instructed not to reveal their randomization status to the IEs prior to each assessment. To further protect blinding, IEs will be located separately from the therapists, and a new rater will be assigned in the event of an unintentional unblinding.

Treatment Conditions and Delivery

WET and PE will be delivered using structured treatment manuals to ensure treatment fidelity. Each treatment session will be recorded to permit close supervision and assessment of treatment fidelity and integrity by an independent rater. Therapists will be licensed mental health providers from the two recruitment sites. We anticipate selecting 4-6 study therapists at each recruitment site.

When conducting a RCT that compares two treatments, one must carefully consider therapist effects. Investigators must choose between nesting therapists within a specific form of therapy

(e.g., a given therapist always conducts PE) or counterbalancing therapists across both forms of treatment (e.g., a given therapist runs both WET and PE). Although counterbalancing can remove therapist effects by equating them across conditions, one runs the risk of diluting both treatment conditions if therapists become confused and mix elements across treatments. On the other hand, nesting therapists within condition allows them to specialize in one treatment. If therapists differ widely with respect to skill and/or enthusiasm for one particular treatment, this choice can confound therapists with condition.

In this proposed study, we elected to counterbalance therapists within condition for two reasons. First, we have no reason to suspect that study therapists will have particular enthusiasm for either treatment, as they have not been involved in the development of this project and therapists at both sites have been using both PE and WET in the clinics. Second, therapists will be equivalent with respect to skill level, experience with veterans, and other factors that potentially could be confounds.

We will conduct guided interviews with approximately 8 of the therapists who delivered PE and written exposure therapy to veteran participants in the study. The interviews will be conducted to better understand their perception of written exposure therapy and how it compares with more time intensive evidence-based PTSD treatment, Prolonged Exposure, that is routinely used in the VA system. This information will be helpful in understanding facilitators and barriers to using written exposure therapy, as well as factors that may affect when providers would use the treatment over other available treatments.

Qualitative interviews with key stakeholders are an ideal method to collect nuanced, comprehensive information about PTSD treatment from a relatively small sample. Qualitative data from providers with firsthand knowledge about the use of given treatments at their facility, as well as the potential fit of more versus less intensive treatment approaches, provide an ideal source for meeting the proposed goals of identifying facilitators and barriers for scale-up of WET.

All study activities will be conducted at VABHS, but the sample of therapists will be drawn from our study recruitment sites at the Charleston and Madison VA medical centers. Clinicians at these VA sites will be interviewed via MicroSoft Teams using audio only by VABHS study staff. No names will be used in the interviews.

This is a retrospective study using exclusively qualitative methods. We will ask providers to take part in a one-time interview lasting up to 45 minutes. No interventions will be implemented, nor will providers be randomized in any way. We anticipate enrolling up to 8 clinicians across both sites.

Process:

1. Study staff will send up to three recruitment emails to the clinicians who provided treatment for the study. The email will describe the interview opportunity and offer recipients a chance to opt-out of receiving follow-up emails or phone calls.
2. After 3 emails, if the provider has neither opted-out of recruitment or responded to indicate their interest, no further contact will be made.
3. If the provider indicates interest, the study will be described. If the provider agrees to take part, a time for the interview will be arranged at their convenience.

4. The prospective agreement will be emailed to the participant in advance of the scheduled interview. (see attached prospective agreement).

Interviews: Interviews will be scheduled to accommodate the providers schedule and, when possible, scheduled during a clinical cancelation to reduce burden. All interviews will be guided by a semi-structured interview guide (see attached). The questions are intended to elicit information from the stakeholders' own experiences. All interviews will be conducted by Dr. Thompson-Hollands or another trained and qualified study team member. Interviews will be audiotaped and transcribed verbatim. Interviews will last up to 45 minutes, and there will be no further follow up with providers after that time. Providers will not be paid for their participation, as they are all VA employees.

Audio recordings will be stored on the PI's dedicated research drive. Transcription will be conducted by the VA Centralized Transcription Services Program (CTSP). CTSP is a VA-based service that employs professional transcriptionists (VA employees) for use across various research projects. Transcriptionists will be given electronic access to one specific folder on the PI's research drive by IRM (the folder containing the audio recordings). They will not have access to other folders within the research drive. The PI will coordinate with IRM to remove the transcriptionists' access following the end of transcription.

Statistical Analysis Plan

Power analyses are not relevant for qualitative studies, as the goal is to conduct a sufficient number of interviews to reach thematic saturation. We expect to reach saturation with the proposed sample size, but we will recruit more interviewees if our analyses do not yield thematic saturation.

We have elected to use a rapid content analysis approach (Hamilton, 2020) to identify key findings that address barriers and facilitators to the use of WET and PE. Rapid content analysis allows data analysis to occur simultaneously with data collection, providing a streamlined pathway for data reduction. Rapid content analysis will be conducted by coders (Dr. Thompson-Hollands and other trained study staff). The coders will use transcript summary templates and matrices to organize and distill key themes. Matrices allow for the identification of systematic similarities and differences across interviews, facilitating the efficient synthesis of findings. Separate matrices will be developed for each site, to facilitate comparisons. As additional interviews are conducted and analyzed, cross-cutting themes are identified. Our analytic approach will incorporate both inductive and deductive elements, ensuring that we evaluate initial constructs of interest and assumptions while also allowing for the emergence of new and unexpected themes.

Ethical Issues

a. Risks

There is a potential risk of loss of confidentiality for providers. While we will not be asking about sensitive personal information, providers may nevertheless describe opinions that could be perceived as critical regarding a given treatment. All data will be coded with a study ID number rather than the providers name, and transcripts will have identifying information removed (e.g., any proper names used by the provider will be replaced with a label indicating the role of that person,

such as [*the veteran*] or [*my coworker*]; the name of the facility/clinic will likewise be replaced by a label such as [*this facility*] or [*this clinic*]).

b. Potential Benefits

No anticipated direct benefits to providers.

1.

c. Analysis of Risks in Relation to Benefits

The risk of loss of confidentiality is low, and is balanced by the potential value of the information to be gathered. Any individual provider may choose not to share opinions or experiences that they feel are too sensitive to disclose, and they will be permitted to decline to answer any question at their own discretion.

d. Stopping Rules

A provider may always withdraw their participation at any time..

7. Study Subject Selection

a. Sample Description

Men and women veterans presenting to VA for mental health treatment services.

2.

b. Subject Inclusion Criteria

a current DSM-5 diagnosis of PTSD (assessed with the Clinician Administered PTSD Scale for DSM-5; CAPS-5),
veteran status
if taking psychotropic medication, on a stable dose for at least 30 days prior to study entry

c. Subject Exclusion Criteria

current engagement psychosocial treatment for PTSD,
current diagnosis of severe substance use disorder (mild to moderate severity will not be excluded; determined with SCID),
current psychosis or unstable bipolar disorder diagnosis (determined with MINI clinician-administered interview),
high suicidal risk (i.e., intent with a plan; assessed with the SITBI),
significant cognitive impairment (assessed with clinical judgement).

d. Recruitment

The primary recruitment strategy will be referrals by mental health providers in the PTC. In addition, we will notify additional mental health clinics about our study and seek referrals from these clinics as well (e.g., General Mental Health, Substance use clinics, Center for Returning Veterans, Behavioral Medicine). Given the study is now being conducted fully remotely due to

COVID-19 pandemic, we will broaden our recruitment to all VA's within the state of MA. For instance, we will recruit from CBOCS in the state (e.g., Lowell, Worcester) and reach out to other VA medical centers in the state for referrals (e.g., Bedford VA, Northampton VA). In addition to referrals from providers within VA medical system, we will post flyers throughout the VA medical centers that will describe the study and direct interested veterans to contact study staff for additional information. We will also announce the study on various social media pages, such as "Massachusetts Women Veterans" and "New England Center and Home for Veterans". The study will track the source of recruitment for each participant in order to continue to evaluate and maximize recruitment strategies throughout the study.

Initial Enrollment and Screening Appointment. Consent and screening will occur during the initial appointment. The study will be explained and the potential participant will read the informed consent document (ICD). Risks and benefits will be discussed and an opportunity to ask questions will be provided. The advising staff member will ensure the participant understands the research prior to signing the ICD, and the participant will be provided with a copy so that they have it as a record and can to discuss the research with family and friends, if they wish. In some cases, informed consent will be conducted remotely rather than face to face appointment. In those situations, the informed consent will be mailed to the participant along with an addressed stamped envelope. A videoconference (VVC) session will be scheduled with the participant during which the study team member reviews the ICF with the participant. If the participant agrees to sign the ICF, they will hold up the signed ICF page to the computer camera so the study team member can take a screen shot of the signed ICF. The screen shot will be printed and saved as documentation of the signed ICF. The participant will be asked to mail the signed ICF back to the study team. If the original signed ICF is received, it will be saved along with the printed screen shot picture of the signed ICF.

After informed consent, eligibility screening will be conducted by an independent evaluator (IE) using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Mini International Neuropsychiatric Interview (MINI) to be administered via a phone interview. We will utilize a centralized telephone assessment using IEs housed at VABHS and supervised by Dr. Brian Marx. IEs, all masters or doctoral-level in clinical psychology or a related field, will be hired to conduct interviews. The training of IEs in administering the CAPS-5 and MINI will be standardized according to assessment training procedure established by Dr. Marx (e.g., Sloan et al., 2016; Schnurr et al., 2015). Specifically, IEs engage in four stages of training, including relevant readings, didactic instruction with experts, mock interviews, and co-rating exercises with previously taped assessments. Following training, IEs engage in bi-monthly calibration exercises. The IE will be informed of any drift in scoring (i.e., failure to match diagnoses or a discrepancy in total score with the trainers) so as to correct this going forward. All interviews will be digitally recorded. The telephone assessments will facilitate completeness by enhancing the convenience for participants, who will not have to travel for assessment sessions. Dr. Marx has successfully used this procedure in several other studies, including VA Cooperative Study 591 in which assessments are conducted for a total of 18 VA sites located across the country and in different time zones

(Schnurr et al., 2015). The psychometric quality and acceptability to research participants of psychiatric phone interviews are now well-established in both Veteran (Aziz & Kenford, 2004; Magruder et al., 2005; Schnurr et al., 2002) and non-Veteran (e.g., Rohde et al., 1997; Sartor et al., 2012; Shalev et al., 2012) samples. Magruder et al. (2005), using the CAPS with a sample of Veterans seeking VA primary care, found 100% agreement across in-person and telephone interviews. In fact, all of these studies except Rhode et al. specifically focused on PTSD and used the CAPS; Rohde et al. (1997) found that the inter-rater reliability of phone interviews was excellent (kappa = .96 for major depressive disorder and .87 for anxiety disorders). In summary, the phone interviews will provide a valid method of assessing PTSD yet be considerably more cost-effective and more convenient for participants than in-person interviews.

Assessment Schedule. Participants will be assessed by an IE at baseline, 10-, 20- and 30-weeks post first treatment session. This study has a challenge of two treatments that possess substantially different number of sessions (e.g., 5 vs 8 to 15). The use of post-treatment assessment would be problematic given that participants in the two treatment conditions would be completing treatment at substantially different time from baseline assessment, with time to post-treatment being significantly greater in the PE condition than the WET condition. This is problematic as differences in outcome could be attributable to time since baseline assessment rather than treatment differences. Thus, in order to assure that time does not serve as a confound, assessments in this study will occur at equal intervals from baseline for both treatment conditions. Although we would expect that the majority of PE participants would complete treatment by the 10 week assessment period, it is well-documented that for CPT and PE the time to complete treatment varies substantially across participants, even when the treatment protocol is to attend twice weekly sessions (Gutner et al., 2016). In our prior study we requested participants attend twice weekly sessions for CPT but even with this system in place only 65% of the CPT participants completed treatment in 12 weeks and only one participant out of 63 completed treatment in 6 weeks (see Sloan, Marx, & Lee, 2018 for a discussion of this issue).

Participants in both treatment conditions will be considered a “treatment drop out” if they do not attend all treatment sessions. Consistent with the intent-to-treat approach, any participant who drops out will be asked to complete all assessments and all participants who are randomized will be included in data analyses for Study Aims 1 and 3. Treatment expectancy, credibility and satisfaction will be assessed to ensure that acceptability and feasibility of WET continues to be high with the veteran sample

8. Data Collection/ Study Measures

Assessment Measures

Assessors: Assessors will be masked to treatment assignment of participants. Assessors are located at the JP campus of VA Boston. Participants will have the option of conducting assessment sessions in person at the JP campus or via telephone. For participants opting to conduct assessments via telephone, self-report measures will be mailed to them in advance of the clinician-administered assessment, and participants will be asked to return completed self-report

measures within two weeks in a self-addressed stamped envelope that will be provided to them. Assessments conducted for the other recruitment sites in the study (e.g., Madison, WI and Charleston, SC) will all be conducted via telephone with self-report measures collected at the recruitment sites.

Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015): The SCID-5 includes questions assessing each of the DSM-5 adult disorders (Spitzer, et al., 1994). Each disorder is coded as present, not present, or probable, based on structured questions that map onto the DSM-IV criteria. Additionally, each diagnosis will be given a Clinical Severity Rating (CSR) of 0 to 8, where a rating of 4 or higher represents clinical levels of interference or distress. Individuals receiving a CSR of 4 or higher for substance dependence disorders or bipolar disorder or reporting any psychotic symptoms will be excluded.

Structured Clinical Interview for DSM-5 Personality Disorders, Borderline module only (SCID-5-PD; First, Williams, Benjamin, & Spitzer, 2016). The SCID-5-PD is a semi-structured diagnostic interview assessing DSM-5 personality disorders using the same coding strategy as described above for the SCID-5. Clinicians will only administer the Borderline Personality Disorder (BPD) section of the SCID-5-PD at each assessment occasion to measure the presence of BPD diagnoses or traits at baseline assessment.

Frequency and quantity of alcohol and substance use will be assessed using clinician-administered measures adapted from the PhenX Toolkit (version June 4, 2019, Ver 26.0). These measures were derived from reliable and valid measures of alcohol and substance use and selected based on scientific community consensus (Hamilton et al., 2011). Specifically, the **Alcohol – 30-Day Quantity and Frequency** is a 2-item measure that assesses the quantity and frequency of alcohol consumption during the past 30 days. The **Substance Use Frequency** measures assess the use of ten categories of substances (including prescription drug misuse) over the past 30 days. This scale also includes an item assessing average quantity of cannabis use episodes per day in the past 30 days. All three of these measures will be administered by clinicians at each assessment occasion in order to examine changes in alcohol and substance use during treatment.

The Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013a). The CAPS-5 is a structured diagnostic interview and the gold standard for assessing the DSM-5 symptoms of PTSD (American Psychiatric Association, 2013). The scale also assesses social and occupational functioning, dissociation symptoms, and the validity of symptom reports. The CAPS-5 uses a single 5-point ordinal rating scale to measure symptom severity. Symptom severity ratings combine information about symptom frequency and intensity obtained by the interviewer. Psychometric properties indicate high criterion and construct validity and high agreement with a self-report measure of PTSD (Weathers et al., 2018). The CAPS-5 requires approximately 40 minutes to administer. Participants' total CAPS-5 severity scores will serve as the primary outcome of interest.

Life Events Checklist-5 (LEC-5). The LEC-5 (Weathers, Blake, Schnurr, Kaloupek, Marx, & Keane, 2013) will be used to determine the presence of a traumatic life event(s). The LEC-5 includes the same list of 16 different potentially traumatic events (PTE) from the original LEC and is designed to facilitate PTSD diagnosis (Weathers et al., 2013). For each PTE, respondents rate their

experience of that event on a 6-point nominal scale. There are no published data on the psychometric properties of the LEC-5, but is nearly identical to the original LEC, which has high internal consistency and test-retest reliability (Weathers et al., 2013). The worst traumatic event identified at the initial assessment is recorded and used for all subsequent administrations of the CAPS-5. The LEC-5 requires approximately 15 minutes to complete.

The **World Health Organization Quality of Life BREF** (WHOQOL-BREF; WHO, 1998) instrument comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment. The WHOQOL-BREF is a shorter version of the original instrument that is more convenient for use in large research studies or clinical trials. This measure requires 5-10 minutes to complete. It is included in this study to examine quality of life improvement as a secondary outcome measure.

The **Personality Inventory for DSM-5 – Brief Form** (PID-5-BF; American Psychological Association, 2013) is a 25-item self-report measure that assesses five personality trait domains associated with personality dysfunction: negative affect, detachment, antagonism, disinhibition, and psychoticism. The PID-5-BF will be administered at each assessment occasion to measure changes in maladaptive personality dimensions as a result of treatment.

Multidimensional Scale of Perceived Social Support (MSPPS; Zimet, Dahlem, Zimet & Farley, 1988) is a 12 item self-report measure of social support. Social support has been found to moderate outcome following a traumatic event. This measure will be included at baseline assessment to examine if social support moderates treatment outcome. In addition, the MSPPS will be administered at each assessment occasion to measure changes in perceived social support during treatment.

Test of Premorbid Functioning (TOPF) is a premorbid estimate of intelligence that takes 5-10 minutes to administer and requires participants to read a list of up to 70 words. This measure will be administered at baseline. In our prior non-inferiority study we found estimated IQ served as a moderator for CPT treatment outcome (with higher IQ predicting better outcome) but estimated IQ did not serve as a moderator for WET (Marx et al., 2017).

Peritraumatic Dissociative Experiences Questionnaire (PDEQ; Mamar et al., 1994) is a 10 item self-report measure of dissociative experiences during and immediately following a traumatic event. We will examine whether PDEQ moderates treatment outcome. This measure will be completed at each assessment occasion.

Posttraumatic Cognitions Inventory (PTCI-9; Wells et al., 2017) is a 9-item self report measure indexing cognitions following a traumatic event, such as self-blame and negative world cognitions. This measure will be completed at each asssessment occasion to examine changes in posttraumatic cognitions as a result of treatment.

The **Openness to Sharing Questionnaire** (OSQ) is a 5-item self-report measure to assess the amount, depth, extent, detail, and difficulty of past disclosure related to a traumatic event. The first two items assess the respondent's amount and depth of disclosure (e.g., "How many times have you talked about this event?") and require a numerical response. The last three items (e.g.,

"When you talk about this event, how much detail do you include?) are rated on a standardized 7-point Likert scale. The measure is administered at baseline and all subsequent assessment timepoints; however, the questions at subsequent timepoints have been modified to explicitly assess disclosure outside of therapy or assessment sessions. The measure was developed by Bedard-Gilligan and colleagues (2012); however, psychometric properties are not published. This measure will be administered at each assessment occasion.

The **Family Involvement Questionnaire** (FIQ) is a self-report measure designed to assess preferences for and beliefs about interpersonal involvement in mental health treatment. The baseline version of the questionnaire includes six items, and the version for subsequent assessment points includes three items. Questions regarding openness/willingness for family involvement are rated on a 10-point Likert scale ranging from 1 (*Completely closed/unwilling*) to 10 (*Completely open/willing*). In a "check all that apply" format, participants are also asked to indicate who they would include in treatment, goals for interpersonal involvement, and concerns about interpersonal involvement. This measure will be administered at each assessment occasion.

The **Insomnia Severity Index** (ISI) is a brief (7 item) instrument that was designed to assess the severity of both nighttime and daytime components of insomnia. It is increasingly used as a metric of treatment response in clinical research and will be used in the current study to assess changes in insomnia symptoms as a function of treatment. This measure will be administered at each assessment occasion.

Safety Monitoring Measures

The PTSD Checklist for DSM-5 (PCL-5; Weathers, Litz, et al., 2013) will be administered at each assessment occasion, including baseline, and the beginning of every treatment session to monitor for symptom worsening, defined as an increase from the initial assessment of at least 10 points that is sustained for at least three consecutive treatment sessions (Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002). The PCL-5 is completed in reference to the identified criterion A event established at the baseline assessment. This is a psychometrically strong measure that is sensitive to change (Weathers et al., 2013; Bovin et al., 2016) and requires no more than 5-10 minutes to complete.

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) is a 21-item self-report measure assessing current depressive symptoms and has well-established reliability and validity (Dozois et al., 1998). The BDI-II will be administered at each assessment occasion, including baseline, and the beginning of every treatment session to monitor exacerbation of depression symptoms associated with treatment, as well as to assess any changes in suicidal ideation. This measure requires no more than 5-10 minutes to complete.

The Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock et al., 2007) is a structured clinical interview that assesses the presence, frequency, and characteristics of a wide range of self-injurious thoughts and behaviors, including suicidal ideation, suicide plans, suicide gestures,

suicide attempts, and nonsuicidal self-injury. The SITBI has demonstrated excellent psychometric properties in multiple samples, including strong interrater reliability, and test–retest reliability over a 6-month period. Moreover, concurrent validity was demonstrated via strong correspondence between the SITBI and other measures of suicidal ideation, suicide attempt, and nonsuicidal self-injury. This interview takes approximately 20 minutes to administer.

Therapy Process Measures

The **Treatment Expectancy Questionnaire (TEQ**) is a widely-used measure of treatment credibility (Borkovec & Nau, 1972). This measure is administered at the conclusion of the first treatment session (after the treatment rationale and specific procedures are explained). The TEQ asks the individual to rate on a 10-point scale how logical the treatment seems, the participant's confidence in undergoing the treatment and recommending it to others, and their expectations for the treatment's success. We anticipate treatment expectancy to be high for both treatments, with no significant between condition effects. The measure requires approximately 5 minutes to complete.

The **Client Satisfaction Questionnaire** (CSQ; Larsen, Attkisson, Hargreaves, & Nguyen, 1979), a measure of participant satisfaction with treatment, is administered at the last treatment session. This 8-item measure assesses satisfaction with treatment and has demonstrated concurrent validity. We expect client satisfaction ratings to be high for both conditions. The measure requires approximately 5 minutes to complete.

The therapeutic alliance will be assessed using the 12-item therapist and client versions of the **Working Alliance Inventory** (WAI; Horvath & Greenberg, 1989; Tracey & Kokotovic, 1989). In addition to the total score, the WAI has three subscales: Goals, which reflects the agreement between therapist and patient on overall goals of treatment; Tasks, which reflects the agreement on the appropriate tasks on which to focus (to achieve goals); and Bond, the quality of the affective relationship between the therapist and the patient. The WIA will be included to examine therapeutic alliance as a potential moderator of treatment outcome, as well as to examine potential treatment condition differences. The WAI therapist version will be completed by the study therapists for each participant they treat, and the client version will be completed by each participant enrolled in the RCT at the end of treatment.

In the PE condition, clinicians will complete Homework Review Forms (HRFs) specific to PE session content to assess homework compliance. There is no homework in the WET condition.

Table of Assessment Schedule

Measure	Baseline	First Tx Session	Weekly During Tx	Last Tx Session	10-week	20-week	30-week
LEC-5	X						
TOPF	X						
SCID-5	X						
SCID-5-PD BPD only	X						
CAPS-5	X				X	X	X
SITBI	X		if needed		X	X	X
Alcohol 30-day	X				X	X	X
Substance Use Frequency	X				X	X	X
PID-5-BF	X				X	X	X
MSPPS	X				X	X	X
WHOQOL-BREF	X				X	X	X
PDEQ	X				X	X	X
OSQ	X				X	X	X
FIQ	X				X	X	X
ISI	X				X	X	X
TEQ		X					
PCL-5	X		X		X	X	X
BDI	X		X		X	X	X
PTCI-9	X		X		X	X	X
CSQ				X			
WAI				X			

INTERVENTIONS

Written Exposure Therapy (WET). The WET condition consists of 5 weekly treatment sessions, with the first session lasting 1 hour and each subsequent session lasting approximately 40 minutes. The first session consists of education about common trauma reactions and the WET rationale. The participant is then given general instructions for completing the trauma narratives and specific instructions for completing the first 30-minute narrative writing session. All WET sessions begin with the therapist reading the specific writing instructions, clarifying any questions the person has, and leaving the instructions with the participant during the 30-minute writing session. Writing instructions begin with a focus on the details of the trauma and then shift to the meaning of the trauma event. After 30 minutes of writing, the therapist stops the writing and conducts a 5-10 minute check-in regarding how the writing session went for the participant. In

response to VA clinician feedback indicating that veterans sometimes avoid writing about traumatic event in the first and sometimes second writing session, we will permit up to an additional two sessions to course correct in such situations. Specifically, if the veteran does not follow writing instructions in the first and/or second session, these sessions should be repeated to allow for necessary level of exposure to the traumatic event. However, additional sessions will not be provided even if patients continue to partially or fully avoid (i.e. do not follow writing instructions).

Prolonged Exposure (PE). PE is designed to be delivered in weekly 90 minute sessions over 8-15 sessions. The sessions are flexible according to the response of the patient. Stopping before 15 sessions should occur because (1) the patient has a stable score (i.e., at least two consecutive sessions) below the probable PTSD diagnosis cut score of 33 (Bovin et al., 2016) and (2) the clinician and patient agree that substantial clinical gain has occurred and no additional sessions are needed. Up to 15 sessions are provided if the score remains above the probable PTSD cut score. Treatment response is determined based on PCL-5 measure administered at each treatment session. The conceptual foundation of PE is based upon emotional processing theory (Foa & Kozak, 1986). The PE model proposes that chronic PTSD develops when there is a failure to process the traumatic memory because of extensive avoidance of trauma reminders. PE mimics the natural fear modification process. During PE, patients are encouraged to confront (or expose themselves) to safe but anxiety-eliciting situations, in both imagination and in vivo, with the goal of overcoming excessive fear and anxiety. Thus, PE includes the following core components: (a) psychoeducation about the common reactions to traumatic events and presentation of the rationale for PE, (b) repeated *in vivo* exposure to situations or objects being avoided due to distress and anxiety, and (c) repeated, prolonged imaginal exposure to memories of the event(s). The focus of treatment initially lies in educating the patient about the PTSD diagnosis, gathering of detailed information about the traumatic event, and providing a sound rationale for PE. Patients' understanding of the rationale for PE is important because recognition of the importance of breaking their patterns of avoidance is a key goal. Patients, together with their therapist develop a hierarchy of feared but safe trauma related situations and objects and are instructed to gradually approach these situations between sessions (*in vivo* exposure exercises). The structure of gradual exposure is fairly consistent with traditional exposure-based interventions such that anxiety-provoking stimuli (e.g., physical or verbal cues) are presented gradually. The 3rd component of treatment is imaginal exposure. During this phase, therapists assist patients in repeatedly recounting their traumatic event in detail, including their thoughts, feelings, and reactions that occurred during the event(s). Imaginal exposure is conducted during sessions and is audiotaped for patients to listen to at home between sessions.

9. Statistical Analysis Plan

Data will be analyzed in SPSS and MPlus software, which licenses are obtained by the Behavioral Science Division of the National Center for PTSD at VA Boston. The software is stored on a password protected server that is behind the VA firewall.

The equivalence of the treatment conditions will first be assessed according to key baseline variables (demographics and outcome variables) using t-tests, nonparametric equivalence, or Chi-square tests, depending on the type (continuous or dichotomous) and distribution (normal or

non-normal) of the data. Any variables that differ among groups will be used as covariates in the final analyses.

We anticipate some participant attrition during the trial. If a subject drops out of the study for any reason, we will vigorously pursue follow-up to minimize missing data. Yet, some data will inevitably be missing. Missing data will be handled in all analyses using direct maximum likelihood or multiple imputation techniques within MPlus 8.0 (Muthen & Muthen, 2018) under a missing at random (MAR) assumption. Modern missing data techniques such as direct ML increase statistical power and provide more accurate estimates of model parameters and standard errors, and are the recommended intent-to-treat approach for clinical trials (Enders, 2010). The primary analyses in this study will be performed on the intent-to-treat population that includes all patients randomized to a condition. Supplementary analyses will also be conducted examining outcomes in the subset of participants who complete a full course of treatment in each condition. In order to better understand the potential reproducibility of our findings, our conclusions from all analyses will be based on both the statistical significance of parameters and the magnitude of associated effect sizes.

Aim 1. Our primary hypothesis that WET will be non-inferior to PE will be evaluated using similar analytic procedures conducted in our previous non-inferiority trial of WET (Sloan et al., 2018). Specifically, the non-inferiority margin of 10 will be used for comparing the two conditions on the primary PTSD outcome of CAPS-5 scores at the 10 week, 20 week, and 30 week assessments. The mean difference score between conditions will be calculated at each follow-up and the hypothesis of non-inferiority will be evaluated based on whether the entire 95% confidence interval of the mean difference is less than the margin of 10 points. We will then supplement this analysis by calculating additional effect sizes to characterize between condition differences in PTSD outcomes. Specifically, we will calculate Cohen's *d* (with 95% CI) for the mean difference in CAPS-5 scores at each time point and will calculate odds ratios (with 95% CI) for the proportion of participants who no longer meet diagnostic criteria for PTSD based on the CAPS-5 at each assessment period.

Aim 2. The comparison of treatment dropout in WET vs PE will be examined by calculating odds ratio effect sizes (with 95% confidence interval) for the proportion of participants who do not complete a full course of treatment (5 sessions) in WET and those who drop out of PE by session 5. The statistical significance of the between-group differences in dropout rates will then be evaluated using a chi-square difference test.

Aim 3. The exploratory analyses of moderators of WET and PE will be conducted using latent growth curve modeling conducted within Mplus. As the focus is not primarily on the nature of the growth trajectory, the intercept of the LGM will be centered on the baseline CAPS-5 assessment (i.e., first slope loading fixed to 0), the slope loading for the final time point will be fixed at 1.0, and loadings for all intermediate assessments will be freely estimated. The mean and variance of the slope factor in this model will reflect the total change in and individual differences in change

in PTSD symptoms across the full assessment period. The hypothesized moderators (age, sex, combat era, social support, time since index trauma event, and estimated IQ) will then be specified as predictors of the slope factor in separate models. These LGM will be conducted for the full sample first, and will then be conducted separately within each treatment condition to examine whether moderators of treatment outcome are consistent across WET and PE. To aid in the interpretation of clinical significance, results from LGM analyses will be converted to effect size metrics within 95% confidence intervals following established procedures (Feingold, 2015). Evaluation of model fit in the LGM models will be examined using fit diagnostics (i.e., standardized residuals) and common fit statistics (i.e., root mean square error of approximation) following the associated cutoff criteria recommended by Hu & Bentler (1999).

We will conduct additional exploratory analyses to evaluate characteristics of patients who require additional WET sessions, as well as characteristics of patients who require more than 12 PE sessions. These analyses will be conducted using logistic regression with dependent variable being more than 12 sessions of PE or more than 5 sessions of WET (conducted separately for each treatment condition). We will include characteristics such as age, time since trauma event, combat era, baseline PTSD symptom severity, baseline depression, baseline social support, baseline estimated IQ.

Aim 4: Follow standard practice for examining secondary outcome measures in a non-inferiority trial (e.g., Thompson-Hollands et al., 2018), we will use hierarchical linear modeling (HLM; Raudenbush & Bryk, 2002) to determine impact of treatment on functional impairment as measured by the WHOQOL-BREF. Analyses will be conducted using an autoregressive covariance matrix at level 1 (within person) and a scaled identity matrix at level 2 (between persons). A between-treatments variable will be included in the analysis, as functional impairment is a secondary outcome and therefore not subject to the same noninferiority analyses. Guidelines from Cohen (1988) will be used to interpret the within- and between-condition effect sizes (*d*).

10. Ethical Issues

e. Risks

Treatment: Some risks are associated with the administration of psychosocial treatment. The primary risk is the evocation of uncomfortable levels of anxiety or other emotions during the treatment sessions. Some participants may find sessions stressful and react to them with anxiety.

Recording: Some participants may feel uncomfortable about the assessment and treatment sessions being recorded. However, this will be a required procedure. The purpose of the recording will be explained, confidentiality will be respected, and both informed consent and authorization for recording will be obtained as per requirements put forth by the Healthcare Information Portability and Accountability Act (HIPAA). Recordings will be marked only by subject identification codes and stored in password protected computer server accessible only to staff directly involved with the project.

Self-Report Measures and Assessor Ratings: No risks are seen associated with these assessment procedures other than discomfort associated with the audio-recording. These will be handled as described above for recording of assessment and therapy sessions.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Consent Procedures

Following the recruitment procedures used in our past clinical treatment studies for PTSD with veterans, we used a variety of recruitment strategies (e.g., posting fliers throughout the medical center, clinic referrals). We will also create a study brochure for clinicians to provide to potential veteran participants. Based on past experiences, we anticipate clinic referrals to be the most effective recruitment strategy. The study announcements and brochure will state that the treatment is part of a research study that is available to qualified veterans. Interested veterans will be instructed to call for further information.

In accordance with HIPAA regulations, written informed consent will be obtained from each veteran after a thorough explanation of procedures by a project staff person and the opportunity for the veteran to ask and receive answers to questions. Veteran participants will be informed of the nature of the investigation, the types of assessments and treatments involved, alternative treatments, and the potential risks involved in participation and will be asked to sign an informed consent statement prior to participating in the proposed study. In addition, the participant will receive an explanation of how information related to their case will be handled including all parties involved, data management, and plans to publish data in group format without identifying information.

Veteran participants will also be informed that confidentiality may be broken under the following circumstances: disclosure of suicidal or homicidal intentions, disclosure of child abuse, disclosure of elder abuse. Confidentiality may be broken in such instances in order for protective measures to be taken.

b. Protection against risk

1. We will carefully screen to identify individuals whose risk for potential adverse outcomes is elevated were they to participate in the proposed research. Such individuals will be excluded from the study. As an example, a person deemed high suicidal risk would be excluded from study participation. These individuals will be followed by study personnel (if they give consent to be followed).

2. Clinical staff will be trained to cope with any anxiety/distress experienced by participants during the assessments and treatment.

3. Careful monitoring of participants during the initial assessment and throughout the study will be conducted by the project staff. Participants will complete the PCL-5 at each assessment and treatment session in order to monitor symptoms (and potential symptom increases). Each participant will see the same clinician for each of their treatment visits and the same assessor for each assessment occasion. Following the clinical trial policy of the VA Boston Healthcare System

(VABHS) all participants will be given an emergency number to call after business hours in case of an emergency. This number will be the psychiatry on call system of the respective VA site.

4. Participants will be instructed to contact study personnel at any time (including during the follow-up period) in the event of worsening of symptoms or relapse. Participants whose clinical condition has substantially deteriorated will be removed from study treatment and appropriate clinical referrals will be made. These veterans will also be followed by study personnel, if they give permission to be followed.

5. Participants failing to benefit from the study treatments will be provided with appropriate clinical referrals. Participants who begin treatment and experience adverse outcomes related to the treatment being received will also be provided with appropriate clinical referrals. The appropriate clinical referrals will be determined by the judgment of clinicians and supervising staff familiar with the specific participant and may include cognitive-behavioral treatment, other psychotherapy, or referral for medication treatment.

6. As in any type of treatment or clinical research program, participants' confidentiality must be carefully guarded and respected. All data with identifying information will be stored in locked files or password-protected computer server. Data being analyzed will be identified by subject codes, and identifying information will be removed. The identity of participants will not be revealed in the presentation or publication of any results from the project. All personnel working on the project will be educated about the importance of strictly respecting participants' rights to confidentiality and will have completed several training courses including proper practice in accordance with HIPAA regulations, protection of human subjects, and computer security.

7. If new information emerges for one or both of the treatments in the study that indicates the treatment is associated with detrimental effects, we will alert participants of this new information and consult with IRB regarding whether or not the study should be stopped given the new information.

f. Potential Benefits

The direct benefit to veterans who enter this study will be to obtain relief from anxiety symptoms, decreased avoidance, decreased disability, and increased quality of life. For many individuals with PTSD the disorder has greatly impeded their social, vocational, and academic functioning among those veterans who are enrolled in college courses. The treatments offered in the study are recommended treatment approaches according to the VA/DoD clinical practice guidelines (2017). Thus, the treatments have strong evidence to support their effectiveness.

More broadly, establishing cost-effective, brief and readily deliverable alternatives to traditional (time intensive) psychotherapy options for veterans with PTSD has broad health and policy implications for the Department of Veteran Affairs given the high prevalence of this debilitating disorder in the veteran population.

3.

g. Analysis of Risks in Relation to Benefits

The risks in the study are low given that the treatments included are first line, recommended PTSD treatments, as outline in the VA/DoD Clinical Practice Guidelines. Moreover, veterans will be receiving high quality PTSD treatment with close supervision monitoring of the therapists, in

combination with greater attention (e.g., calling between sessions or when a session is missed) that is typically possible in routine clinical care. The study anticipates that veterans will reap treatment gain for both treatment conditions in the study. Thus, the potential benefit to the veteran is significant reduction of PTSD symptoms and improvement in quality of life. Overall, the risks to benefit ratio is very favorable.

h. Stopping Rules

A participant may always withdraw their participation at any time.

- A participant will be withdrawn from the study if:
    - They report a substantial increase in PTSD symptoms that is stable for 3 weeks and the participant indicates the increase is the result or likely the result of treatment they are receiving in the study.
    - The participant becomes high risk for suicide and is hospitalized.
    - The participant requires treatment (detox or residential) due to the substance use.
    - The participant becomes verbally or physically aggressive towards research staff.

4.

11. Safety Monitoring Plan

Data and safety monitoring for this study will be provided by the Clinical Science Research & Development (CSR&D) centralized Data Monitoring Committee (DMC). The DMC is provided by CSR&D to ensure independent oversight of the safety and integrity of the project. The DMC is an independent multidisciplinary group, whose members have collectively – through research, education, training, experience, and expertise – the requisite knowledge pertinent to the subject areas to be reviewed. Membership details are available on the CSRD website. The DMC will provide an ongoing independent evaluation of this study focused on safety and feasibility, including participant accrual and retention, adverse events monitoring, and data analyses. Meetings will be held three times per year at which recommendations will be made to the Director of CSR&D for endorsement. These recommendations will range from approval to continue (unconditionally or with conditions to be addressed) to probation or possibly termination, if there are problems with enrollment or safety concerns.

The PI will be responsible for providing these quarterly summaries to the local IRB and CSR&D as part of the annual review process. In addition, the PI will be responsible for executing any recommended changes to DMC and complying with the reporting requirements.

Protocol for Monitoring Adverse Events

Because of the psychiatric nature of the sample to be studied, there is a potential for adverse events to occur. These adverse events include suicidal ideation, homicidal ideation, and an increase in PTSD and depression symptom severity. Although the likelihood of these adverse events occurring in response to PTSD treatment is low (e.g., Foa et al., 2002; Sloan et al., 2018), these adverse events will be closely monitored throughout the study. Apart from these potential adverse events, we do not anticipate the occurrence of any other adverse events related to the treatments to be examined.

There are two reasons suicidal risk will be assessed in the proposed study. The first reason is to determine participant eligibility and the second reason is to ensure the safety and well-being of participants throughout the study. We will assess suicidal risk using the Mini International Neuropsychiatric Interview (MINI) suicide module at each assessment occasion. The MINI suicide module is a clinician administered interview that consists of 9 questions related to suicidal ideation and behaviors, with possible scores ranging from 0 to 53. Low suicide risk is defined as 0-8 points, moderate suicide risk is defined as 9-16 points, and high suicide risk is defined as scoring 17 or greater. We have decided to use this measure because the MINI suicide module is clinician-administered, includes clear guidelines for determining suicide risk, and requires approximately 10 minutes to administer. The MINI demonstrates excellent inter-rater reliability, with kappa values exceeding 0.75 (Lecrubier et al., 1997; Sheehan et al., 1998); and generally good test-retest reliability, with kappa values typically exceeding 0.65 (Lecrubier et al., 1997; Sheehan et al., 1998). Individuals will be excluded from enrolling in our proposed randomized controlled trial if they score 17 or higher (high risk) on the MINI suicide module at the initial assessment. Individuals who are excluded from participating in the clinical trial will be provided with appropriate clinical referrals. The PI will follow up with each of these individuals within one week to make sure they have connected with appropriate clinical care.

To monitor suicide risk throughout the treatment phase, we will administer the BDI-II at each treatment session. If a participant endorses suicidal ideation at any level in response to question #9 (suicidal thoughts or wishes), a licensed psychologist will administer the MINI suicidal module. Participants deemed to be a high risk for suicide on the MINI (i.e., score of 17 or higher) will be removed from the study treatment and appropriate actions will be taken. These actions are described below in the data monitoring section. In addition, if the participant is willing, they will continue to be followed by the PI.

Homicidal risk will be assessed using approach recommended by *VA/DOD Clinical Practice Guideline for Major Depressive Disorder* (2009). At the initial assessment and at the beginning of each treatment session, participants will be directly asked whether they have thoughts of harming anyone. If the participant indicates they do have thoughts of harming someone, then the clinician will ask whether the participant has an active plan or method to harm someone (e.g., weapon in their home) and whom the participant wishes to harm. Further assessment will take place for participants who indicate that they have an active plan or method. Specifically, they will be asked whether they have ever lost control and acted violently and, if so, the severity of reported past violent behavior will be assessed. If a participant indicates that they have thoughts of harming someone and they have an active plan, the participant will be considered potentially high risk and further assessment will be conducted, as described in the section on managing adverse events.

We will monitor for a substantial increase in PTSD symptom severity during the treatment phase using the Posttraumatic Check List for DSM-5 (PCL-5). The PCL-5 is a 20 item self-report measure

of PTSD symptom severity. This measure will be completed at each assessment session and each treatment session. A substantial increase in symptoms is defined as at least 10-point increase in PTSD from the initial assessment and has been sustained for a three-week period (e.g., Foa et al., 2002).

Protocol for Managing Adverse Events

In the event a participant is deemed high suicide and/or homicidal risk, staff will immediately locate the PI or site PI, both of whom are licensed psychologists. The PI or site PI will intervene by a) following up with direct questions about suicidal/homicidal behaviors, b) assess mental status by asking about psychotic symptoms, mood symptoms and drug and alcohol use, c) schedule extra contacts if necessary, emphasizing problem solving, d) help the participant generate short-term objectives, and e) negotiate an action plan. The action plan will be collaboratively generated by the investigator and the participant. The plan will address what actions need to be taken in the succeeding days to solve the problems that precipitated suicidal/homicidal behavior. The plan will also address the use of voluntary and involuntary hospitalization, if necessary. Lastly, in the case of homicidal ideation with explicit intent to harm a named individual, the PI will report the intent to the local police as required legally required to protect the named individual. This procedure will be the same for SI/HI that is uncovered during the course of telephone assessments. That is, the assessor will alert the PI or site PI who will then reach out to the veteran via telephone and take appropriate clinical action.

In addition to these formal assessments, all participants will be given the number of the on-call psychiatry service at the respective VA site and informed that they should call this number after business hours in the event that they are feeling suicidal and/or distressed, or homicidal. This is the local IRB policy for clinical trials conducted at the two VA recruitment sites. During business hours the participants will be instructed to contact the contact the PI (VABHS) or site PI (RHJVA). Should a participant call to indicate suicidal/homicidal risk, then the previously described intervention plan will be followed. Participants will also be informed during the informed consent process that if suicidal and/or homicidal intentions are disclosed confidentiality may be broken in order for protective measures to be taken. The suicidal risk management plan has empirical support for its efficacy (Chiles & Strosahl, 2005) and is the plan that is recommended for use by the American Psychiatric Association. Moreover, the homicidal risk assessment and management plan is recommended by *VA/DoD Clinical Practice Guidelines* (2009).

In the event that a participant experiences an increase in PTSD symptom severity but without suicidal/homicidal risk, the PI or site PI will intervene by asking direct questions about the nature and causes of the distress, conduct a PTSD assessment, and schedule extra contacts (assessments) if deemed necessary. Such individuals will be withdrawn from study treatment from the protocol if they report a substantial increase in the PTSD symptom severity (i.e. at least 10 points higher than their baseline PTSD symptom severity score) that is sustained over a three-week period and the cause of the increase is determined to be related to the study treatment. We have selected

the 10-point increase and 3-week time frame based on Foa, Zoellner et al. (2002) in which they emphasize the importance of using a reliable index score when considering increases (and decreases) in PTSD symptoms. Importantly, Foa and colleagues (2002) have reported that only a minority of participants showed an acute substantial increase in PTSD symptom severity during Prolonged Exposure treatment, and that this acute increase was not associated with an increased risk for dropout or poor treatment outcome. Nevertheless, to protect against risk, we will monitor participants for undue distress reactions and will use a 10-point increase from baseline assessment of PTSD symptom severity that is sustained for 3 weeks as a guide for potentially withdrawing a participant from the study treatment. If a participant is withdrawn from the study treatment, they will be followed by study personnel, if they agree to be followed, to ensure that they have received adequate clinical care. In addition, if they agree, the study will continue to conduct assessments with the participant. In addition, participants who are deemed ineligible to enroll in the trial will be referred to the appropriate VA mental health clinic. The PI or site PI will subsequently contact (within one week) these veterans to make sure that they have not experience any barriers in following through with clinical referrals.

12. Adverse Event/Unanticipated Problems Reporting Plans

Protocol for Reporting Adverse Events

Any study-related unanticipated problem and any type of AE or SAE, will be reported immediately to the PI, who will then report the event to the local IRB per VABHS standard operating procedures. In addition, for SAE's, the PI will submit a SAE form to the local IRB and the DMC within 48 business hours of becoming aware of SAE. Staff will keep a copy of this SAE form on file at the study site. The information to be reported will include the subject number, a description of the event, date of onset, current status, whether or not the treatment was discontinued, the reason why the event is classified as serious, and the PI assessment of the association between the event and the study treatment. Dr. Sloan will provide any significant new information regarding ongoing SAEs promptly (i.e., within 48 business of becoming aware of event) to the DMC. Adverse events not designated as serious will be reported to DMC on a quarterly basis and annually to the respective local IRB.

The other two recruitment sites will follow the same procedures for reporting of adverse events and unanticipated problems, with the addition of also notifying the study PI at VA Boston.

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