Comparative Effectiveness of Two Treatments for Veterans With PTSD

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Department: Mental Health and Behavioral Sciences Service (MHBSS)

Study Title: Comparative Effectiveness of Two Treatments for Veterans with PTSD

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Location of Study:
All assessment and intervention sessions will be conducted at the Veterans Affairs Medical Center in Providence, Rhode Island.

Time Required to Complete the Research:
The project start date is 07/01/2015 and the study will continue until 2019

The study described herein is a multisite study that will take place at the Providence VA Medical Center as well as the Southeast Louisiana Healthcare System in New Orleans, LA. Dr. Sautter is the Director of the Family Mental Health Program and Site-PI in New Orleans. The PVAMC IRB will only oversee activities conducted on site in Providence, RI and the New Orleans site will receive their own IRB approval and oversite. The goal of enrollment is 88 participants at each site.

Purpose

The strong association between posttraumatic stress disorder (PTSD) and interpersonal problems, such as relationship discord (Allen et al., 2010) and social isolation (Lemaire & Graham, 2011), is well documented. Exhibiting behaviors that drive supportive family and friends away while retreating into social isolation, Veterans with PTSD lose opportunities for social processing that could reduce their PTSD symptoms. Consequently, trauma-related isolation often leads to erosion of social and family support, increased PTSD symptoms, and self-destructive behaviors such as suicidality. Indeed, a large-scale Air Force suicide prevention effort implemented from 1990-2002 targeted the reduction of risk factors while increasing protective factors, such as social support and social network, and reported a 33% reduction in suicide risk and decline in suicide rate (Knox et al., 2003; 2010). This shows the potential benefit of systematically targeting protective interpersonal behaviors.

The primary interventions for PTSD at VA facilities, i.e., Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), and trauma-focused CBT, do not directly target the interpersonal problems that prevent Veterans from seeking the relationship experiences that can increase emotional resilience, or focus on increasing emotional engagement and reducing avoidance and isolation (Jakupcak, et al, 2010), so critical for withdrawn, emotionally numb Veterans. Further, relationship problems often prevent Veterans with PTSD from benefitting from more trauma-focused interventions (Price, et al., 2013; Tarrier & Summerfield, 1999), suggesting that treatments targeting interpersonal problems might potentiate the efficacy of these empirically based psychotherapies EBPs. Only a small minority of OIF/OEF Veterans with PTSD referred for trauma-focused psychotherapy actually engage in those treatments (DeViva, 2013; Harpaz-Rotem & Rosenheck, 2011; Maguen et al., 2012; Seal et al., 2010). A more useful strategy might be to allow Veterans to select treatments that target the PTSD problems that they identify during treatment planning (DeViva, 2013). Alternative approaches that provide immediate social reinforcement, like Interpersonal Therapy (IPT), may reduce PTSD symptoms while improving the interpersonal environment that is critical to trauma recovery. In summary, IPT could serve as a useful new tool in the VA PTSD treatment armamentarium.

The association between PTSD and relationship problems led to the development of couple-based PTSD interventions within the VA (e.g., Monson et al., 2012; Sautter et al., 2013), but only a limited number of Veterans with PTSD are appropriate for couple interventions. Logistics may interfere with attendance for both partners, and 30%-40% of returning Veterans are unmarried (Street, et al., 2009), putting these less-connected veterans at risk for social isolation and decreased support. In addition to relationship conflicts, IPT targets social isolation and other types of relationship problems, thus providing the potential to increase social support and relationship satisfaction among a broader range of Veterans

with PTSD.

IPT was recently "rolled out" in VAMCs as a treatment for depression, a frequently comorbid diagnosis with PTSD. Several studies suggest that IPT may also be effective for PTSD (Krupnick et al., 2008; Krupnick, 2010, Bleiberg & Markowitz, 2005; Markowitz et al., in press; Meffert et al., 2014). The aim of the proposed study is to compare IPT for PTSD, a relationship-focused individual treatment, with PE, an evidence-based treatment for PTSD that has been "rolled out" nationally in the VA system. The specific hypotheses to be tested are as follows:

Primary Outcomes:

1) IPT-PTSD will be statistically equivalent to PE in reducing the severity of PTSD symptoms.

2) IPT-PTSD will be superior to PE in improving Interpersonal functioning.

Secondary Outcomes:

3) IPT-PTSD will be significantly more effective than PE in improving social adjustment.

4) IPT-PTSD will be significantly more effective than PE in improving quality of life.

5) (Exploratory) IPT-PTSD will be significantly more effective than PE in reducing suicidal ideation.

Mechanisms of Change (Exploratory):

6) Improvements in interpersonal functioning and perceived social support will mediate improvements in PTSD symptom severity in IPT-PTSD.

1. Background, Significance, and Rationale

PTSD and Interpersonal Functioning

A substantial literature links PTSD and intimate relationship distress and aggression in Veterans (Taft, et al., 2011). Reviewing the psychological sequelae of combat violence, Galovski & Lyons (2004) found the strong association between PTSD and family relationship problems evident across different countries and eras. These studies consistently reveal that Veterans diagnosed with chronic PTSD, versus those exposed to military-related trauma but not diagnosed with PTSD, and their romantic partners report more numerous and severe relationship problems and generally poorer family adjustment (Monson et al., 2009). Several studies indicate that Veterans with PTSD have more marital problems and higher divorce rates than their trauma-exposed counterparts without PTSD (e.g., Jordan et al., 1992). Male Veterans with PTSD, versus those without the disorder, have greater anxiety with regard to intimacy (Riggs et al., 1998), and they are less self-disclosing and emotionally expressive with their partners (Carroll et al., 1985). Further, PTSD has been associated with poorer parenting satisfaction, and there is evidence of greater behavior problems in the children of parents with PTSD (Gewirtz et al., 2010). Findings across settings and study methodologies document that male Veterans with PTSD are more likely to perpetrate psychological and physical aggression against their partners and children than Veterans who do not have PTSD (Carroll et al, 1985; Taft et al., 2011).

Moreover, findings from the National Vietnam Veterans Readjustment Study (Kulka et al., 1990) found that one-third of male Veterans with PTSD exhibited violence, according to their female partners. Taft et al. (2009) found a similar rate of violence among Veterans with PTSD who were seen at a Veterans Administration medical center from 2003- 2008. In a study of Navy recruits (Merrill et al., 2004), PTSD was identified as a risk factor for violence, with an odds ratio of 2.05, compared with recruits without PTSD. Byrne & Riggs (1996) found rates as high as 63% for certain acts of aggression within the past year among Veterans with PTSD.

Studies show links between clusters of PTSD symptoms and specific types of relationship problems. For example, PTSD symptoms of arousal and feeling a lack of control were the most robust predictors of self-reported aggression (Taft et al., 2009). In the only study on spousal abuse specifically in OIF and OEF service members, experiential avoidance was associated with physical aggression perpetration in 49 male National Guard members who returned from deployment to Iraq (Reddy et al., 2011). Numbing and avoidance symptoms have been related to difficulties with intimacy, including sharing and receiving communication about emotions, as well as poorer general relationship satisfaction (Riggs et al., 1998), and with less satisfaction with parenting (Berz et al., 2008). Numbing and avoidance symptoms were also found to be strong predictors of poorer overall interpersonal and social functioning in returning OIF Veterans (Shea et al., 2010). Ruscio et al. (2002) suggest that the inability of Veterans with PTSD to experience and express emotions, and to engage with others, takes a toll on all family relationships.

While the studies cited above provide ample evidence of the association between PTSD and relationship conflicts, far less research has been conducted on the impact of PTSD in other areas of relationship dysfunction, like isolation. These are areas that can be addressed in Interpersonal Psychotherapy (IPT) for PTSD, a relational approach to be tested in the current proposal. In particular, there have been no studies (to our knowledge) aimed at *increasing social interaction and social support among Veterans with PTSD,* even though feelings of detachment and estrangement are symptoms of PTSD, and social withdrawal and isolation are serious problems among Veterans with this disorder (Milliken et al., 2007; Tanielian & Jaycox, 2008). The Interpersonal Theory of Suicide (Van Orden et al., 2010), notes that the most dangerous form of suicidal desire is caused by the simultaneous presence of two interpersonal constructs, one of which is thwarted belongingness. In a study of 185 Veterans (96 women) entering inpatient psychiatric treatment, feeling burdensome to others, interacting with a sense of thwarted belongingness, significantly predicted current suicidal ideation (Monteith et al., 2013).

There is ample evidence of the importance of social connection and social support in preventing or moderating PTSD, however. Social support is associated with a reduced risk for the development of PTSD and other negative mental health outcomes after trauma exposure (Brewin et al., 2000). Social support in the acute aftermath of trauma predicts less PTSD symptomatology, yet has also been documented to diminish over time in the presence of chronic PTSD (e.g., Kaniasty & Norris, 2008; King et al., 2006). There is an especially strong association between support from friends and family and reduced risk for PTSD (Pietrzak et al., 2009). Carter et al. (2011) found that service members had lower levels of PTSD symptoms following deployment when they had communicated more

frequently with their spouses during deployment (if marital satisfaction was high and when delayed forms of communication, e.g., letters, emails, and care packages, were used). In a study of pre, during, and post-deployment risk factors for PTSD following deployment to Iraq, family stress during deployment (negative) and social support following return from deployment (positive) were the strongest independently predictive variables, aside from combat exposure (Shea et al., 2013). Other studies have documented that social support and interpersonal and family functioning affect individual PTSD treatment outcomes in Veterans (Evans et al., 2009; Price et al, 2013; Tarrier et al., 1999).

Erbes (2011) and Monson et al. (2009) note several reasons why relationships, or their absence, may affect the occurrence of and prognosis for PTSD and other outcomes, including biological indices of health. With social support being negatively related to PTSD symptoms (Monson et al., 2009), relationship patterns among intimate partners may prolong or reduce avoidant behavior, or support or discourage emotional expression, each of which can affect the course of PTSD. Research conducted with civilians (Cacioppo & Patrick, 2008) has linked loneliness with an increase in blood pressure over time. In a study of 200 breast cancer survivors, Jaremka et al. (2013) found that lonelier women experienced more pain, depression, and fatigue than those who had stronger connections to friends and family. Those who were more disconnected also had elevated levels of a particular antibody associated with the herpes virus- a sign of a weakened immune system. Thus, social disconnection can be not only emotionally, but also biologically, toxic.

Treatment of PTSD

The vast majority of treatment studies addressing PTSD, both in civilian and military populations, have focused on cognitive behavioral interventions, for both individual and conjoint treatments. Treatments with the greatest evidence base are Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT), both of which have been rolled out across Veterans Administration hospitals and clinics nation-wide. A randomized controlled trial comparing PE to present-centered therapy in 277 female Veterans found that PE was an effective treatment for PTSD (Schnurr et al., 2007). Female Veterans who received PE experienced significantly greater reduction of PTSD symptoms than women who received present-centered therapy. The focus of PE and CPT is on confronting and integrating the trauma; and although they may result in improvement in functioning, they do not directly address the role of interpersonal relationships as a contributing factor to or consequence of PTSD.

We have chosen PE as the treatment with which to compare IPT for PTSD for two reasons: 1) it has the greatest research evidence to support its efficacy as a PTSD treatment (IOM, 2008); it is considered the "gold standard" in addressing PTSD, and 2) its theoretical model presents a sharp contrast to that of IPT. Where PE emphasizes exposure as the mechanism of change, and focuses on fear responses, IPT focuses on the important role of social support and improvement in relationships as a means of overcoming PTSD symptoms.

As Monson et al. (2012) point out, there is increasing recognition that intimate relationships play a potent role in recovery from PTSD and its comorbid symptoms, suggesting that treating relationships, and not just the Veteran's PTSD, may be particularly effective. Indeed, as a result of their randomized controlled trial that demonstrated the effectiveness of cognitive-behavioral couple therapy for PTSD (CBCT; Monson et al., 2012),

this intervention is now being rolled out in the VA system. In their study, 40 couples, in which one partner met criteria for PTSD, were randomly assigned to CBCT or a wait-list condition. The results showed that PTSD symptom severity was significantly more improved in the couple therapy condition than in the wait-list condition. Also, patients' intimate relationship satisfaction was significantly more improved in couple therapy than in the wait-list condition. These findings demonstrate that treatment focused on interpersonal issues can benefit both PTSD symptoms and relationships.

Other studies of behavioral conjoint therapies (BCT) also show evidence for this approach. For example, in Glynn and colleagues' (1999) study of 42 Vietnam Veterans, randomly assigned to directed therapeutic exposure (DTE: Carroll & Foy, 1992), DTE followed by BCT, or wait-list, both treatment conditions were associated with more improvement than the wait-list on "positive PTSD symptoms," i.e., reexperiencing and hyperarousal, although neither was effective in reducing the "negative" symptoms of avoidance and numbing.

Sautter et al. (2009) developed Structured Approach Therapy (SAT), a couple-based PTSD treatment targeting the avoidance/numbing symptoms of PTSD. Data from an open trial conducted with six Vietnam Veterans and their spouses showed significant reductions in self-rated, partner-rated, and clinician-rated overall PTSD severity, in addition to reductions in avoidance and numbing. The investigators modified the intervention for OEF/OIF Veterans and their partners and reported significant improvements in returning Veterans' PTSD and relationship satisfaction and decreases in their partners' depression (Sautter et al., in press). Data from a recently completed randomized clinical trial have replicated these findings with 57 OEF/OIF Veterans with combat-related PTSD (Sautter et al., 2013). Returning Veterans and their partners receiving SAT showed significant reductions in attachment-related avoidance and anxiety, suggesting that improved relationship functioning is associated with decreased PTSD. As Monson et al. (2009) observe, however, in discussing "future directions" with regard to PTSD, "a significant proportion of Veterans is not in a longer-term romantic relationship" and that "parents, siblings, close friends, and/or fellow Veterans may be the Veteran's family" (p. 712). Thus, interventions that are based on couple relationships only may not be appropriate for many Veterans with PTSD. Existing relationship-focused treatments for PTSD also *do not address other relationship difficulties that may be associated with PTSD*, such as loss of a relationship through death of a significant other, or the absence of relationships among Veterans with PTSD who are socially isolated or who have interpersonal deficits that preclude having sustained relationships.

Research on Interpersonal Therapy for the Treatment of PTSD

While IPT has been recognized as a "first-line" treatment for depression and is being rolled out across VA hospitals and clinics for the treatment of that disorder, far less attention has been paid to its potential role as a treatment for PTSD. Nevertheless, findings from recent studies suggest its potential as an effective treatment for PTSD and the relationship problems that may accompany it.

Krupnick and colleagues (Krupnick, Green, Stockton, et al., 2008) first adapted IPT as a group modality for low-income women with PTSD. In this study, 48 low-income, predominantly minority women with extensive interpersonal trauma histories were randomized to group IPT for PTSD or a wait-list. Research participants, recruited from

family planning and gynecology clinics, mostly had histories of sexual or physical abuse beginning in childhood. Results showed that IPT was significantly more effective than the wait- list in reducing PTSD and depression symptom severity. IPT participants also had significantly more improvement than wait- list subjects on four out of five subscales of the Inventory of Interpersonal Problems: Interpersonal Sensitivity, Need for Social Approval, Lack of Sociability, and Interpersonal Ambivalence.

In another study of civilians, Bleiberg & Markowitz (2005) used individual IPT for PTSD in an open trial of 14 men and women with PTSD following a variety of traumas that sought treatment at a university-based psychiatric clinic. Their findings showed that 12 of the 14 no longer met criteria for PTSD at treatment termination; 69% had a PTSD score decrement of at least 50%. They followed this study with an NIMH-funded randomized trial comparing IPT for PTSD with PE and a supportive therapy control condition. Their findings show that IPT for PTSD achieved results that were comparable to those obtained for PE in a civilian population (J. Markowitz et al., in press).

A recently published study (Meffert et al., 2014) examined the impact of IPT on Sudanese refugees living in Cairo, Egypt who had symptoms of PTSD. A randomized controlled trial with 22 Sudanese refugees, assigned to IPT or a wait-list condition, tested 6 sessions of IPT delivered by Sudanese community therapists. IPT showed a significant decrease in symptoms of PTSD, state anger, and depression using a conservative intent-to-treat analysis. The authors observed that this preliminary success has positive implications for developing effective mental health interventions for traumatized populations.

In the only study of IPT for PTSD in a military population, Krupnick (2010) adapted IPT for PTSD in women Veterans. This was an open trial/pilot of IPT for PTSD in women Veterans who had experienced trauma during military service. Of the 15 women who started treatment, 10 completed the intervention. There was a significant decrease in PTSD symptoms among those completing treatment, as well as significant improvement in relationship functioning across patients.

To summarize, there is abundant evidence that PTSD is associated with serious disruptions and impairments in multiple aspects of interpersonal relationships and functioning. Despite the notable advance in effective treatments for PTSD such as PE and CPT, interpersonal difficulties are not the focus of these treatments and there are no data to suggest that, beyond the Veteran's intimate relationship satisfaction, the broad range of interpersonal problems associated with PTSD are addressed by these treatments. Although there is evolving empirical support for couples therapy (Monson et al., 2012; Sautter et al., 2013), a large proportion of Veterans are not involved in intimate relationships. Furthermore, these treatments do not target interpersonal functioning outside of the Veteran's relationship with his/her partner or spouse. There are many aspects of interpersonal functioning that have been shown to be impaired because of PTSD that extend far beyond their primary intimate relationship. These problems affect the Veterans' relationships with everyone with whom they interact, including friends, children, coworkers, employers, and even health care providers. Veterans also have difficulties that keep them socially isolated. Thus, there is a clear need for effective treatments for interpersonal problems in Veterans. Support from previous studies of IPT in treating PTSD, along with evidence of the serious interpersonal difficulties that accompany PTSD in

Veterans, makes a compelling argument for the further study of IPT in treating PTSD in this population.

2. Research Design and Methods

A. Overview

IPT-PTSD or *Prolonged Exposure (PE)* will be provided on an individual basis to patients randomized to one or the other treatment conditions. There will be 4 therapists.

B. Participants

The sample will consist of male and female Veterans over age 18 who meet current criteria for PTSD. Participants will be recruited at the Providence VA. 88 participants will be randomly assigned to one of the two conditions.

Inclusion/exclusion criteria

The inclusion and exclusion criteria are based on an attempt to be as unrestrictive as possible, while ensuring the safety of participants and maintaining the internal validity of the study.

In order to be **included**, participants must:

- Be male or female Veterans over the age of 18
- Have experienced trauma *(combat or noncombat)* while deployed to a war zone
- Meet current DSM-5 (APA, 2013) criteria for PTSD
- Have at least one area of relationship dysfunction
- Consent to be randomized

Potential participants will be **excluded** for any of the following reasons:

- Current severe substance use disorder
- Current psychotic symptoms
- Current Mania or un-medicated Bipolar Disorder
- Current suicidal or homicidal ideation suggesting an imminent threat
- Victim or perpetrator of severe domestic violence in the past 12 months
- Currently receiving Cognitive Behavioral Treatment for PTSD (Patients currently in CBT may be enrolled when they have completed the treatment if they remain interested and continue to have PTSD)
- Psychotropic medication start or dosage change within the prior 4 weeks - Those with a recent medication or dosage change may be considered after they have been on a stable dose with no medication changes in the prior 4 weeks.

Participants with cognitive impairment will be excluded if they would be unable to readily understand the concepts of therapy or assessments. If such impairment is suspected, the MoCA will be administered (see below). Veterans with mild traumatic brain injury (mTBI) will not be excluded, since the typical level of cognitive impairment associated with mTBI is not sufficiently severe to interfere with treatment implementation.

C. Recruitment procedures

Participants will be recruited from a range of sources. The primary recruitment source will be the Providence Veterans Affairs Medical Center, including the OEF/OIF specialty

primary care clinic, the Returning Veterans Outreach Program (REVOC), and the PTSD Clinic. Dr. Shea is a member of the PTSD clinic staff and Director of PTSD Research at the PVAMC. She will coordinate efforts with the appropriate mental health staff to refer patients to the study. PVAMC staff will be told about the study and how to refer patients, and given a brochure to use for this purpose. A flyer with study information will also be posted as a screen saver on computer monitors in the facility. The current PTSD clinic caseload includes close to 1800 Veterans with PTSD, with an average of 7 - 8 referrals per week. Thus, the PVAMC has a very large pool of potential participants for recruitment. Study participants will also be recruited through outreach efforts to local Vet Centers and CBOC's, military family organizations, community-based troop support organizations, and Veteran organizations. Additional outreach efforts will include making presentations at military reintegration events, such as Yellow Ribbon post-mobilization weekend retreats, posting fliers in the community, as well as making presentations to interested community groups. Recruitment will take place over 27 months with an average of 3.2 participants per month.

D. Screening and Informed Consent Procedures

Patients currently in treatment will be informed of the study by their clinician or by flyers. If interested, potential participants will have the option of signing a form giving permission to the investigators to contact them, or they can contact the investigators directly. The project coordinator/clinical evaluator (PC/CE) will contact them by phone to gather demographic information and provide information that will enable them to decide whether they want to be considered for the study (i.e., purpose of the study, the two intervention conditions, use of random assignment, time commitment, and payments). The medical record will be examined to determine whether diagnostic exclusion criteria (e.g. current severe substance use disorder, mania or psychotic symptoms) are present. Interested and eligible individuals will obtain an appointment with the PC/CE. During this next stage of screening, interviewers will review the Informed Consent forms to explain the study in greater detail. The participant will be fully informed of the nature and extent of study participation, the objectives of the study, and the two interventions to which they may be randomly assigned. Participants will also be informed about the follow-up assessments they will complete. PC/CEs will be trained to ensure that participants comprehend the study and the consent form and willingness to adhere to study conditions. Potential participants will sign the consent and receive a copy to take home.

After reviewing the consent form, the interviewer will ask if the participant is interested in proceeding with the next phase of screening to determine if s/he meets all study inclusion/exclusion criteria. If s/he is willing to proceed s/he will also be asked to sign a HIPAA authorization form. In the final stage of screening, interviewers will complete interviews to establish inclusion and exclusion criteria, as described below.

E. Assessment

E1. Screening, Diagnostic, and Sample Characterization Measures

After informed consent is obtained, participants will be evaluated using the diagnostic and screening measures to determine eligibility.

Clinician Administered PTSD Scale (**CAPS-5**; Weathers et al., 2013) will be administered to assess diagnostic criteria for PTSD. Participants must meet criteria on this measure,

considered the "gold standard" for PTSD diagnosis, to be eligible for the study. Participants must also have a total score of 23 or greater, which constitutes at least a moderate (or clinically significant) level of symptom severity. The follow-up version will be used at post-treatment and at follow-ups as a primary measure of outcome. This measure, recently updated to conform to the DSM-5, has excellent reliability and validity for DSM-IV (Blake et al., 1995) and is widely used in PTSD treatment research.

Structured Clinical Interview for DSM-5 (**SCID**; First et al., 1996), patient version: The DSM-5 version of the SCID will be administered to assess for the presence of current (past three months), severe substance use disorder (SUD) and alcohol use disorder (AUD), current psychosis, and current unmedicated bipolar disorder, which are exclusion criteria for study participation. In addition, in order to better describe the nature of the study population, lifetime (12 month period of heaviest use throughout life) SUD and AUD will be assessed.

Conflicts Tactics Scale – Short Form (**CTS2;** Straus & Douglas 2004)**:** This 20-item self-report measure will be used to rule out participants involved in current intimate partner violence. Respondents rate each item on an 8-point scale based on the number of times a particular behavior occurred during the past year in the relationship. Respondents reporting the commission of damaging physical violence in their intimate relationship as either the perpetrator or the victim will be excluded from the study and referred for other services.

Inventory of Interpersonal Problems (**IIP-32;** Barkham, Hardy, & Startup, 1996)**:** The IIP is a self-report instrument that identifies a person's most salient interpersonal difficulties, e.g., assertive, supportive, involved, etc., and will serve as a primary measure of outcome. The 32-item measure, scored by summing scores of 0 ("not at all) – 4 ("extremely") on each item, is similar to the original 117-item version in terms of its psychometric properties. Study inclusion will require a score of at least 2 ("moderately") on one or more areas of relationship dysfunction.

VA screen for suicidal and homicidal ideation and behavior: Standard screens for VA mental health patients will be used. Participants deemed at imminent risk will be walked to VA urgent care for further assessment.

Montreal Cognitive Assessment (**MoCA**: Nasreddine et al., 2005) is a one-page test to assess cognitive impairment in multiple domains, short-term memory, executive function, attention, language, etc. We will use this measure when needed to assess cognitive capacity to participate in treatment and assessments.

E2. Primary Outcome Measures

Primary outcome domains include PTSD symptoms and interpersonal functioning.

The CAPS-5 (past month ratings) will be used to assess change in PTSD symptoms, and the **Inventory of Interpersonal Functioning** (IIP-32) will be used to assess change in interpersonal functioning.

E3. Secondary Outcome Measures

PTSD Checklist-5 (**PCL-5**; Weathers et al., 2013) is a 20-item self-report measure that assesses DSM-5 symptoms of PTSD and PTSD symptom severity on a 5-point scale. The

wording reflects changes to existing symptoms and the addition of new symptoms in DSM-5. The self-report rating scale is 0-4 for each symptom, from "Not at all to "Extremely." We will use this measure to track PTSD symptoms throughout treatment.

Patient Health Questionnaire (PHQ; Spitzer et al., 1999) The PHQ, a version of the PRIME-MD, contains the mood (**PHQ-9**) and anxiety modules in the original PRIME-MD. The **GAD-7** assesses 7 common anxiety symptoms. These self-report measures will be used to track symptoms that are commonly comorbid with PTSD and expected to change along with PTSD.

Work & Social Adjustment Scale (**WSAS**; Mundt et al., 2000) The WSAS is a self-report scale of functional impairment attributable to an identified problem in five different areas: ability to work, home management, social leisure, personal leisure, and maintaining close relationships. This five-item scale, with ratings of each of these areas of functioning from 0 to 8, has been used to study the treatment of depression and anxiety.

Multidimensional Scale of Perceived Social Support (**MSPSS**; Canty-Mitchell & Zimet, 2000; Zimet et al., 1988) is a 12-item self-report measure of subjective social support. Three subscales address different sources of social support (family, friends, and significant other). It has good reliability and moderate construct validity, and is associated with lower levels of depression and anxiety. It is scored on a scale from 1 – 7, indicating agreement or disagreement with statements.

WHO Short Form Quality of Life Measure (**WHOQOL-BREF**; WHOQOL Group, 1998), derived from data collected using the WHOQOL-100, produces scores for four domains related to quality of life: physical health, psychological, social relationships and environment. There is one item from each of the 24 facets of the WHOQOL-100, plus two questions on overall quality of life and general health. Item scores range from 1 – 5.

Concise Health Risk Tracking Scale (CHRT; Trivedi et al., 2011) is a 12-item self-report measure of suicidal ideation, hopelessness, and interpersonal attachment/social support. All items are rated on a 5-point scale. Although the original measure uses the time frame of the past day, for the purposes of this study, we will be using the time frame of the past week. This longer time frame will expand coverage of recent health risk related thoughts, emotions and behaviors.

E4. Additional Measures

Deployment Risk and Resilience Inventory (DRRI): The DRRI-2 (Vogt et al., 2013) is a self-report measure developed to assess deployment-related experiences of military Veterans. Five scales will be used in the current study: pre-deployment life events, combat experiences, relationships during deployment, post-battle experiences, and post-deployment stressors. These scales will thus provide an initial index amount of life-time trauma exposure.

Treatment Utilization: The Longitudinal Interval Follow-Up Assessment (LIFE) treatment section provides information about mental health and medical treatments (Keller et al., 1987), including number of hospitalizations, days spent in hospital, and number of outpatient visits for non-mental health medical treatments, mental health contacts, including inpatient and outpatient treatment, and psychiatric medications,

including dosages. A baseline version (LIFE-Base) assesses mental health treatment received prior to entering the study. We will adapt the LIFE-Base to assess whether prior treatment focused specifically on PTSD or relationship functioning. The LIFE treatment section will be administered at post-treatment and at the 3 and 6 month follow-up assessments to track any non-study treatment received. If other treatment received is unequal between conditions, we will use it as a covariate in analyses.

Childhood Trauma Questionnaire (CTQ): The CTQ (Bernstein et al., 1994) is a self-report measure developed to retrospectively assess experiences of abuse and neglect in childhood, as well as aspects of the child-rearing environment. It consists of 53 items rated on a 5-point Likert scale, and has evidence of good internal consistency and test-retest reliability.

E6. Assessment Schedule (see table below)

Assessments will be conducted at baseline, before each session, after sessions 4 and 8, end of treatment, and 3 and 6 months after the end of treatment (see table for specific measures). For Veterans who do not complete treatment, we will make every effort to conduct assessments at the time of termination and at 12 to 14 weeks after randomization, and at the 3 and 6 months post-treatment follow-ups.

Measure	**Construct**	**Screen**	**Base line**	**All Sess**	**Sess 4**	**Sess 8**	**End of Tx**	**3-mo FU**	**6-mo FU**
CAPS-5*	PTSD Diagnosis	XX					XX	XX	XX
SCID-5	Psychosis, SUD, AUD, Bipolar	XX							
CTS	Domestic Violence	XX							
IIP-32*	Interpersonal Problems	XX			XX	XX	XX	XX	XX
VA Screen	Suicide or Homicide risk	XX							
MoCA	Cognitive Impairment	XX							
PCL-5	PTSD Sx		XX	XX			XX	XX	XX
PHQ	Depression, GAD Sx		XX		XX	XX	XX	XX	XX
CHRT	Suicidal Ideation		XX				XX	XX	XX
MSPSS	Perceived Social sup.		XX				XX	XX	XX
WSAS	Social Adjustment		XX				XX	XX	XX

WHOQOL-BREF	Quality of Life		XX				XX	XX	XX
DRRI	Trauma Exposure		XX						
LIFE - Tx	Treatment Utilization		XX				XX	XX	XX
CTQ	Childhood Trauma Questionnaire		XX						

Measures and Times of Administration
***** CAPS-5 and IIP-32 (primary outcomes measures) obtained at screening will serve as the baseline measure

Assessment Procedures: Every effort will be made to schedule in-person therapy sessions and follow-up assessments. Due to our inability to schedule in-person appointments due to health concerns (e.g., related to COVID-19), we will offer our last participant the opportunity to participate in the assessment phase via phone or by VA Video Connect (VVC) with trained study personnel. VVC enables Veterans to virtually meet with their VA healthcare providers, using encrypted video to ensure the session is secure and private. Veterans will have the option to complete the questionnaires over the phone or by VVC with a trained assessor.

E7. Blinding of Assessments
CEs will be blind to participants' treatment condition. Prior to the outcome assessments, the CE will remind each participant not to reveal his/her treatment condition. At the post-treatment and follow-up assessments, CEs will complete questions including whether they think the blind was broken, and to which treatment condition they think the participant was assigned.

E8. Standardization of Assessments
PC/CE qualifications will include either masters or doctoral training in psychology or social work, with prior experience administering the SCID and CAPS in a Veteran sample. Dr. Krupnick will provide training on the SCID and CAPS. PC/CEs will conduct practice interviews and receive feedback from Dr. Krupnick until judged to be calibrated to an acceptable standard of administration.

All of the CAPS and SCID interviews will be recorded. Ten percent of the interviews will be selected on an ongoing basis to monitor the reliability of the interviewer ratings. Dr. Krupnick will listen to the recorded interviews and provide feedback to interviewers in monthly meetings to maintain reliability. PC/CEs' ratings will be compared with Dr. Krupnick's ratings and any discrepancies in ratings will be discussed.

E9. Procedures to Enhance Completion of Assessment Protocols
A number of procedures will be used to minimize the likelihood that participants will fail to complete the schedule of assessments. Self-report measures will be completed at the time of the assessment and reviewed for completeness before the participant leaves. We will monitor carefully for fatigue and encourage breaks if needed. We will try to schedule assessments on the same day as treatment sessions. We will obtain the name and phone number of a close relative, friend, or other person who is likely to maintain contact with the participant, and to contact that person if attempts to contact the participant are unsuccessful. Post-treatment and follow-up assessments will be conducted in person. An

appointment for the 3-month post-treatment follow-up assessment will be made at termination of the study intervention. The participant will receive a letter or telephone call one week prior to the interview and a similar reminder a few days prior. Appointments for the 6-month interview will be made at the 3-month interview. Participants who do not have telephones will be contacted by mail and asked to call or email for an appointment.

Five contact attempts will be made before a participant is considered to be unreachable at that time point. Participants who fail to appear for a scheduled assessment will be contacted by phone, or mail or email when necessary, for rescheduling. If participants move away during their participation in the study or are otherwise unavailable for an in-person interview, we will perform follow-up assessments over the telephone to avoid missing data. Participants will be compensated $50 for the pre-treatment, post-treatment, and follow-up interviews. Those screening out on the SCID or CAPS will be paid $35 (for partial assessment). Mid-treatment assessments (after sessions 4 and 8) will be compensated at $25.

F. Compensation

Participants will be compensated for the time required to complete all assessments. They will be paid $50 for fully completing baseline, end of treatment, and follow-up assessments. Participants who screen out on the SCID or CAPS or who do not complete the full baseline assessment will be paid $35 (for partial assessment). Mid treatment assessments (after sessions 4 and 8) will be compensated at $25.

G. Treatment

G1. Assignment

Participants meeting study inclusion/exclusion criteria will be randomly assigned to IPT-PTSD or *PE* following completion of the initial assessment. To prevent unequal distribution of variables that might be related to outcome, we will use the urn randomization strategy described by Wei (1978) and Stout (Stout et al., 1994). Urn randomization is a stratified technique that assigns patients of a given subgroup to treatment conditions, but systematically biases the randomization in favor or balance among the treatment conditions of the stratification variables. The urn randomization procedure has been used in several previous treatment outcome studies, including the multi-site Project MATCH (Project MATCH research group, 1997). The urn randomization computer program also enables ongoing monitoring of the effectiveness of stratification and randomization procedures. Three dichotomous balancing factors will be used in randomization: gender (male vs female), War Era (OEF/OIF/OND, Vietnam, or other), and severity of PTSD. Severity will be dichotomized as the equivalent DSM-5 CAPS cut-off to <70 vs $\geq$ 70 on the DSM-IV (when available from CAPS-5 developers). Study staff will implement the randomization.

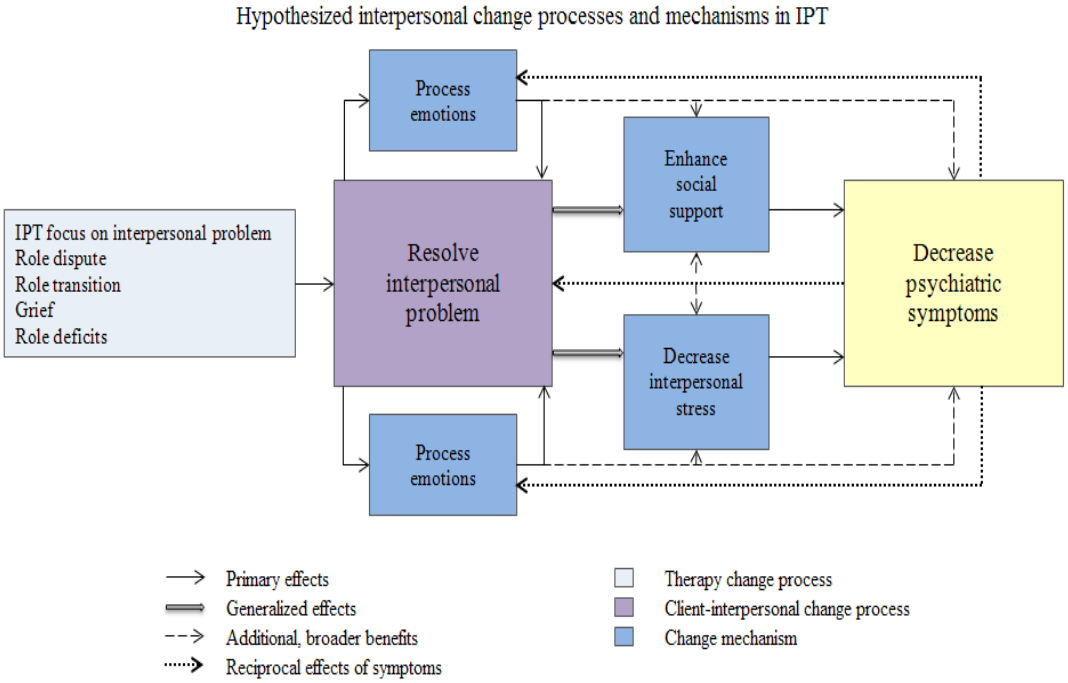
G2. IPT-PTSD

IPT –PTSD is a relationally-focused intervention addressing PTSD symptoms and relationship dysfunctions that are conceptualized as resulting from and contributing to the perpetuation of these symptoms. It is based on the interpersonal and attachment theories of Harry Stack Sullivan (1953) and John Bowlby (1973) that place importance on the role of social support and interpersonal connection in preventing or ameliorating emotional problems. As the model below (Lipsitz & Markowitz, 2013) indicates, its focus on one or two particular problem areas, i.e., role disputes, role transitions, grief, and/or interpersonal deficits (called social isolation for this adaptation) leads to the resolution not only of interpersonal problems, but also a decrease in psychiatric problems. Interpersonal problem resolution involves increasing interpersonal skills as well as processing of emotions. Improving relationships enhances social support while decreasing interpersonal

stress. This, in turn, is theorized as helping with symptom reduction.

Treatment consists of 12 individual weekly sessions of 45-50 minutes duration. The initial phase of treatment (sessions 1-3) involves learning about the Veteran's military and other trauma history, completing a review of PTSD symptoms, presenting PTSD as an "injury" (to allow the Veteran some reduction of pressure while he/she is trying to recover), provision of psychoeducation about the links between PTSD and relationship problems, conducting an interpersonal inventory to determine which relationships (or lack thereof) contribute to the Veteran's difficulties, and establishing an appropriate focus for the treatment.

Learning about significant relationships that may have contributed to and/or affected by the Veteran's PTSD symptoms/diagnosis helps the clinician to determine which problem area(s) would be the best fit for the individual. The intermediate phase (sessions 4-10) addresses the problem areas identified as the most salient for individual Veterans. This is achieved through such strategies as communication analysis, decision analysis, role play, etc. The termination phase (sessions 11 & 12) is focused on consolidating what has been learned, what issues still remain for the Veteran, expressing feelings about ending the therapy, and identifying the types of relationship triggers in the future that could reactivate PTSD symptoms (see Appendix B for IPT- PTSD manual).



G3. Prolonged Exposure

The aim of PE is to allow Veterans to re-experience the traumatic events they experienced during military service in a safe and supportive environment, and to re-engage in activities they had been avoiding because of the trauma. It consists of two types of exposure: imaginal exposure in which the Veteran is asked to confront memories of the trauma, including exposure to all sensory images of the trauma, and in vivo exposure, during which the Veteran is encouraged to visit places and engage in activities that he/she had been

avoiding. The goal is to reactivate the fear structure and then confront that which had been feared.

PE will be delivered according to the standard manual used for the VA PE roll-out, which includes 10 90-minute weekly sessions delivered over 8 to 15 weeks. Although the manual includes 10 sessions, anywhere from 8 to 12 sessions are within the range of standard PE. IPT-PTSD consists of 12 individual weekly sessions, with each session of 45-50 minutes duration. In order to increase comparability in terms of number of sessions while also maintaining the flexibility of PE delivery, we propose a standard of 12 weekly sessions for each treatment, but will allow participants who improve more quickly to complete in 9 or 10 sessions.

After much consideration, we have decided to keep the session length for PE at the standard 90 minutes. The disadvantage of this choice is the difference in total time of each therapy. Literature on the dose-response relationship in psychotherapy has focused on number of sessions and not session length. One small study compared a shorter session length for PE of 60 minutes to the standard 90 minutes (van Minnen & Foa, 2006). Those in the shorter sessions showed less in-session habituation, but there were no differences in outcome. Although these findings were promising, due to limitations of sample size and design, they are not sufficiently strong to conclude that shorter sessions would be as effective as the standard 90 minutes sessions. Because we are examining the effectiveness of IPT-PTSD compared to PE as a "gold standard" comparison condition, we believe it is more important for it to be delivered as developed, previously tested, and currently practiced at the VA, than it is to equate session length. An alternative might be to lengthen IPT sessions to 90 minutes. However, we have concluded that it is also more important to adhere to the standard session length for IPT than to alter it to make it comparable to PE. So each treatment will be tested as typically practiced.

Consistent with the standard manual used for PE (and used in the VA PE roll-out), treatment sessions are audio- recorded and patients are asked to listen to the recounting of the trauma daily. As this audio-recording is not analyzed data, but simply part of the usual and manualized PE treatment protocol, this audio-recording will not be behind VA firewall. Participants may use their own audio-recording device (e.g. cell phone), or if needed, they can borrow a cassette recorder from their PE therapist.

G4. Therapist Selection, Training, and Supervision

IPT-PTSD

Therapists will be Ph.D. level psychologists or master's level clinical social workers with prior experience treating PTSD patients. Initial training will be didactic, involving two days of instruction. Dr. Krupnick will conduct the didactic training for IPT-PTSD. Training will include disguised case examples derived from the pilot study of IPT-PTSD for women Veterans as well as role-plays of interventions. A recently developed DVD of IPT for depression with demonstrations by Kathleen Clougherty, LCSW and Gregory Hinrichsen, Ph.D. (conducted with depressed Veterans, some of whom also had comorbid PTSD) will be shown to demonstrate techniques of IPT with Veterans. This video was developed to demonstrate the core components of IPT for depression in a series of video vignettes and

will be relevant to training in IPT for PTSD.

Following the IPT didactic training, each therapist will have one training case, with weekly supervision based on review of audiotaped sessions. The training case must be a minimum of 8 sessions to count. If the therapist is judged to be sufficiently competent, Dr. Krupnick will approve him/her to see study participants. Approval will be based on consistent ratings of adherence (75% of strategies implemented across sessions rated; see below). Dr. Krupnick will use an adapted version of the IPT Rating Scale (IPTRS), the measure that she has been using to assess the competence of VA clinicians who are learning IPT for depression, to assess the competence of IPT for PTSD therapists. All therapy sessions for study participants in both conditions will be recorded. For the first study case for IPT, every session will be reviewed and feedback will be provided weekly. After therapists have been judged as competent in IPT, Dr. Krupnick will provide bi-weekly group supervision to all therapists providing this treatment. Dr. Krupnick will continue to review audio recordings if needed for difficult cases.

Therapists for the PE condition will be Ph.D. level psychologists or master's level clinical social workers who have been previously certified as PE therapists either through the VA roll-out or by Dr. Foa's training program. Since the therapists will have already been trained and certified in PE, no additional PE training will be conducted with regard to the conduct of PE. However, since it is possible that the therapists may have "drifted" in their practice of this method, we will have a PE expert review early, middle, and late sessions from each of their first two cases to ensure that they are conducting PE according to manual specifications. Sonya Norman, Ph.D., who has been a PE trainer for the VHA, will review audiotapes to ensure PE competency and will provide consultation on PE methods, as needed. Dr. Norman will also provide bi-weekly group supervision to the PE therapists on their PE cases.

G5. Adherence Monitoring

Two Ph.D. level psychologists with experience treating Veterans with PTSD will complete adherence ratings for both treatments. The IPTRS (the rating scale that is used to assess IPT competence and adherence in IPT for depression) will be modified to be consistent with the IPT-PTSD manual (Appendix C). The adherence measure used in prior studies of PE (e.g. CSP-494; Schnurr et al., 2007) will be used to assess adherence for PE sessions (Appendix D). The purpose of the adherence measures is to confirm that therapists are conducting each of the treatments as prescribed and using none of the techniques that are proscribed for each method. Both adherence raters will rate early sessions (a minimum of 20 sessions) to establish inter-rater reliability. Following establishment of acceptable reliability, approximately 20% of sessions will be randomly selected for adherence ratings. All session recordings will be digitized and encrypted and will be used only for the purpose of training, supervision, and adherence ratings.

G6. Collaborative Procedures

Proposed personnel for this study include Dr. Shea, the PI of the Providence site, Drs. Krupnick and Green at Georgetown University, and a statistician. Dr. Shea will have responsibility for administrative coordination of the study, including scheduling of meetings and conference calls, monitoring the progress of the study according to the

proposed time-line, and preparing interim and final progress reports. Dr. Shea will be responsible for hiring study staff, IRB submissions, and reporting of all adverse and serious adverse events. Drs. Shea, Krupnick, and Green will constitute the oversight committee, and will share responsibility for overseeing implementation of the protocol, ensuring consistency of procedures, and monitoring quality control of data. They will meet weekly via conference calls, with PC/CEs joining calls that involve study procedures. The study statistician will be responsible for data analyses, and Drs. Shea, Krupnick, Green, and the study statistician will participate in data interpretation and manuscript writing. The PIs and their staff will have weekly meetings to review progress and address any questions that arise regarding study procedures at their site. Local site issues will be resolved at the site, but issues affecting delivery of the overall protocol will be discussed with the larger group to ensure consistency of procedures. Dr. Krupnick will conduct training of PC/CEs, and will implement ongoing reliability studies of PC/CEs to ensure consistency of assessments. Dr. Krupnick will monitor appropriate delivery of the interventions for IPT and PE respectively.

H. Data Management and Analysis

H1. Data Management

All data collected for this study will be used for research purposes only. Study data (all de-identified) will be managed using REDCap electronic data capture tools (www.project-redcap.org). REDCap (Research Electronic Data Capture) is a secure, web-based application for building and managing databases. It is specifically designed to support data capture for research studies. The REDCap application allows users to quickly and securely build and manage online databases and has features for tracking data manipulation and export to common statistical packages (Harris et al., 2009). Multiple users can access the database from different locations, and different levels of use and restriction can be specified. REDCap is approved for use in the VA, and is being used by many VA researchers. The PC/CE will oversee data management procedures. He/she will be responsible for initial editing and correction of forms before the research assistant enters them into REDCap. As forms are entered into the REDCap database, they will be checked against the participant-tracking file to ensure that all data that are gathered have been entered. Furthermore, (1) data sheets will be stored in locked offices of research study staff, building 32 of the PVAMC) (2) data will be entered in coded form, (3) data will be stored on a secure server behind the VA firewall (\\vhaproappres01.v01.med.va.gov\research_protocols\Shea\IPT_PE-R), (4) data will be protected from unauthorized access by passwords, (5) information that might potentially allow an individual participant to be identified will not be allowed in any publications or reports sent to individuals outside the study, (6) all employees who are to handle data will be trained in confidentiality policies and procedures, and (7) all data-related incidents will be reported to the local ISO and PO per VA policy. Study files will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1. De-identified data from the New Orleans site will be entered from that site into an integrated study data base. Only personnel involved in the study will have access to the REDCap data base. Subsets of de-identified data files may be downloaded onto personal computers for data-analysis, only by approved study personnel.

H2. Power and Data Analyses

H2.1 Power Analysis.

Our study is designed as a 2-arm randomized clinical trial comparing IPT-PTSD with PE using analysis of equivalency of the clinical outcomes between treatment groups. We hypothesize that the effectiveness of the IPT-PTSD intervention will be at least as good as the effectiveness of the well-established PE treatment in reducing symptoms of PTSD. By powering our study for an equivalence hypothesis based on two-sided significance testing at the 95% confidence level rather than a non-inferiority design based on one-sided testing or the usual 90% confidence level for equivalence, we allow for a rigorous comparison between the two treatments. We further expect that IPT-PTSD will be more effective than PE in improving interpersonal functioning. We will test this hypothesis as a superiority analysis to show that the change in the interpersonal functioning outcome in the IPT-PTSD group will be significantly superior to the change in the PE group. De-identified data from the Providence VAMC and New Orleans VA will be entered into separate REDCap databases, and then combined for analysis for an ideal total of 88 per site. Taking into account a dropout rate of 20% the goal is 70 participants in each treatment condition, 140 in sum.

The first primary outcome measure is the CAPS-5 total score measured at screening, post-treatment (12-weeks), and at 3-month and 6-month follow-up. Sample size calculations were conducted in PASS (Hintze, 2013) using the change in the CAPS total score from screening to post-treatment as the primary endpoint. Due to unavailability of CAPS-5 data at this time, our estimates for the expected changes were based on the DSM-IV CAPS. Using a two-sample t-test algorithm with equal variances in an equivalence test of means design, our study reaches 81% power to infer equivalence at 5% significance level (95% confidence level) with sample sizes of 70 in both groups (140 in total). The assumptions of the test are 1) the true difference between the mean change scores is zero ($\Delta=0$), 2) the within-group standard deviation for the change measure is 10 (corresponding to a minimum clinically effective decrease of 15), and 3) the equivalence limits are -5 to 5 units. Past studies report that a 10-unit difference between treatment methods in the post-treatment CAPS total score represents a minimum clinically meaningful difference. For this study, we consider a 5-point difference ($\Delta=5$) between the groups in the pre to post-treatment change scores in CAPS (for instance -15 vs -20) to be the smallest difference that would lead the methods to be declared equivalent (Hypothesis 1). The proposed sample size for this study will be 88 patients to be randomized to each group with a 1:1 ratio (176 in total from both sites) and includes an assessment dropout rate of 20% (140 in total).

Our study will reach 81% power with the same number of subjects to detect superiority of IPT in improving interpersonal functioning, measured post-treatment with the IIP-32 score using a one-sided, two-sample t-test at alpha=0.05 with a margin of superiority of -0.05 and assuming that the true difference between the means is -0.2, and within-group standard deviations are 0.35 (expected scores for post treatment IIP-32 mean for IPT=1.2, SD=0.35; for EP=1.4, SD=0.35). The estimates about IIP-32 scores were taken from past studies where the IIP-32 overall mean score was found to be 1.62 (SD=0.45) for patients who were about to start psychotherapy and 1.21 (SD=0.57) post-treatment, 0.98 (SD=0.50) for a non-clinical sample (Barkham et al., 1996), 1.69 (SD=0.58) for patients with anxiety and depression and 1.57 (SD=0.61) for patients with eating disorders (McEvoy et al., 2013). We could not find comparable data for Veteran populations.

H2.2 Data Analysis

Basic statistical analysis**:** Initial statistical analysis will provide descriptive statistics on the demographic and clinical characteristics of the study participants using means, standard deviations, median and range for continuous variables and frequencies and percentages for categorical variables. To examine potential differences between the study groups at baseline, descriptive statistics will be obtained for each group and compared statistically using two-sample t-tests, nonparametric rank tests, chi-square and Fisher's exact test as appropriate. All outcome variables will be summarized using similar methods for pre and post-treatment, 3 and 6-month follow-up.

Outcome Assessment: The changes in the primary and secondary outcome measures from pre-to post-treatment will be compared by groups and tested via confidence intervals to examine the precision of equivalence (Hypothesis 1) and superiority (Hypothesis 2). Equivalency of the treatment groups in improving PTSD severity measured by CAPS (H_a: $-5<\Delta<5$) will be concluded if the two-sided 95% confidence interval for the difference between the change scores (Δ) lies within the interval (-5,5). Superiority of the IPT in improving interpersonal functioning measured by IIP-32 (H_a: difference between the IIP-32 mean post treatment [IIP for IPT-IIP for PE]<0) will be concluded if the upper bound of the two-sided 95% confidence interval for the difference is smaller than -0.05 (Rothman et al., 2012) Changes in the secondary outcome measures for social adjustment, quality of life and suicidal ideation will be compared post-treatment and at follow-ups using traditional hypothesis testing where H_a: absolute change in the IPT score is larger than the change in the PE score at alpha=0.05 (Hypotheses 3-5). Due to increasing chance of evidence in favor of non-inferiority in intent-to-treat (ITT) trials, we will analyze both ITT and per protocol (treated) samples for the primary outcome measures. To handle missing data, we will employ multiple imputation models for the ITT analyses. We will also examine the difference between patients who complete the study and those who were lost to follow-up based on baseline demographic and clinical characteristics to evaluate type of missingness, adherence to therapy and limits to generalizability.

Multivariate and Longitudinal Analyses: We will conduct secondary/advanced analyses by specifying multivariate and longitudinal regression models of the primary outcome measures, in order to estimate treatment differences adjusted by potential confounders, and to explore individual and group trajectories using available repeated measures data. Specifically, multiple linear regression analyses will be used to adjust the post-treatment change scores for baseline values of the outcome variable as well as age, gender, site and war era. These models will be estimated using cluster options (Intercooled Stata, command cluster) to account for the correlations between patients who were treated in the same hospital/site. Final analyses will include multi-level, mixed effect and/or linear growth curve models of the CAPS and the IIP-32 by combining the data across all time points to explore individual and group trajectories over time. The primary outcome measures will be regressed on a treatment group indicator and on covariates such as age, gender, war era, site and dummy variables for time points as fixed effects, along with random effects at hospital site and individual level. The statistical evaluation of the coefficient estimate for the treatment indicator (average difference between the groups across time points) will be based on both confidence interval and p-value approaches described earlier.

Exploratory Analyses: One of our goals is to better understand how IPT works towards the improvement of PTSD symptoms. Our study is not powered to detect the indirect effects of the IPT on decreasing PTSD severity through interpersonal functioning and social support scores. However, we propose exploratory analyses to test the mediating effect of the improved interpersonal functioning and social support on the relationship between the treatment methods and CAPS and Quality of Life Outcomes. We will employ commonly used linear regression models for mediation analysis to evaluate our hypothesis (Hypothesis 6) about the mechanisms of change (MacKinnon et al., 2007; Shrout & Bolger, 2002; Sobel, 1982).

H3. Time-Line

Activity	0-6 Mo	6-12 Mo	12-18 Mo	18-24 Mo	24-30 Mo	30-36 Mo	36-42 Mo	42-48 Mo
Hire, IRB, Train	XX							
Recruitment		XX	XX	XX	XX	XX		
Treatment		XX	XX	XX	XX	XX	XX	
Follow up		XX	XX	XX	XX	XX	XX	
Data entry		XX	XX	XX	XX	XX	XX	XX
Data analysis								XX
Manuscripts								XX

I. Dissemination and Future Plans

The proposed study is a randomized clinical trial of the effectiveness of IPT-PTSD for the treatment of PTSD and relationship problems in Veterans. We will register with ClinicalTrials.gov, which contains over 100,000 trials sponsored by a variety of federal and private industry sources, and receives over 50 million page views per month and over 65,000 visitors daily. Study findings will be submitted to a peer-reviewed journal and presented at professional conferences, such as the International Society for Traumatic Stress Studies, the APA, and appropriate VA and DoD conferences. If IPT-PTSD is found to be equivalent to PE in addressing PTSD (and superior in addressing interpersonal problems as hypothesized) we will consider multiple methods for further dissemination. We will create a fact sheet describing the intervention and findings to circulate to VA, National Guard, and other military officials, and relevant DOD programs, such as the Defense Centers of Excellence. The manual will be made available free of charge. After receiving permission, we will offer to begin dissemination by implementing the treatment at the Providence and New Orleans VAMCs. We would provide the manual and training to the mental health clinicians in the PTSD and Mental Health clinics, and encourage the use of relevant self-report outcome measures to provide an index of effectiveness in a naturalistic setting.

If there is interest in national VHA dissemination, the recent initiative to train mental health staff in Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE) therapy and facilitate implementation of these treatments throughout the VHA provides an ideal model for dissemination (Karlin et al., 2010). CPT and/or PE training has been provided to thousands of mental health staff through the VHA. National training initiatives have also provided training in additional treatments, including Cognitive Behavioral Therapy for Depression, Behavioral Treatment for insomnia, and others. Thus, the infrastructure and methods for broad dissemination already exist, and could be applied to IPT for PTSD, if this were determined to be a priority.

4. Human Subjects

A. Risk to Subjects

A1. Human Subjects Involvement, Characteristics, and Design

The total sample to be collected in this study will consist of 88 adult (age 18 and over) male and female Veterans with PTSD.

A2. Inclusion/exclusion criteria.

Inclusion criteria: Eligible participants will: (a) be at least 18 years of age, (b) meet current DSM-5 criteria for PTSD as assessed by the CAPS-5, (c) have a total CAPS-5 score of at least 23, (d) experience trauma during military service, and e) report impairment in at least one area of interpersonal functioning.

Exclusion criteria: Potential participants will be excluded if they: (a) have a DSM-5 diagnosis of current severe substance use disorder, (b) have current mania or unmedicated bipolar disorder, (c) have current psychotic symptoms, (d) have current suicidality or homicidality requiring hospitalization, (e) are a victim or perpetrator of severe domestic violence within the prior 12 months, (f) are currently receiving Cognitive Behavioral Treatment for PTSD, (g) have had psychotropic medication start or dosage change within the prior 4 weeks, or (h) have cognitive impairment precluding the ability to understand the ability to understand the concepts of the therapy or assessments.

A3. Sources of Materials

Research materials to be used for research purposes include (a) questionnaires and interviews measuring demographic variables, PTSD symptom severity, psychosocial functioning, concurrent treatment, lifetime and current psychiatric disorders, and symptoms of anxiety and depression; and (b) digital recordings of diagnostic interviews.

A4. Potential Risks

Potential risks include emotional distress due to discussing traumatic experiences, and breach of confidentiality.

B. Adequacy of Protection against Risk

B1. Protection against Risk

Risk: Emotional distress due to discussing traumatic experiences.
Minimization: Veterans will participate in assessments that may include discussion of

upsetting events that they experienced while deployed. Discussion of these experiences may make them feel uncomfortable.

However, the assessments are unlikely to be more upsetting than standard clinical assessments, and since participants will be recruited from VA mental health clinics, they will be familiar with these types of assessments. Veterans will be informed that they can refuse to answer any question they wish or stop the interview at any time. Any participant verbalizing or showing signs of distress will be asked to remain in the assessment or treatment setting until their distress is at a manageable and comfortable level. All study personnel who interact with study participants will have been professionally trained to respond to negative emotions if these should occur and to access emergency services if necessary. Dr. Shea or another licensed clinician will be available if needed during all assessments.

Risks: Breach of confidentiality.
Minimization: In terms of confidentiality, every effort will be taken to protect the confidentiality of the participants in this study. All information about the Veteran that is gathered during the research (including recordings) will be kept strictly confidential. However, Veterans will be informed that there is no guarantee that the information gathered during the research cannot be obtained by legal process or court order. Furthermore, Veterans will be informed that complete confidentiality cannot be promised to subjects, as federal and non-federal monitoring agencies such as the Department of Veterans Affairs may also access the Veteran's research records related to this study to monitor the security of the trial. All data will be received stripped of personal identifiers. Measures will be identified with a study ID number not based on a personal identifier. A cross-index of names and ID numbers will be stored in a restricted and password protected file on the Secure Research Server separate from all data files. Data entry and management will take place in VA offices in Bldg. 32. Additional precautions include: (1) Data sheets will be stored in locked offices**,** (2) data will be entered in coded form, (3) data will be stored in computer files on the secure Research Server and protected from unauthorized access by passwords, (4) information that might potentially allow an individual participant to be identified will not be allowed in any publications or reports sent to individuals outside the study, and (5) all employees who are to handle data will be trained in confidentiality policies and procedures. Records will be maintained per Veterans Affairs Record Control Schedule 10-1.

Regarding audio recordings used for treatment purposes (PE condition only), participants who borrow cassette recorders are advised to keep them in a secure, safe place when not in use. At each session, the audiotape content from the previous session is deleted. Participants, as outlined in the consent form, assume responsibility for the borrowed cassette recorders and information contained therein.

Adverse Event Reporting
In the case of an Adverse Effect (AE) or a Serious Adverse Effect (SAE), a written report of the AE or SAE will be prepared for the Chair of the IRB at the Providence VA Medical Center. Any such AEs or SAEs will be presented to the full IRB committees. SAEs will be reported

within 24 hours. Examples of serious adverse effects include death, life- threatening adverse events, suicide attempts, and inpatient hospitalization. The report of such AEs or SAEs will include whether they were expected or unexpected, a rating of severity of the event, a brief narrative summary of the event, a determination of whether a causal relationship existed between the study procedures and the event, whether the informed consent should be changed as a result of the event, and whether all enrolled participants should be notified of the event. The annual progress reports to the IRB require summary information regarding all AEs and SAEs occurring during that year.

Data Monitoring Committee

Additionally, a Data Monitoring Committee(DMC) will be constituted and will be responsible for monitoring the safety of participants and the quality of the data, as well as providing recommendations on the appropriate termination of the study either when significant benefits or risks have been uncovered or when it appears that the clinical trial cannot be concluded successfully. Members of the DMC will not be involved with the proposed project and will include a medical expert, a clinical trials expert, biostatistics expert, and PTSD expert. The DMC will meet 2-4 times per year. A report, submitted to the DMC prior to each meeting, will include concerns about significant safety and data monitoring issues such as recruitment, retention, and quality of data collected. The specific content of the reports to the DSM include information about AEs and/or SAEs, treatment retention, recruitment, reasons for drop-out, and interim efficacy data.

As they deem necessary, the members of the DSMB will evaluate whether the presence of early unanticipated therapeutic results or adverse consequences are significant enough to warrant amendment, suspension, or early termination of the study and will independently make recommendations to the PI to continue, to amend or to terminate the trial. Recommendations related to the study will be made in a written DSMB Report by the Board's Chairperson to the Principal Investigators and shared with the Providence IRB. Significant changes or amendments to the protocol, such as sample size or safety issues, will be reported to the IRBs should they occur.

C. Potential Benefits of the Proposed Research to the Subjects and Others

The risks to participants are judged to be acceptable relative to the anticipated benefits. The anticipated benefits of the study include advancement of knowledge about the potential efficacy of IPT-PTSD for Veterans with PTSD. By participating in the study, participants may benefit from the intervention that they will receive.

Given the level of risk(s) to the participants and the likelihood that some will benefit from the treatment (or from the additional assessment contacts) and the even greater possibility of benefits to the larger population of individuals with PTSD, the risk/benefits ratio seems favorable.

D. Importance of the Knowledge to be Gained

More research is necessary in developing treatments for PTSD that address the serious interpersonal problems common among this population. Some Veterans refuse or are not comfortable with initiating trauma- focused therapy, and alterative effective treatments are necessary to provide the range of treatment options to meet the needs of this population. It is hoped that information gained from this study will improve treatment for Veterans, even

if the Veterans themselves do not experience any improvement during their participation in the study.

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