Trauma Informed Guilt Reduction Therapy

NCT02512445

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8. Aims and Objectives

Primary Aim: To evaluate the efficacy of TrIGR for reducing deployment-related guilt in Veterans of OEF/OIF/OND.

Hypothesis 1: Veterans in TrIGR compared to Veterans in supportive care therapy (SCT), will have significantly greater reductions in deployment-related guilt severity at the end of treatment and post-treatment follow-up.

Secondary Aims: To examine whether TrIGR reduces distress and shame and improves quality of life. We are also interested in the degree to which gains are maintained during the follow up periods.

Hypothesis 2: Veterans in TrIGR, compared to Veterans in SCT, will have significantly greater reductions in distress, shame, guilt cognitions, avoidant coping, and significantly more improvement in their quality of life at the end of treatment and at post-treatment follow-up.

Hypothesis 3: Per the NAG model, guilt cognitions, distress and avoidant coping will partially mediate the treatment effect on guilt severity.

Exploratory Aim: By including Veterans with a variety of deployment-related presenting problems, we will be able to conduct exploratory analyses that will inform future research regarding for whom and under what conditions TrIGR is most effective.

Objective 1: To explore relationships between TrIGR effects and PTSD and depression symptom severity, suicidal ideation (SI) and alcohol/substance use.

Objective 2: To explore whether reductions in guilt, shame, and avoidant coping will partially mediate the treatment effect on PTSD symptoms among **Veterans with a PTSD diagnosis** and/or depression symptoms among **Veterans with a depressive disorder.**

9. Approach

9.1. Design. This prospective, randomized, controlled trial will assess **the efficacy of TrIGR as compared to SCT** for the treatment of male and female Veterans with guilt related to a traumatic event that occurred during deployment. 150 participants will be enrolled through the San Diego and Providence VAs and randomized at the individual level. All eligible participants will complete an in-person baseline assessment, receive 6 sessions of TrIGR or SCT in individual format, complete weekly measures related to the primary and secondary aims, and complete a follow-up assessment immediately post-treatment, and 3- and 6-months later.

9.2. Timeline. We propose a study lasting 4 years including:

Phase I Set up (months 0 - 5): Start-up activities will include finalizing approvals, hiring and training of the research staff and therapists providing the study interventions, and setting up data entry and management procedures in collaboration with study statistician, Dr. Golshan. Patient recruitment protocols will be developed, tested, and revised.

Phase II RCT (months 6 - 42): Participant recruitment and enrollment will occur in months 6 to 34, with the intervention period occurring from months 6 to 36. Assessment will continue for an additional six months past the end of the intervention period (to month 42) to complete the final follow-up assessments. Methods and procedures are consistent with CONSORT guidelines for conducting and reporting RCT's [49]. We expect to recruit 2-3 participants per site per month, which will allow us to meet our recruitment target of 150. Data entry and management will begin with preliminary statistical analyses in the second year and will continue through the end of the study.

Phase III Dissemination (months 43 - 48): The final six months will be used for data analysis and dissemination of results via conferences and in manuscripts.

9.3. Procedures. Eligible Veterans will be recruited from two VA Medical Center sites, one in San Diego, CA, and one in Providence, RI. Potential participants will be receiving or presenting to care at VA enrollment, primary care, mental health, MST, or other VA services and will be referred by clinicians or staff in those clinics (see letters in Support 2e - 2g). Veterans may also self-refer to the study in response to advertising materials that will be distributed in patient areas and in the community. All potential participants will undergo a brief (15 minute) screen (following informed consent to be screened) conducted by the site project coordinator to determine preliminary eligibility. Veterans who meet the screening requirements will complete consenting procedures and will be invited for a full baseline assessment. Participants who meet inclusion/exclusion criteria as confirmed by the baseline assessment will be randomized to TrIGR or SCT. All participants will be assessed at baseline, immediately post-treatment, and at 3- and 6-month post-treatment follow-ups. Participants will be compensated for completing each of the four assessments with $40 per assessment. We anticipate that baseline assessments will take approximately 3 hours and follow-ups will take approximately 2 hours. Participants will also complete brief weekly self-report assessments (15 minutes) during treatment. We will attempt to obtain follow-up data on all participants, regardless of whether they complete the intervention.

9.4. Participants: Inclusion/Exclusion Criteria, and Rationale. Participants will be male and female OEF/OIF/OND Veterans, at least 18 years of age, who endorse distress from guilt related to an event or events that occurred during a military deployment. Women and members of diverse ethnic and racial groups will be recruited for this project. Eligibility criteria were designed to recruit a heterogeneous and representative sample of Veterans with guilt and distress related to trauma that occurred on deployment. Eligibility criteria are broad in order to capture the many manifestations of distress related to guilt among Veterans.

Inclusion criteria: (1) having been deployed during Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), or Operation New Dawn (OND); (2) a score of 3 or higher ("very true" or "extremely true") on feeling posttraumatic guilt much or all of the time and scoring 3 or higher ("very true" or "extremely true") on at least one guilt cognition factor (hindsight bias/responsibility, wrongdoing, or lack of justification) on the Trauma Related Guilt Inventory [TRGI; 18]; (3) distress as indicated by an initial [BSI-18; 50] score over 63 and a Clinical Global Impressions Severity Scale [CGI-S; 51] rating of at least markedly ill; (4) not currently receiving trauma-focused treatment such as PE or CPT (those currently in treatment may qualify following completion); (5) English literacy; (6) intention to stay in Providence or San Diego area during study participation; (7) willingness to attend psychotherapy and assessment sessions; and (8) if meeting diagnostic criteria for mild or moderate AUD/SUD, willingness to set goals to reduce alcohol and/or substance use during the treatment period [52].

Exclusion criteria: Moderate or severe cognitive impairment on the Brief Neuropsychological (NP) Assessment Battery [53] as this may interfere with ability to benefit from treatment. Acutely suicidal individuals (assessed using the suicide items from the depression measures described below) will be referred for more appropriate treatment (see Human Subjects section). Current severe AUD/SUD (in the past two months) based on DSM-5 criteria will be excluded as these Veterans may require a higher level of care. Current psychosis or mania independent of substance use will be excluded because the presence of these disorders can impede therapy progress. Veterans residing more than 50 miles from their nearest study site, with life threatening or unstable medical illness, or inability to read will be excluded.

Who will not be excluded: Veterans with mild cognitive impairment, mild to moderate alcohol and substance use disorders, suicidal ideation without acute suicidality, and anxiety and depressive disorders will not be excluded because of their high co-occurrence with traumatic guilt [13-17] and recent findings that individuals with mild to moderate TBI can benefit from cognitive behavioral treatments [54]. We elected to allow Veterans to continue to engage in TAU other than trauma-focused treatments, as we do not expect TrIGR to be a stand-alone treatment for disorder specific conditions. Accordingly, all participants will be encouraged to continue to receive AUD/SUD and mental health treatment as needed, including pharmacotherapy, with their current providers throughout the study. TAU in both San Diego and Providence VAMCs consists of outpatient treatment for SUDs including relapse prevention using a

cognitive behavioral model, complementary groups such as relaxation training, sleep hygiene, and smoking cessation. Additionally, Veterans may be engaged in psycho-educational groups about PTSD (e.g., PTSD 101) that do not include trauma processing. Participants will be asked not to take part in any trauma-focused treatment such as PE, CPT, or Eye Movement Desensitization and Reprocessing (EMDR) during study participation. We will carefully track all treatment received during the active treatment and follow-up phases of the study and will evaluate whether differences in TAU are roughly equivalent across treatment groups and sites. If differences across sites exist, site will be included as a fixed effect in our analyses.

9.5.1. Recruitment. We will use a multi-pronged recruitment strategy to obtain an intake rate of approximately 2-3 participants per month per site during the study. Veterans can contact our study in response to (1) a referral from staff or providers in mental health, primary care, MST, and substance use treatment programs; and (2) advertisements in print and web-based media posted throughout the study sites. Additionally, Veterans newly referred for mental health treatment first attend an orientation group or an initial mental health assessment where the services provided in the program are explained. Providers will describe this study as one of the options for Veterans who they deem to be potentially appropriate. The Project Coordinator at each site will also attend the orientation groups to present information about the study. Interested Veterans will complete a "Consent to Contact" form that gives research staff permission to contact the Veteran to further explain the study and conduct an initial screening. Potential participants who contact us by telephone will first provide verbal consent and undergo the initial screening over the telephone.

Whether by telephone or in person, the screening takes approximately 15 minutes to complete and is intended to identify guilt and distress related to a traumatic event that occurred during deployment. For those who screen positive, an appointment will be made for written informed consent and a full baseline assessment. Similarly, the primary methods of recruitment for existing mental health patients will be through provider referral or self-referral. Provider referral has proven successful for recruitment in our previous trials. The study team will reach out to relevant mental health providers at each site on a regular basis (e.g., by presenting in clinic meetings and/or targeted emails) to educate providers about the study and maintain their awareness of the opportunity. Providers will share information about the study and request permission for the study team to contact potentially eligible patients. If a Veteran is interested in participating in the study, he/she will be contacted by study staff and complete the telephone screening as described above. Alternatively, Veterans may self-refer to the study based on advertisements or word of mouth.

9.5.2. Randomization. Dr. Golshan will prepare the randomization table prior to the start of recruitment for each site. Randomization will be conducted separately at each site. We will use a permuted block randomization system, in which treatment assignment order is random within each block, with an equal number of participants assigned to each treatment. Block sizes will vary in random sequence between 2 and 4. We will stratify randomization by gender. We will evaluate successful randomization of other factors, such as symptom and substance use severity and demographics, and control for these factors if needed as described in section 9.11.2.

9.5.3. Feasibility of recruitment. VASDHS will serve as one of the two recruitment sites for the proposed research. We expect that three clinics within mental health services from which we will recruit heavily will be the PTSD treatment program, the Substance Abuse Mental Illness (SAMI) program, and the MST clinic. The PTSD clinic (which Dr. Norman formerly directed) completes over 50 new intakes with OEF/OIF/OND Veterans each month. During Q4 of FY2014, 540 OEF/OIF/OND Veterans with a PTSD diagnosis were seen for mental health services (either three or more sessions of psychotherapy or one medication appointment). The SAMI program has 34 OEF/OIF/OND Veterans enrolled in in the past three months. The program completes approximately 8 new intakes with OEF/OIF/OND Veterans each month. The MST Clinic sees approximately 18 new Veterans and 60 ongoing Veterans per month who are OEF/OIF/OND. We will have access to eligible participants based on the relationships and approvals we have already secured as part of Drs. Norman and Allard's ongoing research programs and through their roles in the PTSD and substance use treatment programs at the San Diego VA. Dr. Norman's current VA-

funded RCT is recruiting a similar population (although not limited to OEF/OIF/OND Veterans) and has been recruiting an average of 4-5 Veterans per month, 42% of whom (n = 33) are OEF/OIF/OND. Recruitment in the current RCT will be coming to completion as recruitment for the proposed study would be beginning, thus we will continue to receive a steady flow of referrals to our program of research.

Within VASDHS, we assessed feasibility of recruitment for the proposed study in regard to the inclusion criteria of having guilt related to trauma and having served in OEF/OIF/OND, neither of which are required in our current studies. Specifically, we examined what percent of participants enrolled in Dr. Norman's current studies during the past year would meet the criteria regarding trauma related guilt using the Trauma Related Guilt Inventory (TRGI) and having served in OEF/OIF/OND. 27% (n = 84) of Veterans initiating outpatient PTSD treatment and 36% (n = 13) of PTSD/AUD Veterans enrolling in Dr. Norman's current RCT met the OEF/OIF/OND and TRGI guilt criteria described in section 9.4 under Inclusion Criteria. We will have 28 months of active recruitment, and thus need to recruit 2-3 Veterans per month per site to reach our target of 75 at the San Diego site. Given recruitment rates in our current projects (4-5 per month), the high rates of guilt endorsed by our current OEF/OIF/OND participants, and the fact that neither AUD nor PTSD diagnosis is required for the proposed study, **our recruitment target is highly feasible.**

The Providence VA Medical Center (PVAMC) is the other site for the proposed research. The PVAMC is a 120 bed general medical facility that provides acute inpatient and outpatient care to the Veteran population throughout Rhode Island and Southeastern Massachusetts. During Fiscal Year 2014, over 2200 OEF/OIF/OND Veterans sought mental health treatment in the outpatient PTSD, General Mental Health, Returning Veterans, and Substance Abuse Treatment Program clinics. These numbers are more than sufficient to meet our recruitment goals of 2-3 Veterans per month for a total of 75 OEF/OIF/OND Veterans with deployment-related guilt and distress.

9.5.4. Attrition. Based on attrition rates in comparable research studies of exposure-based treatment for trauma related distress and our own preliminary work, we conservatively estimate that approximately up to 20% of participants will be lost to measurement follow-up prior to the final (6-month post-treatment) assessment [55]. Completion of TrIGR is defined *a priori* as attending 75% or more of the planned treatment sessions (see section 9.11.1. regarding the data analysis plan, including the plan for handling missing data and attrition).

9.5.5. Patient Retention Methods. The investigators have extensive experience in maintaining study cohorts over substantial periods of time. For example, in Dr. Norman's current VA RCT, drop out has been 15% of 60 participants randomized to one of two psychotherapies for concurrent treatment of AUD and PTSD. Based on other studies with similar populations [56], we have estimated our dropout rate prior to the final assessment to be 20%. The following steps will be taken to insure high retention: (1) at all assessment points, participants will be asked to provide contact information for at least two close friends or relatives and permission to contact them; (2) a database accessible only to study staff will be maintained as a participant tracking system; and (3) computer public search engines (e.g., Accurint) will be used to locate those lost to follow-up. Prior research has given some indication of reasons why individuals may drop out of treatment [57]. We address these barriers by offering therapy at a centrally located site that is accessible by public transportation and offers free parking, by offering transportation reimbursement, and by offering therapy in individual format during daytime and early evening hours. We will encourage all participants to have a case manager through the VA so that case management issues are addressed in both treatment modalities.

9.5.6. Women and Minorities. Women comprise 11% (e.g., SAMI clinic) to 60% (Military Sexual Trauma clinic) of the Veterans seen in the clinics from which we will be recruiting and approximately 24% of Veterans in the program are minorities. Consistent with these demographics as a whole, 11% of participants in our integrated PTSD/AUD intervention studies have been women. Based on the 2010 US Census figures and consistent with our other research, we anticipate enrolling the following ethnic minority breakdowns in San Diego: Hispanic/Latino (32%), Other (including mixed race; 19%), Asian (11%), African American (5%), and Native American/Alaskan/Pacific Islander (1%). Given that this study will include recruitment from the Military Sexual Trauma Clinic, the increasing numbers of women in the

military, and increasing Hispanic proportion of the population in southern California, we will continue attempts to oversample these groups to obtain adequate recruitment of females and minorities to examine effect sizes for these groups relative to male and Caucasian counterparts.

9.6. Compensation. Participants will be compensated up to $160 for their time and effort for completing assessments: $40 each for baseline, post-treatment, and for the 3- and 6-month post-treatment follow-ups.

9.7. Treatment Conditions

9.7.1. Experimental condition – TrIGR.

TrIGR will be administered during six 90-minute individual sessions. **Module 1** (delivered over 2 sessions) includes an overview of common reactions to trauma and provides psycho-education regarding posttraumatic guilt and shame. We review the NAG model and then review common sources of deployment-related traumatic guilt and shame [58, 59], such as taking part in or witnessing atrocities, failing to perform a duty, failing to stop a sexual assault, or enjoying or feeling nothing when killing.

Module 2 (delivered over 2 sessions) uses cognitive restructuring to help patients evaluate the four types of cognitive errors contributing to posttraumatic guilt identified in prior research [60]. Many Veterans have more than one trauma over which they experience guilt. Two sessions of Module 2 gives us adequate time to review up to three traumatic events. To identify cognitions that are associated with guilt (e.g., "I should have…" or "I shouldn't have…"), the therapist conducts a detailed review of the traumatic event(s) with the patient. This detailed review is needed because what may initially appear to be the source of guilt (e.g., "I killed someone") may turn out be a more nuanced cognition upon further exploration (e.g., "I was justified in killing the insurgent, but I shouldn't have enjoyed it"). Each of the four cognitive errors is reviewed; however, the amount of time dedicated to each is tailored to the patient's needs and experiences.

In reviewing hindsight bias, a patient may express beliefs that "I knew the combatant wasn't a threat, but I shot anyway." The therapist leads the patient through several exercises to normalize how common it is to come to believe after the fact that someone had information that they did not actually have until later. Therapists then explore with patients what they actually knew at the time versus what they came to believe they knew after the fact given the negative outcome.

In the justification analysis, the therapist and patient explore what choices were truly available at the time of the trauma as people frequently believe after the fact that there must have been a way for a better outcome to have occurred. Patients write down all of the choices available to them during the event (e.g., shooting the person who is suspected to be strapped with a bomb who is ignoring orders to not come any closer, not shooting) and the potential pros and cons of each option. This examination generally leads to the realization that there were no "good" options, all options would have led to some undesirable outcome that could also contribute to regret, that an idealized option did not exist at the time, or that the option taken was either the best of the available options in some way or no worse than the other available options.

In the responsibility analysis, the patient initially rates his/her perception of responsibility for what happened on a 0-100% scale. The therapist then leads the patient through an exercise to demonstrate that there are multiple factors responsible for all outcomes. The patient and therapist brainstorm together to identify all of the other factors that contributed to the traumatic event (e.g., orders, rules of engagement, how much sleep the patient had had in the days leading up to the event, etc.) and the percent to which the patient feels each was responsible. Patients are then able to view their self-assigned level of responsibility relative to the total of these other factors.

Finally, in the wrongdoing analysis, the difference between intentionally setting out to do harm and an unfolding bad outcome is discussed. This discussion is generally straightforward for many deployment traumas where Veterans can acknowledge that they did not intend to cause harm (e.g., switching patrols with someone who ended up getting killed). However, this discussion may be more complicated with a Veteran who hurt or killed others outside of the rules of engagement. In such cases, helping the Veteran

consider the context of war, emotions that were at play such as anger and grief, the extent of the Veteran's guilt/remorse now and how much he or she has suffered since the event, or if the person intends to do anything similar again, can help give context to the concept of wrongdoing. The goal is not to lead someone to believe that the trauma "was not his fault" but rather to help put the traumatic event and actions/choices into context to help the patient move toward a more positive life marked by less suffering and impairment.

Module 2 ends with a discussion of the function that guilt and shame have served in the patient's life (e.g., "It keeps me from hurting more people") and what it might mean to feel less guilt/shame. This discussion allows the therapist and patient to transition to **Modules 3 and 4** (1 session each) where the focus is on identifying the patient's values and setting goals to live a more value-driven life. The point is made that certain values must be very important to the patient since violating a value during the trauma has caused a great deal suffering since. Patients cannot undo the past, but can take action to live a more value-driven life going forward. Positive ways to express values rather than through guilt and shame are discussed with an aim of setting goals toward value driven growth. Norman and colleagues describes the protocol in more detail [43].

9.7.2. Comparison Condition – Supportive Care Therapy (SCT). Supportive Care Therapy (SCT) is a non-directive therapy and quite distinct from TrIGR both theoretically and in practice. SCT applies Rogerian principles of unconditional positive regard, genuineness, and empathic understanding in session and emphasizes the therapeutic relationship as the mechanism that enhances well-being and facilitates healing. SCT therapy will employ specific techniques to convey a deep understanding of emotions, thoughts, and behaviors of the Veterans receiving this treatment. Specific techniques include content-focused paraphrasing, exploration through open-ended questions (with a goal of empathic understanding), and emotion-focused reflection and validation. At the end of each session, therapists will offer an integrative summary of the session's content and process.

SCT will be offered in six 90-minute sessions in order to parallel the dose of TrIGR. Because this is a client-centered therapy, Veterans will be free to choose the content of each session. If Veterans elect to discuss their trauma experience, this will be allowed and therapists will respond to this content as they would any other content area – with an open, nonjudgmental stance and unconditional positive regard. Consistent with the SCT model, therapists will be explicitly instructed not to provide advice, assign activities, or suggest strategies and techniques employed in TrIGR or any other evidenced-based intervention (e.g., in vivo exposures). Otherwise, there are few guidelines in terms of the structure and content in SCT. The first few sessions will emphasize rapport building and the remaining sessions will have an increasing focus upon a review of the process of the therapy as a whole and the relationships that were formed between the therapist and Veteran.

The SCT condition has been used in previous psychosocial intervention studies, and the PI and her collaborators have utilized SCT in other RCT's with OEF/OIF/OND Veterans (e.g., NCT01009112). Drop-out in our past trial did not differ between SCT and other conditions. The rationale for using SCT as a comparison condition is to provide a credible therapeutic alternative to control for nonspecific therapeutic factors [61, 62]. In addition to controlling for passage of time, testing, and statistical regression toward the mean, this non-specific comparison condition will control for the nonspecific aspects of therapy that characterize most forms of therapy and are distinct from the hypothesized active mechanisms of TrIGR.

Selection of control groups for psychosocial treatments is complex. Unlike in medication trials, it is not possible to create a placebo treatment that controls for all aspects of the treatment delivery except the active mechanism(s). A variety of control conditions have been used in behavioral treatment research, but the optimal control depends on the stage of research. For early Stage II trials [63, 64] such as the proposed study, non-specific comparison designs have been recommended [e.g., 62]. Dr. Shea, who has extensive experience delivering and supervising non-specific therapies across multiple trials ([e.g., 62] , NCT02157779), will train and supervise the therapists on SCT (see below). The manual can be found in Appendix 12e.

9.7.3. Therapist Training. Two therapists will be hired for ten hours per week each at each site (four therapists in total). All therapists will deliver both therapies with careful ongoing fidelity assessment to monitor for cross-over effects. We considered hiring one therapist for twenty hours per site but decided on

two per site to be better able to control for therapist effects. The team of investigators will train study therapists on both TrIGR and SCT using audio recordings, role plays, and evaluating fidelity on at least two patients, and will hold weekly ongoing supervision sessions. Therapists will first receive didactic training in both protocols, including a review of the research on guilt related to trauma, featuring demonstrations and role-plays of specific components of each intervention. Therapists will treat at least two patients to fidelity with each protocol (see 9.7.4) before treating a study patient. Therapists will be carefully supervised using audio recordings of therapy sessions. Weekly clinical supervision will be provided by Dr. Allard for TrIGR and Dr. Shea for SCT and will examine clinical issues and adherence to the study protocol. Dr. Norman and Dr. Allard developed TrIGR, Dr. Capone has conducted research with TrIGR, and Dr. Shea has delivered and supervised supportive non-specific therapy protocols in several large trials [e.g., 62] including her current research (NCT02157779).

9.7.4. Treatment Fidelity. Our approach to treatment fidelity and adherence utilizes accepted standards [65] including: (1) treatment manuals with weekly objectives, outcomes, and agendas, (2) therapist training (to avoid bias, therapists will be trained for both interventions), and (3) ongoing evaluation of treatment fidelity through audio-rating of therapy sessions and supervision. To identify problems early, Dr. Browne will listen to audio-recordings of each therapist once per week for a period of 6 weeks post-training and complete fidelity rating sheets for each session (see Appendix 12f-g). Corrective feedback will be provided as needed. Thereafter, Dr. Browne (who is trained to fidelity and experienced in delivering and rating fidelity for both TrIGR and SCT) will rate 10% of remaining audio-recorded sessions at random as determined by the study statistician, Dr. Golshan. Further, Drs. Allard (for TrIGR) and Shea (for SCT) will have weekly supervision of therapists to evaluate their implementation of and adherence to the therapy manuals. The participant evaluation method of quality assurance involves asking each participant to complete a brief checklist that queries the content of the session (e.g., "Did the therapist discuss the relationship between guilt and trauma?"). This method provides estimates of inter-rater reliability. We will maintain inter-rater reliability at ? = .90. In addition, therapists will keep a session-by-session "TrIGR Session Tracking Form" and "SCT Session Tracking Form" which includes self-ratings about the "% of time" of each session was spent "using the manual" and covering the relevant module content.

9.7.5. Standard Pharmacotherapy. In regard to pharmacotherapy, the VA follows treatment guidelines that require standardized prescribing practices for individuals with PTSD, depression, and AUD. We expect at least 85% of participants will be receiving medications based on these guidelines. We recognize that pharmacotherapy and changes in medications will be an uncontrolled source of variance but expect that any changes will be similar across treatment conditions and thus balanced by randomization. We considered recruiting participants who were not on medication or asking participants to be medication stable prior to study entry. However, psychotropic medications have well documented effectiveness for the treatment of PTSD, anxiety and depression and withholding such medication would be inappropriate for this high-risk population. Study coordinators will record from VA medical records and patient self-report all treatment (psychotherapy and medication) in which Veterans participate in the VA. Participants will also be asked about any treatment outside of the VA. We will compare treatment as usual between our two conditions and, if differences in any variables are found, include these as covariates in our analyses.

9.7.6. If Participants' Alcohol/Substance Use Worsens During Treatment. If a therapist or assessor identifies worsening alcohol or substance use, the investigators will evaluate whether best clinical care indicates a need for more intensive SUD treatment. PIs will be contacted if a participant reports increased or risky substance use. If more intensive treatment is needed for any reason, we will assist in establishing treatment, then discontinue study participation following a final evaluation. Please see the Human Subjects section for the plan to address clinical worsening during study participation, including if participants display safety concerns such as suicidality or risk of violence.

9.8. Research Assessments

9.8.1. Outcomes. The primary efficacy outcomes of interest are reduction in the severity of guilt related to a deployment trauma at post-treatment and follow-up. We will also examine distress, shame,

quality of life, PTSD symptoms, depression symptoms, alcohol and substance use, suicidality, and potential mediators and moderators including avoidant coping, guilt cognitions, treatment process variables (e.g., attendance, homework completion), gender, and cognitive performance. All measures can be found under Support Documents.

Primary Outcome. Trauma Related Guilt Inventory [TRGI; 18] is a 32-item validated self-report measure assessing traumatic guilt. The TRGI has three scales – Guilt Severity, Distress, and Guilt Cognitions. We will use the TRGI as one of our eligibility criteria (see inclusion criteria, section 9.4) and to monitor changes in guilt and related cognitions over time. Guilt severity will be the primary outcome of interest. It is computed by adding items regarding guilt frequency and guilt intensity. Changes in guilt cognitions will be examined as a partial mediator of treatment outcomes. Internal consistency is high for the TRGI (guilt severity = .90, distress = .86, guilt cognitions = .86).

Secondary Outcomes. The Brief Symptom Inventory-18 [BSI-18; 50] will be used for inclusion criteria and to assess change in self-reported distress over the study period. The 18 items are on a five-point Likert scale assessing the degree to which participants were distressed or bothered by mental health problems in the last seven days. The BSI-18 generates four scores: a total score [global severity index (GSI); scores ranging from 0 to 72], and three subscale scores for depression, somatization, and anxiety (scores ranging from 0 to 24). Internal consistency for the BSI is adequate (α = .89 for GSI, α = .84 for depression, α = .74 for somatization, and α = .79 for anxiety) and concurrent validity with the longer-form measure the BSI-18 was derived from ranges from .91 to .96. A Clinical Global Impressions Severity Scale [CGI-S; 51] rating of at least markedly ill will be required for study entry. The CGI-S requires clinicians to make two ratings on a 7-point categorical scale: (1) severity of illness within last seven days, and (2) global improvement from baseline. The CGI-S is commonly used in clinical trials to assess changes in distress severity, and has shown predictive utility in studies of schizophrenia, depression, social anxiety, and PTSD. We will use the CGI-S to assess clinician ratings of change in distress severity. In combination, the BSI-18 and the CGSI-S will allow us to have multi-modal assessment (i.e. self-report and clinician rating) of distress severity.

We will measure shame using the Internalized Shame Scale [ISS; 66], a 30-item self-report measure assessing shame proneness scored on a 5-point Likert scale. The ISS yields sum scores for two subscales, self-esteem and internalized shame and has been well-validated with research and clinical populations. The World Health Organization Quality of Life [WHO-QOL-BREF; 89] is a 26-item measure that assesses quality of life across four domains: physical, psychological, social relationships, and environment. The WHO-QOL-BREF has excellent internal validity and test-retest reliability.

The Clinician-Administered PTSD Scale for DSM-5 [CAPS; 67] is a semi-structured interview used to assess PTSD diagnostic criteria and severity. Respondents select up to three of the most traumatic events they have experienced, and those events are used as the basis for assessing PTSD symptoms. The CAPS assesses each of the 20 items from the DSM-5 criteria B, C, D, and E and it has demonstrated high levels of internal consistency, good interrater reliability, and excellent convergent validity. The CAPS can be administered in about 60 minutes, and it has the advantages of categorical (diagnostic) or dimensional scoring of PTSD. The PTSD Checklist – 5 [PCL-5; 68] is a brief self-report instrument to measure PTSD symptom severity. It consists of 20 items, scored on a 5-point scale (0 = not at all to 5 = extremely), that correspond to the DSM-5 symptoms of PTSD. The PCL-5 is still being evaluated; however, preliminary studies report high internal consistency (alpha ranges between .95 and .97) and high correlations with the original PCL (between .88 and .97) [69].

Depression. The Patient Health Questionnaire [PHQ-9; 70] is a self-report scale listing common symptoms of depression. It is among the most widely used self-report depression measure in clinical populations, facilitating comparison between this investigation and others.

Exploratory outcomes. The Timeline Follow-back [TLFB; 71] will be employed at all assessment points to evaluate alcohol and other substance use during the 90 days preceding each interview. The Quantity-Frequency Index[72] and maximal consumption will be calculated for alcohol use. Drug use indices will be similarly derived for opiates, marijuana, and other drugs. The TLFB will be used at each follow-up to establish: percentage days heavy drinking, percent days abstinent, length of initial

abstinence, length of use episodes, severity of relapse and current alcohol/drug use pattern. A self-report Substance Use Inventory [SUI; 73] will be administered bi-weekly at treatment sessions. The inventory asked patients on which of the preceding seven days they had used alcohol or any of seven major types of drugs. Participants will be administered the AUD and SUD sections of the SCID for DSM-5 at baseline.

The Columbia-Suicide Severity Rating Scale [C-SSRS; 74] is a standardized 8 point clinician-administered rating system designed to track suicidal adverse events across a treatment trial and cover the wide spectrum of suicidality including ideation and intent.

The Brief COPE [75] is a 28-item measure of cognitive and behavioral coping scored on a Likert scale. It assesses coping styles including avoidant coping (e.g., denial, substance use, behavioral disengagement).

9.8.2. Baseline Measures. The Brief Neuropsychological (NP) Assessment Battery targets neurocognitive skills previously associated with substance abuse treatment outcomes [e.g., 53] and is limited in length (30 minutes) to facilitate compliance. All NP measures will be administered by the trained assessors in a standardized fashion designed to minimize fatigue and possible carryover effects (i.e., if a participant performed poorly on any one task). The measures, grouped by cognitive domain, include: 1) General Intelligence: American National Adult Reading Test (ANART); 2) Executive Functioning/Problem Solving: Wisconsin Card Sort; 3) Attention: WAIS-III Digit Symbol; 4) Verbal Learning and Memory: Hopkins Verbal Learning Test (HVLT). Each raw test score will be transformed into a T-score (M = 50, and SD = 10) based on the degree of deviation from the normative age-referenced mean score. Then, domain T-scores will be calculated for each subject by averaging T-scores within that domain. This brief battery takes approximately 30 minutes and is a shortened version of the assessment utilized in our previous studies.

Mental Health Problems. Modules of the Structured Clinical Interview for DSM-5 [SCID; 76] will be used to assess depressive disorders, alcohol and substance use disorders, and bipolar and psychotic disorders (for exclusion criteria). The research version of the SCID for DSM-5 will be available by the end of 2014 [77] (well in advance of when we would initiate this proposed study).

9.8.3. Treatment Process Measures. The Expectancy of Therapeutic Outcome (ETO), a 5-item self-report scale that evaluates treatment credibility, will be administered by the therapist in Session 1 after the therapist has provided the overall rationale for the treatment program. Questions are rated on a 0 to 8 Likert-type scale, with total scores from 0 to 32. The Additional Treatment Inventory (ATI) assesses additional treatment sought after the completion of study treatment. It asks about both psychiatric medications and psychotherapy. The Client Satisfaction Questionnaire [CSQ; 78] is an 8-item self-report scale measuring satisfaction with treatment. It has excellent internal consistency and correlates with therapists' estimates of client satisfaction. This instrument will be used to measure participants' satisfaction with the interventions.

Table 3. Measures

9.8.4. Medication Adherence. The ACTG Interview of Antiretroviral Medication Use (AIAM) will be used to assess medications that participants are taking and adherence to medication regimens. This interview was developed by the Adult AIDS Clinical Trials Group (ACTG) to assess in detail HIV medication adherence over the previous four days and takes about 10 minutes to complete [79]. The measure was modified for the current study to assess adherence for prescribed psychotropic medications by omitting references to HIV or AIDS and omitting the last item that lists side-effects that are common to HIV medications. The accuracy of self-reports of medication adherence has been questioned, and more objective methodologies are available, such as unannounced pill counts and medication bottle caps containing microchips that record medication adherence. However, for the current study, we have selected this self-report measure that requires less time, effort, and costs and has been validated when compared with other methods. Additionally, based on our prior research with Veterans, there are substantial differences in number and types of medications prescribed, complicating alternative non-self-report assessment procedures.

9.9.1. Assessor Training and Evaluation. Each site will have a primary assessor (15 hours per week) and a back-up assessor (up to five hours per week) who will be utilized if the primary assessor is unavailable or unblinded. Both will be blind to treatment condition. Dr. Lang, Dr. Norman, and Dr. Capone will train the assessors at both sites using audio-recordings recordings, role plays, and jointly conducted interviews and will hold weekly ongoing supervision. Dr. Lang will also view randomly selected audio-recordings of assessment sessions to provide feedback and ensure inter-rater reliability. During each assessment, the assessors will evaluate any major changes in health (e.g., overnight hospitalizations), possible adverse events, suicidal ideation, and general well-being. Therapists will also assess for clinically significant worsening during therapy sessions. Any exacerbation of symptoms or alcohol/substance use will be reported and discussed with Dr. Lang and the supervising investigator so that appropriate action can be taken if necessary. Data collection staff and intervention staff will be strictly separate. All assessors will complete standardized training to criterion for the CAPS, SCID, NP, and TLFB assessments. The assessor will observe a minimum of two assessments for each measure and then be observed for a minimum of two assessments. Additionally, the assessors will be tested for reliability (once every six months), and participate in weekly staff meetings to address questions. Training is also provided on common issues associated with self-report measures. These training procedures are all in place and have been on-going in Dr. Norman's, Dr. Schnurr's, Dr. Capone's, and Dr. Lang's research labs.

9.9.2. Other Personnel. The San Diego site will have a full time coordinator who manages day-to-day operations and communication between the study sites and governing bodies. The Providence VA will have a half-time coordinator who manages the day-to-day operations of the Providence site. Each site will have two part time (10 hours/week) therapists (see section 9.7.3.) and two assessors, blind to treatment condition, who conduct study assessments (see section 9.9.1.).

9.10.1. Quality Control. Data Safety Monitoring will include periodic review and reporting of participant accrual, adverse event rates, treatment compliance, and drop-out rates. Study termination will be triggered by excessive drop-outs or adverse events. If treatment is needed during the follow-up phase due to increased substance use or serious psychiatric/medical symptoms, patients will be referred to appropriate treatment and followed by the PI and study psychiatrist until treatment is initiated. Adverse events will be reported to the DoD and VA IRBs and R&D (serious adverse events within 48 hours) and clinically managed as appropriate, including hospitalization if necessary. A summary of all adverse events will be submitted to the DoD annually. The PIs and a co-investigator (licensed psychologists in their respective states) will be available by pager 24-hours a day. The PI will be responsible for initial determination of serious adverse events from non-serious adverse events.

Tonya Masino, M.D. will serve as the medical monitor. Her functions include the following: (1) Review of research protocol and plans for data safety and monitoring; (2) Evaluation of the progress of the study every 6 months, including the quality of data collection, security and quality, participant recruitment/retention, participant risk and benefit, and any other factors affecting study outcome; (3) Consultation regarding continuation or termination or other modifications of the trial in the service of protecting safety of study participants; and (4) Evaluation of study adverse events and consultation to maximize protection of participants. Progress evaluations every 6 months will be provided to VA IRB, R&D, and HRPO, and study investigators. The medical monitor is not an investigator in the study and does not have any conflict of interest.

9.10.2. Data entry and management. All data are collected on forms, which are identified by a unique participant ID number, protocol ID number, and protocol phase and visit, and are entered into already exiting Microsoft Access© database. A protocol data collection schedule is used to monitor participant progress through the protocol, missing assessments, and other protocol deviations during the study. Participants will be queried immediately to complete or clarify blank or illegible responses. Refusal or inability to respond to items will be coded, with explanations documented. Data entry screens incorporate range checks or lists of valid responses for each item. Forms with missing or invalid data in key identifying fields are referred back to raters for correction before entry. Other missing or invalid data will not prevent the form from being entered, but will be flagged for correction. Participant confidentiality

is maintained by methods described in the Human Subjects protocol by keeping identifying information separate from study data in secure location and restricting study data access to specified personnel. Only approved study personnel will have access to study data, and all study personnel will be trained regarding privacy and security issues. Most authorized personnel will have read-only access to digital data; write/ edit access will be restricted to study data management staff. Data management and statistical analysis will be performed/supervised by the study statistician, Dr. Golshan.

Secure information will be accessed, stored, and destroyed according to a data security plan that will promote security and privacy. Data entry and security procedures have been in place in Drs. Norman, Lang, Schnurr, Capone, and Shea's studies over the course of many trials.

9.11. Statistical Considerations.

9.11.1. Statistical Analyses. In the initial 3-6 months, data management procedures will be developed and put into practice. Data will be entered as it is collected and quality assurance checks conducted on an on-going basis (e.g., double entry and cross validation). Data analysis will be performed in multiple stages. In the initial stage, analyses will be conducted on an on-going basis to assure strict adherence to important issues for clinical trials, such as treatment fidelity, therapeutic alliance, and therapist effects. Next, preliminary analyses will be performed by examination of the distribution of variables to assess their characteristics (means, standard deviations, and skewness). Descriptive statistics and graphs will be used to summarize the characteristics of the study population. Continuous measures will be tested for normality and homogeneity of variance. Non-normally distributed variables will be transformed to meet the normal distribution assumption for linear models. Randomization will be assessed by performing a series of Wilcoxon-rank sum tests, $?^2$ or Fisher's exact tests to compare the groups on demographic and initial baseline clinical variables. Any variables on which the groups differ initially will be explored as covariates in subsequent analyses, as described in detail for each hypothesis, and we will take this into account in the interpretation of the outcome.

In the second stage, we will perform sensitivity analyses for the impact that potentially informative missing data may have on the analyses. The selected method of data analysis is robust with respect to drop-out and missing data, unless the drop-out mechanism or cause of missing is informative. We will use pattern-mixture models to assess if there is bias due to drop out or missing data. These mixed models allow us to assess whether important estimates are dependent on missing data patterns, and provide overall estimates of effects by averaging over the various missing-data patterns [80]. In addition, we will consider the extension of the Pattern-Mixture models [81], which includes the incorporation of random effects in the Pattern mixture model, which allow subject-to-subject heterogeneity. All hypothesis tests will be intent-to-treat, using SPSS version 21, and will be two-sided at the .05 level where applicable. We will adjust p-values for multiple testing within each hypothesis separately by using a Bonferroni correction whenever more than one variable is being tested.

Type I error will be controlled through the following steps. The data analysis method we selected reduces the number of dependent variables drastically. We have restricted potential predictors to those with strong evidence and/or strong rationale for having an effect on the dependent variable, and in most cases we have further restricted potential predictors to one representative of each. Also, an adjusted significance level (.01 rather than .05) will be used if applicable.

Missing data values will be minimized by intensive training of the assessors in techniques of clarifying answers and checking questionnaires while participants are on-site. When missing values are identified, several approaches to acquire the necessary data will be employed: 1) if at all possible, participants will be rescheduled within 24 hours of completion of tests or interviews; 2) if a participant cannot be rescheduled, an effort will be made to send a tester to the individual's place of residence within the same period; 3) missing data will be examined to assess randomness. We expect missing data to be randomly distributed and will impute appropriate values (see below). Missing data (i.e., loss to follow up) will be tested to determine if it is informative, and the methods developed by [82] and [83] to test for completely random dropouts will be applied. If necessary, the techniques of [84] applicable to generalized

estimating equations models will be used to impute missing values.

We will test whether drop-out is random or systematic by comparing the drop-outs with the study completers on the baseline data. An absence of significant differences would support the random nature of drop-outs. Effect of drop-outs will be minimized by the following steps: First, selected data analysis method allows the inclusion of subjects who drop-out or were terminated early in the study, without relying on data imputation procedures. Therefore, no subjects will be excluded from the analyses due to their study status. Second, effect of any systematic differences between the drop-outs and completers will be explored by including the variable of concern to the model as a covariate.

9.11.2. Primary Outcome Analyses.

Hypothesis 1: Veterans in TrIGR, compared to Veterans in SCT, will have significantly greater reductions in deployment-related guilt severity (TRGI) at the end of treatment and follow-up period. This hypothesis will be tested using Mixed Effects models. We will examine two specific forms of the Mixed effects model strategy; random regression models (RRM), also known as hierarchical models (HLM), Linear Mixed Effects models (LMEs) or multilevel models; and mixed model analysis of variance (MMANOVA). The Hierarchical Linear Model assumes that change over time is linear while MMANOVA considers time as a categorical classification variable and does not assume any specific profile between the outcome variable and time. Each outcome variable will be graphed versus time for each subject to evaluate what function of time bests describes the data. If the change is linear we will precede with the LMEs structure. If the time pattern is not immediately apparent we will proceed with the MMANOVA. This method allows the inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen based on Akaikes Information Criterion (AIC). Random group level treatment effects will also be evaluated for importance based on the model AIC. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction.

Data will be analyzed from all randomized subjects on whom we have a baseline assessment and at least one post-baseline evaluation. Responses at baseline through 6 months follow-up will be nested within subjects. Slope (change in outcome over time) will be entered into the model as a random factor and interacted with treatment group. Intercept and slope will be modeled as random effects nested within subject, and treatment group will be a fixed effect. If it is needed based on analyses in stage one, baseline covariates (e.g., demographics) will also be entered as fixed effects. Site and the Treatment by Site interaction will be included as "nuisance parameters;" that is, they must be included to account for possible overall site effects (Site) or possible site differences in treatment effects (Treatments X Site). With the balanced design (equal numbers at each site in each group), ignoring these would not increase the probability of Type I error, but it would increase the Error Sum of Squares, thus increasing the probability of Type II Error. The main effect of treatment represents the common effect size across sites if there is one, or the average site effect, if there is heterogeneity across sites. This is true because sample sizes will be balanced across treatment groups and sites. In any case, the analysis procedures will include site and site interaction effects to avoid allowing site effects to bias treatment comparisons. However, if we detect any imbalances between the treatment groups within each site, we will follow the primary analyses above with subsequent analyses considering the imbalances to verify that the conclusions are not affected by the imbalances.

Hypothesis 2: Veterans in TrIGR, compared to Veterans in SCT, will have significantly greater reduction in distress (BSI-18), shame (ISS), and significantly more improved in their quality of life (WHO-QOL-BREF) at the end of treatment and at follow up periods. This hypothesis will be analyzed using a method similar to that for testing hypothesis 1.

Hypothesis 3: Per the NAG model, guilt cognitions (TRGI Cognitions Scale), distress (BSI-18) and avoidant coping (COPE) will partially mediate the treatment effect on guilt severity (TRGI). For this hypothesis, we will use the same mixed effect model procedure identified in hypothesis 1. We will utilize the analytic strategy described by [85] [86] to test the mediation effect. Based on this strategy, four conditions must be met: (1) a significant relationship between the independent variable (i.e., intervention

condition) and the dependent variable, (2) a significant relationship between the independent variable and the proposed mediator, (3) a significant relationship between the mediator and the outcome, and (4) the relationship between the independent variable (intervention) and outcome must be significantly lower after controlling for the proposed mediator. To test for significant mediation, we will conduct a Sobel test. We will also use the formula provided by [87] to determine the percentage of the intervention condition to primary outcome path that was accounted for by change in our mediator [88].

Exploratory Analyses. The first exploratory objective, whether TrIGR, as compared to SCT, is associated with greater decreases in PTSD and depression symptom severity, greater reductions in suicidal ideation (SI) and greater reductions in alcohol/substance use, will be explored using mixed effect method as explained for hypothesis 1. The second and third objectives—whether reductions in guilt, shame, and avoidant coping will partially mediate the treatment effect on PTSD symptoms among Veterans with a PTSD diagnosis and among Veterans with a depressive disorder—will be explore using analytic strategy as described for hypothesis 3 [85].

Power analysis. Overall, assumptions for our sample size estimation were: (1) sufficient power to test different hypotheses using different analytical models; (2) the reality of recruiting subjects and conducting the study; (3) project cost considerations; and (4) study duration. Therefore, for hypotheses 1 and 2, we performed our calculations using several different methods, each with varying levels of complexity and selected a sample size that provided us with a minimum of 80% power for medium to large effect sizes in each case. The medium effect size was chosen based on the findings reported above. First, we estimated the power using an analysis of variance (ANOVA) in which the person-specific regression coefficient can be used as the dependent variable. Second, we used the method provided by Hedeker and colleagues for the Random Regression Model [80] and finally, we used the RMASS program provided by Hedeker (http://tigger.uic.edu/~hedeker/ml.html). Overall, we believe that the proposed sample size of 150 subjects would provide us with minimum of 90% power to detect the medium effect size for hypothesis 1 and 80% for hypothesis 2. Note: Medium effect size is defined as a between-group difference increasing linearly from 0 at baseline to .5 SD units at the last time point. The minimum power estimation is based on sample size calculation for 10% to 20% attrition, correlations of 0.2, 0.5, and 0.8 between the repeated measures, and for medium and large effect sizes. For hypothesis 3, we used the procedures defined by [89] for estimating sample sizes needed to achieve 80% power to detect the mediated effect. They defined regression coefficients of .14, .39, and .59 to be small, medium, and large, respectively. For mediation analysis, we also assume a medium effect based on finding reported above. Using the Sobel test procedure, we estimated that with the proposed sample we will achieve 80% power to detect a mediated effect.

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