Treatment of Trauma-Related Anger in OEF/OIF/OND Veterans

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Department: Mental Health and Behavioral Sciences Service (MHBSS)

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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 08/01/2014 and the study will continue until 07/31/2018.

1. Purpose

Building on findings from our randomized pilot study, the specific aim of the current proposal is to conduct an adequately powered randomized clinical trial designed to test the effectiveness of a manualized cognitive behavioral intervention (CBI) for the treatment of anger problems in OEF/OIF/OND veterans, compared to a manualized supportive therapy intervention (SI) control condition. Our study will expand on preliminary evidence of the efficacy of this intervention in improving multiple measures of anger outcome including risk for impairment in family, social, and occupational functioning. The study will supplement current research on anger problems in combat-exposed veterans, which has focused primarily on Vietnam Veteran samples and has been conducted decades after return from the war-zone. The longer term significance of this project lies in the potential for adapting the CBI anger intervention for use in VA hospitals nationwide. Future dissemination of this approach can result in high public health significance by decreasing adverse anger consequences for Veterans, including risk for divorce, domestic violence, job loss and instability.

The overall objective is to conduct a randomized clinical trial with 120 Veterans who were exposed to one or more DSM-5 criterion A traumatic events during their deployment. We will address the following specific aims and hypotheses:

(1) To investigate the efficacy of CBI on primary measures of anger treatment outcome. We hypothesize that:

a) Compared to SI, CBI will be associated with significantly larger reductions in anger and aggressive behaviors at post-treatment and at 3 and 6 month follow-ups.

(2) To investigate the efficacy of CBI on secondary measures of anger treatment outcome. We hypothesize that:

a) Compared to SI, CBI will be associated with significantly more improvement in social functioning, occupational functioning, quality of life, and PTSD symptoms at post-treatment and at 3 and 6 month follow-ups.

(3) To examine mechanisms of action of CBI. We hypothesize that:

a) Change in arousal, cognitive, and behavioral domains of anger will mediate outcome for anger and functioning in the CBI condition.

(4) To examine the effectiveness of CBI for those with and without PTSD. We hypothesize that:

a) CBI will be superior to SI on primary and secondary outcome measures (aims 1 and 2) for those with and without PTSD.

2. Background, Significance, and Rationale

Anger Problems in Military Personnel and Veterans: Poorly controlled anger is a common

problem with often devastating effects in veterans who have served in a warzone. As early as World War II, anger and aggression were identified as common responses to combat stress [1, 2], and the association between combat experience and symptoms of anger and hostility has repeatedly been demonstrated in empirical research [3, 4, 5]. Findings from the National Vietnam Veterans Readjustment Survey[4] showed that Vietnam veterans exposed to high levels of war stress expressed higher levels of hostility and committed more violent acts compared to Vietnam era (non theatre) veterans, civilians, and theatre veterans exposed to lower levels of war stress. Excessive anger and difficulty managing anger were also shown to increase risk for divorce, domestic violence, job loss and instability, and other serious impairments in family, social, and occupational functioning [4].

Anger problems have also been documented in veterans who served in the first Gulf war, with up to 40% reporting moderate to extreme levels of irritability at a six-month follow-up [6]. Most relevant to the proposed study, emerging evidence indicates that anger and aggression are likely to be problems for a significant proportion of veterans of Iraq (Operation Iraqi Freedom, OIF; Operation New Dawn, OND) and Afghanistan (Operation Enduring Freedom, OEF). Our data (described in preliminary studies) show that nearly half of National Guard and Reserve personnel reported anger or irritability of moderate or worse severity following return from deployment. A survey of reintegration problems among 754 OEF/OIF combat veterans receiving VA Medical care, showed that anger was the most commonly reported problem, with 57% reporting increased problems in controlling anger [7]. In a sample comprised of 117 OEF and OIF combat veterans presenting to a VA Deployment Health Clinic, 39% reported at least one act of aggression such as destroying property (15%), threatening physical violence (21%) and/or physical fights (10%) within the past four months [8].

Anger and aggression are strongly associated with PTSD [9, 10], and rates of anger problems tend to be higher in trauma-exposed veterans with PTSD compared to those without [4, 11]. Nonetheless, serious anger problems are also elevated in trauma exposed veterans without a diagnosis of PTSD [4, 8, 12]. Anger has also been shown to predict the development of PTSD[13, 14, 15] across a variety of trauma populations, and among those with PTSD, anger is associated with poorer treatment outcome [16, 17]. Finally, anger is a prominent concern for veterans seeking treatment [18, 19], and for their partners [18].

Treatments for Anger Problems: There is a considerable amount of evidence supporting the effects of cognitive-behavioral treatment (CBT) of anger, and several meta-analyses summarizing this research [20, 21, 22, 23, 24]. Beck & Fernandez[21] completed a meta-analysis of studies that used cognitive-behavioral interventions. They reported a mean weighted effect size of .70 based on 50 studies incorporating 1640 participants. The studies included a wide range of populations, with the majority including children or adolescents (50%), inmates (14%), and college students (14%). In addition to the heterogeneous samples, limitation of this meta-analysis is that effect sizes from studies using between-and within group designs were pooled. DiGiuseppe and Tafrate[22] conducted a meta-analysis of 57 studies of adult samples examining a range of intervention types for treating anger problems in adults. Although the types of sample

included were not described, the reference list suggests a high proportion of studies with cardiac or hypertensive samples, abusive parents, inmates, and college students. The majority of intervention types would be considered CBT approaches (e.g. stress inoculation training, cognitive restructuring,

relaxation, systematic desensitization, behavioral skills training, and combined approaches). They reported an overall effect size of .71 averaged across a wide range of outcomes, with moderate to large improvements on anger self-report, aggressive behavior, positive non-angry behaviors, attitudes and cognitions, type- A behavior, and physiological measures. Average effect sizes were .71 for anger and 1.12 for aggression, and treatment gains were maintained at follow-up for the subset of studies including follow-up assessments. They also reported that the use of treatment manuals and integrity checks produced higher effect sizes, and that treatments provided on an individual basis were associated with higher average effect sizes (1.16) than those delivered on a group basis (.68).

The most recent meta-analysis by Del Vecchio & O'Leary[23] was more restrictive in study selection. They included studies of adults only, and required subjects to have a score in the clinical range on a standardized measure, random assignment, a control group (including no treatment, minimal treatment, wait-list, or other defined by the investigator), and at least 5 subjects in each cell. The average effect size for CBT (18 studies) was .68, and for Cognitive Therapy (7 studies) was .82. Seventy-three percent of the studies in this review focused on college student samples, however, limiting generalizability to more typical clinical samples. Thus, the research on non-veteran samples is promising in terms of the potential of cognitive behavioral treatments for anger problems, but given the nature of the samples studied, generalizability to veteran samples is unknown.

Research on Treatments for Anger in Military Personnel and Veterans: Much less is known about the efficacy of such treatments for anger problems in military personnel following exposure to war zone trauma. There is one published study to date involving the use of Novaco's intervention with veterans[25]. Vietnam combat veterans with chronic PTSD and severe problems with anger and aggressive behavior received 12-sessions of treatment provided on an individual basis, in addition to routine care. Despite a small sample (total of 15 in anger treatment and control condition completing treatment), they found significant effects for the anger treatment (relative to a control group receiving routine care) for multiple self-report measures of anger reactions and anger control. The significant differences in anger control were maintained at an 18-month follow-up [25]. These preliminary findings are promising, particularly given the chronic and severe nature of the symptoms in the individuals studied and the general treatment refractoriness in the population as a whole.

Two studies examined cognitive behavioral treatments for veterans in open trials. One included four sessions delivered in a group format in a military/occupational setting to a sample of 91 participants including active duty military members (82%), civilian employees, and spouses of military members (9% of each) [26]. The other study [27] included

a sample of 51 male veterans, most of whom (72%) served in the Vietnam war. Both studies showed statistically significant pre to post treatment decreases on state and trait anger scales, but in the absence of a control group, it is not possible to rule out other factors that may account for these findings.

Most recently, Morland and colleagues [8] conducted a noninferiority trial to determine whether delivery of a 12 session group based cognitive behavioral anger management treatment by videoconferencing was as effective as an in-person group for male veterans with PTSD. The sample included primarily Vietnam Veterans (76%). Both groups were associated with significant and comparable reductions in anger symptoms, leading to the conclusion that video-conferencing is an effective and feasible way to deliver treatment for anger problems. As with the open trials, a limitation of this study in terms of establishing efficacy is that the absence of a control condition precludes conclusions regarding the specific effects of the cognitive behavioral interventions in both conditions, as distinct from the benefits of common factors such as group support, mobilization of hope, and contact with therapists.

To summarize, problems with anger are common and have serious adverse consequences in military personnel and veterans who have served in warzones. Early indications are that the current cohort of OEF/OIF veterans is no exception. Although promising findings for cognitive behavioral treatments have been reported, to date there is not a single adequately powered randomized trial designed to test the efficacy of an anger treatment compared to an active control condition in veterans. Furthermore, research on anger treatment for veterans has relied on self-report measures, and there are no studies to date including the use of a blinded structured interview to assess outcome. The limitations of existing studies of anger treatment in veterans was highlighted in a recent review[29] that was published as part of a series of articles commenting on the updated VA/DOD guidelines for management of PTSD: "Given the lack of rigorous research studies evaluating anger interventions with this [veterans with PTSD] population, additional research in this area is sorely needed. This research should involve the use of randomized controlled studies to evaluation anger management strategies and should include measures that assess both anger and aggression" (Taft et al., 2012, p. 783).

Furthermore, research on anger treatment for veterans has relied on self-report measures, and there are no studies to date including the use of a blinded structured interview to assess outcome. The limitations of existing studies of anger treatment in veterans was highlighted in a recent review (Taft et al., 2012) that was published as part of a series of articles commenting on the updated VA/DOD guidelines for management of PTSD: "Given the lack of rigorous research studies evaluating anger interventions with this [veterans with PTSD] population, additional research in this area is sorely needed. This research should involve the use of randomized controlled studies to evaluation anger management strategies and should include measures that assess both anger and aggression" (Taft et al., 2012, p. 783).

To determine whether there are current or completed studies of anger treatment in veterans, we searched lists of funded research on grants.gov. We also searched the

funded grants list for VA HSR&D, and for all VA funded MIRECs. We did not find any currently funded studies examining treatment for anger in veterans. Completed studies listed included the Morland study described above, and a pilot study of a cognitive behavioral group therapy for male veterans with a history of intimate partner violence. We have collaborated with the PI (Dr. Casey Taft) of the pilot study in a DoD funded clinical trial of the same treatment which is nearing completion. Recruitment for that study is open to veterans of all eras with IPV, and has drawn heavily from the court system. It is not restricted to OEF/OIF/OND veterans, and does not address anger problems outside of those that have already resulted in domestic violence. We also contacted the Office of Mental Health (Dr. Karlin) to inquire whether there are any clinical initiatives with a focus on anger treatment, and were informed that there are no current or planned initiatives on this topic at this time.

Models of War Related Anger: Why are problems with anger so prominent in veterans who have served in war zones? One explanation is that higher levels of arousal and hypervigilance following repeated exposure to life threatening situations result in a lower threshold for anger reactions. Second, military training focuses on responding to threat with aggression, and response to threat with aggression is associated with the powerful reinforcement of survival in combat experiences. Novaco and Chemtob[11] proposed a model for the relationship between anger and trauma that incorporates the adaptive value of anger and aggression in life threatening situations. Their model also builds upon Novaco's earlier model that conceptualizes anger as the result of the cognitive processing of environmental circumstances, physiological arousal, and behavioral reactions, which interact with each other and with environmental circumstances [30]. This three-domain framework was subsequently integrated with Chemtob et al.'s[25] information processing model of dysregulation. They describe a "survival mode" of functioning involving over- activation of cognitive structures that facilitate a response to life threatening situations.

Once triggered, the "survival mode" preempts all other cognitive processing including a loss of self-monitoring. Additional characteristics associated with "survival mode" include specific cognitive biases such as a tendency to react more quickly by requiring less evidence of threat to engage action and decreasing capacity to regulate arousal level [25].

These processes explain the dysregulation, or inability to adaptively regulate behavioral responses to threat, and the persisting response of excessive anger and aggression in situations perceived as threatening, even in the absence of real threat. Thus, a response that is highly adaptive during combat becomes maladaptive with the loss of the ability to regulate the intensity and expression of anger appropriate to the current social and environmental conditions [11]. Thus key elements of poorly controlled anger include cognitive processing characterized by overestimates of threat, high levels of arousal, and inability to regulate the intensity of emotion and behavioral response.

Summary of Significance**:** Given the frequency, severity, and chronicity of anger problems in combat-exposed veterans, there is a critical need for further research to establish optimal interventions using larger samples and adequate control groups. Since cognitive

behavioral interventions require more intensive training and experience than supportive therapy approaches, it is important to determine whether such treatments exceed the effects of a positive therapeutic relationship, therapist support, and an opportunity to talk about problems. Furthermore, the research to date has focused primarily on Vietnam Veteran samples and has been conducted decades after return from the war-zone. For these veterans, no treatment was available until many years after anger had negatively impacted relationships, jobs, and health. Potential advantages of earlier intervention, before the secondary consequences of anger problems are established, highlight the significance of testing interventions in military personnel and veterans earlier on after their deployments. The goal is to prevent anger-related problems following deployment from becoming entrenched and chronic, that is, before these problems take their toll on social and occupational functioning, quality of life, and physical health.

Promising findings from our pilot work suggest that the adapted cognitive behavioral intervention has the potential to effectively treat anger problems in this new cohort of veterans. If shown to be effective in a fully powered clinical trial, with subsequent dissemination this intervention may result in a significant reduction in the negative consequences associated with ongoing anger-related problems and the extensive personal and societal costs of these consequences.

3. Preliminary Studies

Veteran PTSD Risk Factors Study: We recruited a sample of National Guard and Reserve Veterans following their return from deployment in Iraq or Afghanistan for a study of risk factors for and early longitudinal course of PTSD. Participants were recruited at post-deployment health screenings and re-screenings. The Clinician Administered PTSD Scale (CAPS) was used to assess PTSD symptoms. A portion of the initial sample of 238 participants was re-assessed as funding allowed, including 215 at 6 months and 169 at 12 months post-return. (The smaller sample at 12 months was due primarily to not having funds to continue the follow-up as opposed to attrition). Although only 10.5% met criteria for PTSD at the first month post-return, PTSD symptoms were common. Hyperarousal symptoms were the most frequent, with percent of individual symptoms ranging from 21% to 55% at the first month post return, in contrast to re-experiencing symptoms (range 9% to 17%) and numbing/avoidance symptoms (2% to 21%) (figure 1). Among the hyperarousal symptoms (see figure 2), hypervigilance and anger were the two most common symptoms at all time points assessed. Even at 12 months post-return, 38% of participants still met the CAPS anger symptom criteria.

Examination of the associations between PTSD symptom cluster scores and measures of functioning and distress showed that while symptoms of numbing and avoidance were the strongest predictors of impairment in interpersonal and social functioning, hyperarousal symptoms were the strongest predictors of overall severity and distress [31]. When individual symptoms were examined in relationship to measures of functional impairment, anger was the strongest predictor of impairment in overall adjustment (Global Assessment of Functioning Score) and social functioning [31]. Thus, with the

exception of hypervigilance, anger was the most frequent symptom of PTSD at all three time points, and was the strongest predictor of impairment in social and overall functioning.

Pilot study of CBI: We completed a treatment study designed to adapt the cognitive-behavioral intervention (CBI) for the treatment of anger to specific needs of military personnel returning from Iraq and Afghanistan, and to conduct a randomized pilot study to examine feasibility, acceptability, and preliminary evidence of efficacy of the adapted intervention in this population [32]. The first phase involved adapting the manual, administering the adapted CBI to 12 participants, and piloting a supportive intervention (SI) to two participants. The SI manual was an adapted version of the Present Centered Therapy (PCT) that the Dr. Shea adapted as a control condition for a Cooperative Studies Program #494 "Treatment of PTSD in Women Veterans". Our experience in Phase I led to further revisions of both manuals. The goal of the second phase was to conduct a randomized pilot study of male and female participants assigned to receive either CBI or SI.

Table 3: Between groups differences at post-treatment adjusting for pre-treatment scores (ANCOVA) and effect sizes

Variable	F	P	Effect Size
STAXI-2			
Anger Expression Index	7.6	.019	1.12
Expression In	9.9	.004	1.13
Expression Out	24.0	<.001	0.98
Control In	5.7	.034	1.08
Control Out	6.0	.031	1.22
OAS-M			
Aggression	4.28	.059	0.78
Total	4.55	.053	0.82
Outcomes Questionnaire			
Interpersonal Relations	6.24	.028	1.24
Symptom Distress	1.40	.260	0.59
Social Role	5.81	.033	1.20

Despite the small sample size, CBI was statistically superior to SI in reducing anger problems on the primary outcome measures. CBI showed significantly more improvement than SI ($p < .05$) on the STAXI-2 expression and control scales and the anger expression index. The OAS-M was administered by trained interviewers who were blind to treatment condition. Differences on the aggression scale score and the total OAS-M score were close to significance ($p < .06$). On the self-report Outcomes Questionnaire, CBI improved significantly more than SI on two of the three scales. Between group effect sizes reflecting the greater improvement for CBI compared to SI were large, ranging from .78 to 1.24.

4. Research Design and Methods

A. Overview

The goal of this proposal is to investigate the effectiveness of CBI in treating anger problems in OEF/OIF/OND veterans. This is consistent with the goal of the RR&D Deployment Health Research (OEF/OIF) Funding Opportunity (RX-11-016) to increase research addressing the health care needs of Veterans returning from Afghanistan and Iraq, including studies that seek to increase participation in family and social activities, maintain employment, and improve overall quality of life.

B. Participants

The sample will consist of 120 OEF/OIF/OND male and female veterans who were exposed to one or more DSM-5 criterion A traumatic events during their deployment, and are experiencing excessive irritability and/or outbursts of anger and at least two additional hyperarousal symptoms of PTSD (i.e., difficulty falling or staying asleep, difficulty concentrating, hypervigilance, exaggerated startle response).

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 current or former members of the military (active duty, National Guard or Reserve)
- have served in OEF, OIF, or OND
- have experienced trauma during deployment
- report clinically significant anger as measured by the CAPS-5 anger criterion (rating of 2 or higher on the item describing experiencing persistent negative mood states, with anger being one of the intense emotions experienced, and/or the item involving problematic expression of anger/irritability in behavior) report a minimum of two additional symptoms from the PTSD hyperarousal symptom cluster
- be interested in receiving treatment for anger
- consent to be randomized
- not receive other active PTSD or Cognitive-Behavioral treatment, or any individual or group treatment focused on problems with anger management during the intervention phase
- not have had new psychotropic medication or dosage changes with the prior 4 weeks.

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

- the presence of a severe substance or alcohol use disorder in the last 3 months
- current psychotic symptoms (in the last 3 months)
- current mania or manic episode within the last 3 months
- current suicidal or homicidal ideation requiring hospitalization

- any severe cognitive impairment or history of Organic Mental Disorder

Considerations in determining inclusion/exclusion criteria

All of our listed exclusion criteria are designed to exclude those who would need alternative treatment or would be unlikely to benefit from the proposed treatment. In terms of inclusion criteria, several require further comment. First, although we originally proposed excluding women, we have taken the reviewers recommendation to reconsider this decision and will include both men and women. Although research has shown that females tend to have lower levels of physical aggression than males [33], reviews have suggested that sex differences for verbal aggression are generally much smaller [34]. Given that there are increasing numbers of female veterans with exposure to warzone trauma (as well as military sexual assault), many of whom are likely to have problems with anger, it will be important to have effective treatments for both genders. We will balance randomization and examine possible differences in outcome by sex, and include sex as a covariate in analyses if needed.

A second important consideration was whether to restrict the sample to those with a PTSD diagnosis. Many studies report more severe anger problems in veterans with PTSD than in those without, and it is possible that anger problems differ in other ways in those with and without PTSD. Further, two of the existing treatment studies of anger in veterans required PTSD diagnoses. On the other hand, significant anger problems are also common in combat exposed veterans without a PTSD diagnosis [12, 8], and not requiring a PTSD diagnosis will make the findings relevant to a larger proportion of returning veterans. We decided not to require a PTSD diagnosis for inclusion, but we will require exposure to trauma during deployment, and the presence of at least three hyperarousal symptoms (one being anger and irritability). This requirement is consistent with the conceptualization of anger as linked to hyperarousal in veterans exposed to war-zone life threat. We will include presence of a PTSD diagnosis as a balancing factor in urn randomization and will conduct exploratory analyses to examine whether treatment effects are the same for participants with and without a PTSD diagnosis.

We will exclude participants with severe cognitive impairment who would be unable to readily understand the concepts. If such impairment is suspected, a mental status exam will be conducted. Veterans with mild traumatic brain injury (mTBI) will not be excluded as 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. In FY 2011, 1261 unique OEF/OIF/OND veterans were seen in these clinics, with 10 to 15 new consults per week across the two programs. Dr. Shea is on the staff of the PTSD clinic, and Dr. Lambert is the director of the REVOC clinic and acting director of the PTSD clinic.

The Providence VAMC has established a new women's specialty clinic in primary care, which is housed in a new building adjacent to our offices as well as the PTSD and Returning Veterans Clinics. We will draw upon these resources as well as the additional outreach methods described to recruit OEF/OIF/OND women veterans.

Study participants will also be recruited through outreach efforts to military family organizations, community-based troop support organizations, veteran organizations, as well as to the active military community. Additional outreach efforts will include making presentations at military reintegration events, such as Yellow Ribbon post-mobilization weekend retreats, posting fliers at military bases and in the community, as well as making presentations to interested community groups. Potential participants will also be recruited with the assistance of our study recruiter, Paul Darcy, who will seek to engage Veterans in study treatment from the community, Veterans' court, and other VA facilities (e.g., Vet Centers). Veterans who express interest in participating in the study will be asked to contact study staff directly or to sign a form giving permission for the study staff to contact them.

Study advertisements will also be posted on the official PVAMC online posting sites (i.e. the PVAMC Twitter and PVAMC Facebook pages) according to the guidance of the PVAMC Public Affairs Officer. All advertisements will be reviewed and approved by the PVAMC IRB prior to release.

Screening and Informed Consent Procedures

Potential participants who are referred through one of the sources described above or who contact study personnel directly will enter the screening phase. Where possible, the medical record will be examined to determine if war era (i.e. OEF, OIF, OND) criterion is met, and whether diagnostic exclusion criteria (e.g. current severe substance use disorder, mania or psychotic symptoms) are present.

Potential participants will have telephone contact with a study interviewer who will provide information that will enable potential participants 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 required for both treatment and assessment, and schedule of payments). Those who are interested will obtain an appointment with the interviewer.

During the 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 also will be informed of the fee payment structure that applies to the follow-up assessments they will complete following the treatment phase. Interviewers will be trained to ensure that all participants comprehend the nature of the study and the wording of the consent form, and will provide a copy of the forms for potential participants 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. We will ask participants if they are willing to have a significant other complete anger outcome measures for the purpose of providing an additional perspective on amount and types of change following treatment (as described below). If the participant agrees, s/he will be asked for permission to contact the nominated individual as part of the consent process. Although encouraged, identification of collaterals will not be required for inclusion in the study.

In the final stage of screening, interviewers will complete interviews to establish inclusion and exclusion criteria. The Structured Clinical Interview for the DSM-V (SCID) will be administered to assess for the presence of current (in the last 3 months) psychosis, mania, or a substance use disorder. The Clinician-Administered PTSD Scale (CAPS) [37] will be used to establish recent exposure to a traumatic stressor. The CAPS includes a lifetime trauma checklist and questions about stressor exposure, which will be used to ensure that participants meet the DSM-5 criterion of stressor exposure that is required for diagnosis and for inclusion in the study. This checklist will be supplemented with additional questions inquiring about common stressors associated with current hazardous deployments. The trauma checklists will provide descriptive information about participants at study entry. After establishing that the potential participant has experienced at least one combat-related criterion A stressor, the interviewer will skip to section E (hyperarousal) to assess for the presence of trauma-related anger and arousal. Inclusion criteria for the study involve endorsement of at least two arousal symptoms, in addition to experiencing persistent negative mood states, with anger being one of the intense emotions experienced, and/or the item problematic expression of anger/irritability in behavior. If the participant does not rule out based on these measures, the interviewer will administer the remainder of the CAPS interview and SCID and the remaining questionnaires and interviews of the assessment battery.

In addition to documenting that inclusion and exclusion are met, a screening form completed at this point records referral source, all prior deployments, and date of return from most recent deployment.

D. Assessment

D. 1. *Screening, Diagnostic and Sample Characterization Measures*

Structured Clinical Interview for DSM-IV (SCID), patient version. The DSM-5 version of the SCID[35] will be used during screening to establish exclusion diagnoses (substance use disorders, psychosis, and mania). It will also provide assessment of non-excluded Axis I disorders, which will be examined for possible effects on treatment outcome, and used as covariates in the outcome analyses as needed.

Clinician Administered PTSD Scale (CAPS): The CAPS [36] (updated for DSM-5) will be administered at screening to assess the DSM-5 diagnostic criteria for PTSD. It will also be used at post-treatment and follow-up as a secondary measure of outcome. The CAPS has excellent reliability and validity[36], [37] and is widely used in PTSD treatment research. Each

one of the DSM-5 PTSD symptoms is rated on a 0-4 (low to high) scale to determine symptom severity. The cutoff used to establish the presence of an individual symptom is a score of 2 or greater. In addition, overall PTSD severity is computed by summing the totals for all items.

Hoge Combat Experiences Scale: This scale is included as a measure of trauma exposure in the warzone because it was developed specifically to assess trauma exposure in the Iraq and Afghanistan theatres [38]. As such it includes items more specific to these wars (e.g. IEDs, searching homes). Items assess frequency of being in serious danger, number of firefights, injury including head injury, and frequency of exposure to 13 combat and other trauma events rated on a scale from 0 (never) to 4 (10 or more times).

Childhood Trauma Questionnaire: The CTQ 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 [39].

Brief Symptom Inventory: The Brief Symptom Inventory (BSI) is a 53-item version of the Symptom Checklist 90- Revised. It includes 9 symptom scales and global measures of symptom severity and psychological distress[40].

Schedule for Nonadaptive and Adaptive Personality-2 (SNAP-2): The Schedule for Nonadaptive and Adaptive Personality-2 (SNAP-2) is a 390-item self-report measure of personality. It includes 12 trait scales assessing maladaptive personality and three temperament scales of Negative Temperament, positive Temperament and Disinhibition assessing higher order personality domains. It has been shown to demonstrate good reliability and validity[41, 42].

Brief Addiction Monitor. The Use subscale of the Brief Addiction Monitor will be used to assess for frequency of alcohol and substance use within the past month at baseline and follow up assessments. This measure has been shown to be valid and reliable in prior research[43].

D. 2. *Primary Outcome Measures: Anger and Aggression*

Two measures will serve as the primary outcome measures for anger: the Anger Expression Index (AXI) from the State-Trait Anger Inventory-2[44] and the Aggression Scale score from the Overt Aggression Scale-Modified[45].

STAXI-2: The STAXI-2 [46] is a revision of Spielberger's State-Trait Anger Expression Inventory (STAXI), expanded from 44 to 57 items on the basis of over a decade of research. It is a self-report questionnaire consisting of six scales and an Anger Expression Index (AX). Scales include State Anger, which measures the intensity of current angry feelings; Trait Anger, which measures the frequency of angry feelings over time; Anger Expression-Out, which measures how often angry feelings are expressed in verbally or physical aggressive behavior; Anger Expression-In, which measures how often angry feelings are experienced but not expressed; Anger Control-Out, which

measures how often a person controls the outward expression of angry feelings; and Anger Expression-In, which measures how often a person tries to control angry feelings by calming down. The Anger Expression Index is an overall measure of the expression and control of anger based on responses to the two anger expression and the two anger control subscales. The original STAXI and the STAXI-2 have been widely used in treatment studies, including veteran samples [25, 27, 28] and has substantial psychometric evidence, including convergent and discriminant validity, and sensitivity to change[45].

OAS-M: The OAS-M is a 25-item clinician-administered, semi-structured interview with nine subscales [45, 47]. It was designed to evaluate various manifestations of aggressive behaviors in outpatients, including the severity, type, and frequency of aggressive behavior. The scale assesses three overall domains: Aggression (Verbal Aggression, Aggression Against Objects, Aggression Against Others, and Aggression Against Self), Irritability (Global Irritability and Subjective Irritability), and Suicidality (Suicidal Tendencies, Intent of Attempt, and Lethality of Attempt). Only the Aggression and Irritability subscales will be used in the current study. The two Irritability subscales are rated on Likert-type scales from 0 = none at all to 5 = extreme. The Aggression scale uses a different format in which each specific behavior is scored separately by frequency and then multiplied by assigned weights. For each Aggression subscale, seven specific behaviors are listed in order of severity and then weighted by their respective rank. The weighted frequencies are summed to form each subscale score. Subscale scores are then multiplied by their own assigned weight: Verbal Aggression by 1, Aggression Against Objects by 2, and Aggression Against Others and Self each by 3. Weighted subscales are added to obtain a final scale score for Aggression. Evidence for inter-rater and test-retest reliability has been documented for the OAS-M, with intraclass correlations (ICCs) of .91 and greater for inter-rater, and ICCs of .46 to .54 for test-retest reliability, and the OAS-M has demonstrated sensitivity to pharmacotherapy-induced changes in aggression [47, 48]. The time frame of the OAS-M is restricted to the past week. The OAS-M will be administered by interviewers blinded to treatment condition.

Anger Consequences Scale (ACQ): The ACQ is a brief self-report measure developed to assess the frequency of negative anger-related behavioral consequences. Internal consistencies of .75 to .91 were reported on the original 42 item version; the revised version shortened the measure to 33 items based on factor analysis [49]. This scale includes items not covered by the other anger measures, including for example, trouble with the law, driving recklessly, getting into an accident, damaging relationships, etc.

Dimensions of Anger Response (DAR): The DAR, developed by Novaco[50] is a 7-item self-report measure of anger reactions. A more recent report on the psychometrics of the DAR showed it to be unidimensional, reliable, and sensitive to change over time [50, 51]. The DAR will be administered at each session.

D. 3. *Collateral Assessments*

Data from collaterals can provide an important additional perspective on treatment outcome. We will ask participants if they are willing to have a significant other complete

anger outcome measures for the purpose of providing an additional perspective on amount and types of change following treatment. For each participant who agrees, we will ask him or her to identify the person or persons with whom they spend the most time, and/or have sufficient interactions to be familiar with the participant's typical behavior. A minimum of 5 hours of contact a week will be required to qualify as a collateral reporter. If there are multiple possible candidates, we will ask the participant to identify the one who they believe would be the best able to provide a valid assessment of their anger. Participants may take up to two days to consider the request and to discuss with the potential collateral. If the participant agrees, s/he will be asked for permission to contact the nominated individual as part of the consent process. Although encouraged, identification of collaterals will not be required for inclusion in the study. Collaterals will be fully informed of the study requirements and if they are willing to participate, will be asked to sign informed consent. Collaterals will also be provided with the Notice of VHA Privacy Practices. They will be asked to complete the STAXI-II (excluding the state anger scale), the Sheehan Disability Scale, and the Overt Aggression Scale interview at pre- and posttreatment. These measures will be adapted from first to third person for this purpose. We will record demographic information, the nature of the relationship (e.g. spouse, family member, friend) and the average number of hours of contact per week with the participant. At post-treatment, we will also administer a collateral version of to the Patient Satisfaction form.

D. 4. *Secondary Outcome Measures: Functioning and Quality of Life*

Longitudinal Interval Follow-Up Evaluation: Psychosocial functioning scales from the clinician administered Longitudinal Interval Follow-up Evaluation[52] will provide assessment of functioning in areas of work (employment, household, or student), familial and nonfamilial interpersonal relationships, recreation, and global social adjustment on separate 6 to 8-point scales. Ratings will be based on the past month. The psychosocial functioning ratings have been found to be of generally high reliability [52, 53].

Outcomes Questionnaire: Functioning will also be assessed by the self-report Outcomes Questionnaire (OQ) which was developed as a psychotherapy outcome measure [54]. The OQ includes three subscales: symptom distress, interpersonal relations, and social role functioning. Test-retest coefficients in the mid .70s and .80s and internal consistency in the low .90s provide evidence for reliability. Concurrent validity has been demonstrated in relation to other measures, the OQ has been shown to be fairly stable in untreated individuals and sensitive to change in those individuals in treatment [55].

World Health Organization Quality of Life (WHOQOL-BREF): The World Health Organization Quality of Life (WHOQOL-BREF), is 26 item self-report measure used to assess quality of life in multiple domains (i.e., physical, psychological, social, and environment). Psychometric properties suggest that the measure is valid and reliable across cultures and nations[56].

D. 5. *Mediators of Outcome*

Novaco Anger Scale (NAS): The three subscales of the NAS (cognitive, arousal, and

behavioral) will be examined as possible mediators of CBI treatment outcome. The revised version of these scales includes 48 items measuring impairment in the three components of Novaco's model [57, 58]. As described further below, the intervention in the current study, adapted from Novaco's stress inoculation anger control treatment, includes strategies to address each of these components. The published manual for the NAS-PI[57, 58] reports findings of high levels of internal consistency across a number of normal and psychiatric samples. Of particular relevance to the population to be addressed in this study is the data provided by Chemtob and colleagues on 114 Vietnam veterans which yielded alpha coefficients of 0.97 and 0.96 for the NAS and PI, respectively [25].

D. 6. ***Additional measures***

Treatment Satisfaction: a brief 4 item measure adapted from the Treatment Satisfaction Form used in the NIMH Treatment of Depression Collaborative Research Program will be used to assess satisfaction with treatment.

Treatment Utilization: The Longitudinal Interval Follow-Up Assessment (LIFE) treatment section provides continuous recording of mental health and medical treatments [52]. For the latter, number of hospitalizations, days spent in hospital, and number of outpatient visits for non-mental health medical treatments are recorded for the time period covered. Types and amounts of all mental health contacts, including inpatient and outpatient treatment, are recorded on a monthly basis. All psychiatric medications, including dosages are recorded on a weekly basis (see Appendix 4 for list of medications). We will also assess all prescribed non-psychiatric medications, over the counter medications (including caffeine), and herbal and other supplements taken for any reason.

A baseline version (LIFE-Base) assesses mental health treatment received prior to entering the study. We will adapt the LIFE-Base to indicate whether prior treatment occurred before, during, or after deployment, and also to assess whether prior treatment focused specifically on anger or PTSD.

D. 7. ***Schedule of Assessments***

The schedule of assessments is shown in Table 1. The CAPS and the SCID will be administered during the screening process prior to randomization to ensure that only eligible participants are entered into the study. Only eligible participants will complete the full CAPS and SCID and other pre-treatment measures. Assessments will be conducted at pre-treatment, during treatment (after sessions 4 and 8), end of treatment (week 12), and at three and six months following completion of treatment. We estimate that completion of the SCID and the CAPS will take 2 hours on average, and that the remaining pre-treatment measures will take about 2 ½ hours. The pre-treatment assessment will be conducted in 2 sessions. Mid-treatment assessments should take about 45 minutes. We estimate that post- treatment and follow-up assessments will take about 2 ½ hours on average.

We will aim to complete the post-treatment and follow-up assessments in a single

session, providing breaks if needed. If necessary due to participant burden, we will schedule a second assessment session. We will prioritize the order of measures administered to ensure that in all cases the anger outcome measures (OAS-M, STAXI-2, and ACQ), and the Outcomes Questionnaire are completed. Telephone assessments will be used if participants are unable to come in for assessments. Every attempt will be made to perform post- treatment and follow-up assessments within one week of their scheduled date.

Table 1. Schedule of Assessments

Domain	Screening	Pre-Tx	Sessions 4 and 8	Post-Tx	Follow-up (3 and 6 months)
Inclusion/exclusion Criteria					
SCID	X				
CAPS	X			X	X
Sample Characterization					
SNAP-2		X			
CTQ		X			
Combat Exposure		X			
BSI		X	X	X	X
BAM (Use subscale)		X			X
Anger					
*OAS-M**		X	X	X	X
STAXI-2*		X	X	X	X
*ACQ**		X		X	X
DAR (weekly)					
Function/QOL					
LIFE psychosoc		X		X	X
OQ		X		X	X
Disability Scale		X		X	X
WHOQOL-BREF		X		X	X
Mediators					
NAS arousal		X	X	X	
NAS cognitive		X	X	X	
NAS behavioral		X	X	X	
Other Measures					
Tx Satisfaction				X	
LIFE Tx section		X		X	X

Clinician administered interviews are in italics. ACQ = Anger Consequences Scale; *BAM = Brief Addiction Monitor; BSI = Brief Symptom Inventory; CTQ = Childhood Trauma Questionnaire; DAR = Dimensions of Anger Scale; NAS = Novaco Anger Scale; OAS-M = Overt Aggression Scale Modified; OQ = Outcomes Questionnaire; SNAP-2 = Schedule for Nonadaptive and Adaptive Personality-2nd Edition; STAXI-2 = State Trait Anger Inventory-2; WHOQOL-BREF = The World Health Organization Quality of Life*

**Collateral assessments will be administered at pre- and post-treatment*

D. 8. ***Blinding of Assessments***

All interviewers will be blind to participants' treatment condition. Each of the outcome domains (anger, functioning/quality of life) includes one blinded interview. Prior to the outcome assessments, the interviewer will remind each participant not to reveal his treatment condition. At the post-treatment and follow-up assessments, interviewers will complete questions including whether they think the blind was broken, and to which treatment condition they think the participant was assigned.

D. 9. ***Standardization of Assessments***

Interviewer qualifications will include masters or doctoral level training in psychology or social work, or bachelor's level training combined with at least 2 years of prior experience using structured interviews. Research study staff will provide training on the SCID and the CAPS. This research study staff member has formal training and experience training others on these interviews. Dr. Shea will conduct training on the OAS-M. Interviewers will conduct practice interviews and receive feedback from Research Study staff and Shea until judged to be calibrated to an acceptable standard of administration.

All of the clinical interviews (CAPS, SCID and OAS-M) will be recorded. Ten percent of each of the interviews will be randomly selected on an ongoing basis to monitor the reliability of the interview process. Research study staff will listen to the recorded interviews and provide feedback to interviewers in biweekly meetings to maintain reliability. Interviewer ratings will be compared with research study staff's ratings and any discrepancies in ratings will be discussed.

D. 10. ***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. Participants will be compensated for all assessments.

Permission will be requested at the time of informed consent to 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 at appointments scheduled for this purpose. An appointment for the three-month follow-up assessment will be made at termination of the study intervention, and for the six-month follow-up at the three-month interview. Participants will receive a letter one week prior to the interview and a reminder call a few days prior. Participants who do not have telephones will be contacted by mail and asked to call 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 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.

D. 11. *Compensation*

Participants will be compensated for the time required to complete all assessments. They will be paid $100 for the pre-treatment baseline assessment and $60 for the subsequent post-treatment and follow-up assessment periods.
Participants who screen out on the SCID or CAPS or who do not complete the full baseline assessment will be paid $40 (for partial assessment). Mid treatment assessments (after sessions 4 and 8) will be compensated at $25. Collaterals will be compensated $25 for the pre- and post-treatment assessments. Participants can receive their compensation in the form of an electronic funds transfer or gift card. Collaterals will be compensated with gift cards.

E. Treatment

E. 1. *Assignment*

Participants meeting study inclusion/exclusion criteria will be randomly assigned to CBI or SI 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[59] and Stout[60] to help insure balance among treatment groups. Urn randomization is a stratified randomization technique, which randomly assigns patients of a given subgroup to treatment conditions, but systematically biases the randomization in favor of balance among the treatment conditions on the stratification variables. We have successfully used the urn randomization procedure in several previous treatment outcome studies, including the multi-site Project MATCH[61] and have developed a computer program that conducts the randomization. This program also enables ongoing monitoring of the effectiveness of our stratification and randomization procedures. Three dichotomous balancing factors will be used in randomization: gender (male vs female), and presence of a PTSD diagnosis (yes vs no).

E.2. *Cognitive Behavioral Intervention*

CBI was adapted from a cognitive behavioral treatment developed by Raymond Novaco, targeted at reducing anger frequency, intensity, and duration, and at moderating the expression of anger [50, 57]. It includes training in self-monitoring, cognitive reframing, arousal reduction, and behavioral coping. It also utilizes a "stress inoculation" approach, which involves therapist-guided, progressive imaginal exposure to provocations (including trauma triggers) in session and in vivo, in conjunction with modeling and rehearsal of coping skills. Adaptations of the original treatment for OEF/OIF veterans included 1) addition of psychoeducation using "Battlemind", developed by researchers at Walter Reed (consistent with Battlemind principles, throughout the treatment, anger is conceptualized within the context of adaptive function in the warzone that becomes nonadaptive at home); 2) additional emphasis on arousal reduction through relaxation training; 3) including the option of a session involving a spouse or family member focused on psychoeducation; and revisions of the manual organization to facilitate therapist delivery. Key elements of CBI include:

- Psychoeducation about responses to trauma, particularly following deployment in a war-zone, trauma-related anger difficulties, stress, and aggression
- Arousal reduction, including diaphragmatic breathing, and guided imagery training
- Cognitive restructuring of anger schemas (identification and modification of beliefs and interpretations)
- Behavioral coping strategies (training in communication, assertiveness, and strategic withdrawal)
- Inoculation training (practicing the cognitive, arousal regulatory, and behavioral coping skills while visualizing progressively more intense anger-arousing scenes from personal hierarchies).

E.3. *Supportive Intervention Control*

The Supportive Intervention adapted for the pilot study included the same "Battlemind" psychoeducation as the CBI condition. Following the psychoeducation component, the rest of the intervention focuses on providing support and using problem solving strategies to help in managing behavior and feelings in current day-to-day life. Cognitive behavioral interventions are excluded. In addition to the exclusion of cognitive or behavioral strategies, SI is less structured; the patient has more input into the agenda of the sessions.

E.4. *Therapist Selection, Training and Supervision*

Therapists will be Ph.D. level psychologists or masters level clinical social workers with prior experience in cognitive behavioral therapy and prior experience treating PTSD patients. Therapists will receive training in both interventions. There are advantages and disadvantages to using the same or different therapists for study conditions. The primary concern with using the same therapists is the possible effect of a different level of enthusiasm and investment in the active treatment condition, which can bias results. However, bias can just as easily occur when therapists are assigned to deliver different treatment conditions. Our experience in the pilot study was that therapists appeared to be equally comfortable with both conditions, and ratings indicated adherence to the manual. Retention was slightly higher in the SI condition. An advantage of using the same therapist for both conditions is reduction of between treatment variance associated with therapist effects. Another advantage is the increased flexibility of assigning study participants to therapists to facilitate accommodation of study participants' availability for appointments.

Initial training will be didactic, involving two days of instruction for CBI, and one for SI. Drs. Shea and Lambert will conduct the didactic training for both conditions. Training will include disguised case examples derived from the pilot study sessions and role plays of interventions. Following the didactic training, each therapist will have one CBI training case, with weekly supervision based on review of audio recorded sessions. The training case must complete a minimum of 8 sessions to count. If the therapist is judged to be sufficiently competent, he or she will be approved to see study participants. This judgment will be based on mutual agreement by Drs. Shea and Lambert who will supervise therapists, and on consistent ratings of adherence (75% of strategies

implemented across sessions rated). All therapy sessions for study participants in both conditions will be recorded. For the first two study cases for each therapist, every session will be reviewed and feedback will be provided weekly. Supervision will become less frequent with subsequent cases, although a minimum of three sessions will be reviewed for each case and feedback provided as needed.

E.5. *Adherence Monitoring*

Current standards in psychosocial treatment research require monitoring of therapist behavior and interventions to ensure treatment fidelity (i.e., that therapists are delivering the interventions specified in the manual and not using interventions that are not part of the treatment). In the proposed study, the first objective is particularly important for the Cognitive Behavioral Intervention, and the second is particularly important for the Supportive Intervention. We have developed adherence scales for both conditions, and findings from our pilot work showed good adherence in both conditions. Adherence ratings for both conditions will be completed by research study staff, and will include three sessions (early, middle, and late session) for each study participant. Ten early sessions will also be rated by Dr. Shea to establish reliability with research study staff.

F. Design Considerations

F.1. *Treatment Format*

The treatment we are studying is delivered in an individual format. An alternative choice would be to test the efficacy of a group format, which could be more cost-effective. We decided to use an individual format for several reasons. First, many patients with anger problems are unwilling to participate in group treatment. Second, the logistics of group interventions can be challenging, given the need to find a time that all potential group members can make. This may be particularly for OEF/OIF/OND veterans who often have time restrictions due to work and family. Further, in practice since groups are typically 10 to 12 weeks long, new veterans often have to wait until another group is available. Third, the intervention in the proposed study includes an imaginal exposure component, which would be difficult to implement in a group format. Finally, it is possible that individual delivery of anger treatment may be more effective than group delivery given the greater amount of time and more intensive focus that is possible in individual treatment. If CBI is found to be effective compared to SI, the next step would be to compare individual and group delivery of CBI.

F.2. *Control Condition*

Selection of control groups for psychosocial treatments is complex. Unlike medication trials, it is not possible to derive true "placebo" conditions that control for all aspects of the treatment delivery except the active ingredient (drug). A variety of control conditions have been used in behavioral treatment research, but there is no consensus regarding an optimal or standard control condition. There is increasing recognition that the design and selection of an optimal control condition depends upon the particular intervention being studied and the research question being addressed. One important consideration is how

much is known about the treatment being studied. Rounsaville and Onken[62] outline a three stage framework including an initial stage (feasibility, pilot studies), RCTs / efficacy trials, and effectiveness studies. The proposed study would be considered a stage 2 efficacy trial according to this model; for such trials non-specific comparison designs have been recommended [63]. In addition to controlling for passage of time, testing, statistical regression towards the mean (all of which may be controlled for by a wait-list control), a non-specific comparison condition controls for the aspects of therapy that characterize most forms of therapy and are distinct from the hypothesized active mechanisms of the treatment being studied. This type of control allows for inferences about the benefits of the specific treatment interventions, beyond the benefits of for example, meeting with a therapist, receiving attention and support, and expectations of improvement. The control condition proposed for the current study, which was adapted from the control condition used in the CSP clinical trial testing the efficacy of prolonged exposure [58], was designed to achieve this goal.

A treatment as usual control condition in some settings might serve the same purpose, if the "usual treatment" is clearly defined and consistently used, and does not include the hypothesized active mechanisms of the treatment being studied In the setting for the proposed study, however, treatment as usual is not uniform, includes a range of providers, and could include a range of interventions, including medication only, group therapy, and/or individual therapy possibly including some aspects of cognitive or behavioral interventions. Because treatment as usual may vary in different settings, the findings could have limited generalizability. Even with careful assessment of type and dose of any additional treatment received in both conditions, we are concerned that the heterogeneity of treatment and the potential overlap of some cognitive behavioral interventions would make it more difficult to achieve the goal of allowing inferences about the efficacy of the specific cognitive behavioral interventions included in CBI.

G. Data Management and Analysis

G.1. *Data Management*

Research study staff will oversee data management procedures. Study data will be collected and managed using REDCap electronic data capture tools hosted at the Department of Veterans Affairs. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Through REDCap, participants are able to respond to survey items electronically and additionally research study staff can manually enter responses. All study software and licensing, such as SPSS IBM (which will be used for data analyses) will be managed by PVAMC IT and IRM. For data that is entered manually, the project coordinator will be responsible for initial editing and correction of forms before they are data entered by the research assistant. As forms are entered into the master database, they will be checked against the participant tracking file to assure that all data that are gathered have been data entered. The data will be verified after entry and verification status will be tracked by the software. Validity checks will also be done as the data are entered, and questions or problems will be resolved by discussion between research study staff and the Interviewer. All data will be received stripped of personal identifiers. Because of the sensitive nature

of some of the data gathered, a number of precautions will be taken to prevent disclosure of information to unauthorized parties: (1) data sheets will be stored in locked offices of Dr. Tracie Shea (PI), 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 (\\vhaproapp12\Research_Protocols\Shea\Anger-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. Data protection and precaution measures are further detailed in the Protocol Appendix – ISO (see page 31).

G.2. ***Data Analysis***

All major variables will be screened for inconsistent or abnormal values, and continuous measures will be assessed for skewness and outliers. Transformations to improve normality may be applied to continuous variables. Missing data rates and patterns will be assessed; in particular, missing data rates by treatment group will be studied. Although urn randomization tends to produce well-balanced treatment samples [59] analyses will be carried out to determine any baseline differences between the treatment groups on demographic or other prognostic variables, using chi square analyses for discrete variables and ANOVA for continuous ones. If significant treatment group differences are found on potentially important baseline variables, these variables will be covaried in outcome analyses. Data from all randomized study participants will be used to compare the outcome of the two interventions on an intent-to-treat basis. Hypothesis tests will be two-tailed.

Participants will be counted in the intervention group to which they were randomized, regardless of the number of sessions they completed. We will make every attempt to complete a post-treatment and 3 and 6 month follow-up assessments on any participants who do not complete treatment. We will also conduct supplementary analyses including only those cases completing the full 12 sessions.

Aim 1*: Investigate the effectiveness of CBI on primary measures of outcome*

Hypothesis: Compared to SI, CBI will be associated with significantly larger reductions in anger and aggressive behaviors at post-treatment and at 3 and 6 month follow-ups.

Aim 2*: Investigate the effectiveness of CBI on secondary measures of outcome*

Hypothesis: Compared to SI, CBI will be associated with significantly more improvement in social functioning, occupational functioning, quality of life, and PTSD symptoms *a*t post- treatment and at 3and 6 month follow-ups.

For aims 1 and 2, we will use hierarchical linear modeling (HLM) for repeated measures to test for differences due to treatment condition, covarying for the baseline score of the dependent variable[65]. The primary significance test will be the treatment group main

effect over time, though there will also be a test for the time by treatment interaction. Significant time by treatment interactions will be followed up by post hoc tests at specific assessment points by calculating simple intercepts, simple slopes, and regions of significance. Relevant covariates will be included to adjust for any imbalances across treatment conditions.
Missing data will be dealt with as follows. HLM analyses can include cases with some time points missing. In the primary analysis, we will include all cases with at least 3 of the 5 outcome time points (4 & 8 weeks, posttreatment, and 3 & 6 months) non-missing. Then, we will conduct a sensitivity analysis including all randomized participants, in which any missing outcome values will be filled in with baseline scores, which is an extreme assumption. Consistency of results from the two approaches will bolster the credibility of the primary analysis.

The primary dependent variables for aim 1 are the STAXI-2 Anger Expression Index, and the OAS-M Aggression Scale score. Outcome on these measures is assessed at 4 and 8-week points during treatment, at post-treatment, and at 3 and 6 months follow-up assessments. DVs for aim 2 include two LIFE scales (global social and work functioning), the Outcomes Questionnaire total score, the WHOQOL-BREF total score, and the CAPS total score. Outcome on these measures is assessed at post-treatment and 3 and 6-month follow-up assessments.

For aims 1 and 2 the alpha will be set at .025 to account for multiple dependent variables.

Supplementary post-treatment outcome analyses will be conducted using collateral measures (including the STAXI-II, Anger Control Scale and Modified Overt Aggression Interview). We will calculate Pearson correlations of participant and collateral scales as an indication of agreement. If outcome analyses based on collateral measures are consistent with analyses of participant measures, this would bolster the validity of the participant outcome findings. Divergent findings could be due to multiple factors that could influence the validity of the participant and the collateral reports. In this case we will conduct analyses using integrated collateral and participant scores, calculated by averaging the participant and collateral responses to each item.

Aim 3: (Exploratory) Examine hypothesized mechanisms of action of CBI
Hypothesis: Change in arousal, cognitive, and behavioral domains of anger will mediate outcome for anger and functioning in the CBI condition.

In order to examine the mediating role of arousal, cognition, and behavior (NAS scales), we will use arousal, cognition, and behavior at post-treatment as mediators of the effect of treatment in predicting later anger and functioning at months 3 and 6. Therefore, these mediation tests will be fully prospective, as recommended by Kazdin & Nock[66], and as exemplified in prior mediational research done by Dr. Stout [67]. These analyses will covary for the baseline scores of the mediators. Mediation of treatment effects through NAS scales will be tested using the Sobel test [69, 70]. Simulation tests indicate that we will have more than 80% power to detect mediation when both paths have small to medium effect sizes [71].

Aim 4: (Exploratory) Examine the effectiveness of CBI for those with and without PTSD We will test for an interaction between CBI vs. SI and PTSD status by calculating simple slopes. Since we will not have 80% power to test this interaction, we will calculate treatment effect sizes separately for the PTSD and the no-PTSD cases.

G.3. *Power Analysis*

Power for our repeated-measures design was estimated using methods described by Faes et al.[71]. We obtained intervention effect sizes ranging from 0.78 to 1.12 in our pilot study, but given the small sample and the instability of effect sizes derived from pilot studies [72] we have conservatively based our statistical power analysis for detection of medium effects.

We will use a two-sided alpha level of .025 in the primary and secondary outcome analyses to correct for the number of dependent variables; i.e., each DV will be tested individually with an alpha level of .025, keeping the study-wise alpha at .05. With this alpha level and an estimated 80% follow-up, a sample size of 120 will provide 90% power to detect a medium effect size of .60.

H. Time-Line

We anticipate the following time-line for the study:

Months

0-6 Hiring, Training, IRB approvals	12-42 Follow-Up (6 month)
6-33 Recruitment	6-43 Data Entry and Management
6-36 Treatment	43-48 Final Data Analyses and Manuscript Writing
9-39 Follow-Up (3 month)	

I. Dissemination and Future Plans

The proposed study is a randomized clinical trial of the efficacy of a cognitive behavioral intervention (CBI) for the treatment of trauma related anger in OEF/OIF veterans. Prior to the start of the study, we will register with ClinicalTrials.gov. This website 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. Dissemination will include submission of the study findings to a peer-reviewed journal. The findings will also be presented at professional conferences, such as the International Society for the Study of Traumatic Stress, and appropriate VA and Department of Defense conferences. If CBI is found to be significantly superior to the supportive therapy control (SI), we will consider multiple methods for further dissemination. We will create a fact sheet describing the intervention and findings and 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. We could begin dissemination efforts by implementing the treatment at the Providence VAMC. We would

provide the manual and training to the mental health clinicians in the PTSD and Returning Veterans clinics, and encourage the use of relevant self-report outcome measures to provide an index of effectiveness in a naturalistic setting. A proposal of a multi-site study through the Cooperative Studies Program would be considered, to more formally test the effectiveness of the intervention across multiple VA settings.

5. Privacy and 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, particularly to subjects who are military personnel, because information bearing on their health may be required to be reported to appropriate medical or command authorities. Additionally, 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 separate locked location from all data. 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 in Bldg 32 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.

Assessments and intervention sessions will occur at the Providence VAMC. The veterans will be informed that their VA medical records will note their enrollment in a research study with a copy of their consent form attached. In addition, their attendance at each AE or HEC session will be noted in their medical records. This will include, if applicable, any safety issues (e.g., suicidal or homicidal statements they made) and how these were addressed in session. The veteran will be informed that none of the other data from this study will be included in their medical records, except for attendance at intervention sessions. All study data, stripped of identifying information, will be locked in a file cabinet as described above. Records will be maintained per Veterans Affairs Record Control Schedule 10-1.

6. Data Safety and Monitoring

Monitoring of safety in the proposed study will be the responsibility of all personnel on the project, with primary responsibility and supervision by Dr. Shea. The Institutional Review Board at the Providence VA Medical Center will approve the protocol and the

Statement of Informed Consent for the study and will provide oversight of data and safety issues.
Separate review of the protocol and consent form are made by the safety officer at the VA Medical Center. The study protocol will receive IRB approval prior to soliciting or requesting consent from any participants. Moreover, the study will be reviewed on an annual basis by the IRB committee with regard to recruitment and retention and annual reports will be made by the PI to the IRB chair of the Providence VA Medical Center regarding the progress of the proposed project, including any issues pertinent to recruitment, retention, confidentiality, and safety of human subjects. Any incidents that involve a breach of this plan or serious accident/injury will be reported to the IRB chair at the Providence VA Medical Center. As discussed, potential risks, albeit minimally likely, include distress or discomfort with questions regarding trauma history.

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. We have appointed Thomas O'Toole, MD as our medical monitor. Dr. O'Toole is a Providence VA Medical Center physician and researcher who works independently from our research. He will be called upon to review all AEs and SAEs, and to provide input regarding the possible connection to the study protocol.

7. Risks / Benefits Assessment

A. Protection Against Risks

Potential risks include distress associated with discussing traumatic or other disturbing events or emotions, and breach of confidentiality.

Risk: Emotional distress associated with discussing traumatic or other upsetting events or emotions.
Minimization: Study participants will participate in assessments and treatment sessions during which they may identify and discuss difficulties they are having with anger and with their adjustment home from a hazardous deployment. They also may discuss upsetting events that they experienced while deployed. Although the assessments are

unlikely to be more upsetting than standard clinical assessments, discussion of these experiences may make them feel uncomfortable. Should this happen, 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. No participant judged to be in danger of hurting him/herself or others will be allowed to leave the study setting unaccompanied. 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.

Collateral participants will also be informed that they may refuse to answer any question or stop the interview at any time. It is unlikely, but possible, that a collateral participant may show signs of distress. The same procedures will apply to these participants, i.e. if distressed they will remain in the assessment setting until their distress is at a manageable level. Dr. Shea will be available by phone or in person to study personnel during assessment and treatment sessions. She will be contacted immediately if there are any concerns about the participant's emotional state, or upon any signs of suicidal or homicidal risk. All participants will be eligible for emergency services including referral to the Veterans Affairs Medical Center interim care during normal business hours or the emergency room after hours and on weekends and holidays, and inpatient hospitalization.

Additionally, therapists will be doctoral level psychologists or masters level social workers, and trained to help veterans reduce and manage feelings of intense anger. Assessments will be conducted by trained staff with prior experience in conducting clinical interviews in psychiatric samples. Veterans will have the opportunity to discuss any uncomfortable feelings with the assessment interviewers and treatment providers. The veteran will also be informed that the therapist and assessment interviewer will always place the veteran's well-being and safety over research considerations. Furthermore the veteran will be informed that should they experience any problems, they should report them to their therapist or to the principal investigator of this study.

Risk: Breach of Confidentiality
Minimization: All employees who handle data will be trained in confidentiality policies and procedures. All data and medical information obtained about the veteran, as an individual, will be considered privileged and held in confidence; the veteran will not be identified in any presentation of the results. Assessments and treatment sessions will occur at the Providence VAMC. Veterans will be informed that their VA medical records will note their enrollment in a research study with a copy of their consent form attached. In addition, their attendance at each therapy session will be noted in their medical records. This will include, if applicable, any safety issues (e.g., suicidal or homicidal statements they made) and how these were addressed in treatment. The veteran will be informed that none of the other data from this study will be included in their medical records, except for attendance at treatment sessions. All study data, stripped of identifying information, will be locked in a file cabinet. Study files will be maintained in

accordance with the Department of Veterans Affairs Record Control Schedule 10-1.

All of the study data will be coded without the use of the veteran's name and social security number and will be done in accordance with the law. Research information about the veteran will remain in Dr. Tracie Shea's (PI) locked private research files and will be available only to staff connected with this study or individuals involved in human subjects protection. It will not be given to other medical care personnel at the veteran's VA or the Department of Veterans Benefits without an additional written consent from the veteran. Any reports or publications of this study will not include information that could be used to identify the veteran.

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 separate locked location from all data. Transfer of data will include only de-identified data, and will use encryption for any electronic transfer. Additional precautions include: (1) Data sheets will be will be stored in locked offices of Dr. Tracie Shea (PI), building 32 of the PVAMC, (2) data will be entered in coded form, (3) data will be stored in computer files 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.

Digital recordings will be made of all treatment and assessment sessions. These recordings will be reviewed by study personnel who are providing ongoing supervision to study therapists and interviewers, and by individuals conducting reviews of how well we followed study procedures (adherence ratings). These recordings will be coded without the use of the veteran's name or social security number, or any other identifying information.
Digital recordings may also be downloaded into a file transfer program (FTP) which is password protected. Research staff will be the only people to have access to the FTP. Study files will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1.

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

Poorly controlled anger is a common problem with often devastating effects in veterans who have been exposed to trauma while they served in a warzone. Additionally, individuals who have experienced trauma may continue to respond with excessive anger and aggression in situations that they perceive as threatening (even in the absence of life-threat) resulting in destruction of property, threats of physical violence and/or physical fights. Although this response may have been adaptive during trauma, it is maladaptive when individuals cannot regulate the intensity and expression of anger as appropriate with current socio-environmental conditions. There is empirical support for the use of Cognitive Behavioral Therapy (CBT) similar to what we propose in the treatment of other populations with anger, and preliminary support for positive effects in veteran

samples.

Through participation in this study, the veteran receives a comprehensive psychological assessment and treatment at no cost. Additionally, potential effects of the interventions could possibly lead to an improvement in the veterans' ability to manage their anger and adjustment to being home following deployment. Furthermore, it is hoped that information gained from this study will improve treatment for veterans who have served in hazardous deployments, even if the veteran themselves do not experience any improvement during their participation in the study. Given the published reports and our own experience, the potential benefits outweigh the risks.

C. Importance of the Knowledge to be Gained

Problems with anger are common in veterans who have been deployed to a warzone, and can lead to devastating consequences in terms of family, social, and occupational functioning. Although promising findings for cognitive behavioral treatments have been reported, to date there is not a single adequately powered randomized trial designed to test the efficacy of an anger treatment compared to an active control condition in veterans. The goal of the proposed research is to determine if the Cognitive Behavioral Intervention to be tested can provide an effective treatment for anger problems in OEF/OIF veterans, and reduce the toll that these problems take on social and occupational functioning and quality of life. The potential of the research to ultimately benefit veterans with anger problems, and the provision of comprehensive assessment and treatment compares favorably when weighted against the potential risks of discomfort or distress, which are expected to be mild.

PROTOCOL APPENDIX - ISO

All VA sensitive information will be stored on the secure VA server located at:
\\vhaproapp12\Research_Protocols\Shea\Anger-R

All data is collected using a study code that does not identify the patient. The cross-link matching the patient with the code is saved in a password-protected file, separate from the rest of the data files, on the same secure VA server that only the PI and research staff have access to. Paper versions of the assessment will be stored in locked filing cabinets in locked offices of Dr. Tracie Shea (PI), in building 32 of the PVAMC. Additionally, no VA sensitive data will be transmitted outside the VA. Only VA non-sensitive data will be transmitted electronically via internet for discussion during study meetings. Data collected from this study will be used for research purposes. No patient identifiable information will be released or published without written permission unless required to do so by law. Records will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1.

In the event that theft, loss of other unauthorized access of sensitive data or storage devices and non-compliance with security controls occur, study staff has been instructed to follow the Providence VA Medical Center's standard operating procedure on incidence reporting.

Transcription records will be maintained according to RSC 10-1. All digital recordings will be uploaded to the server for storage. Once the records are copied and verified from the recording device, the device will be turned into the ISO for final disposition.

Original data files on portable storage media, i.e., CDs, USB Flash Drives, etc, will be uploaded to the server for storage. Once the files are copied and verified from the device/media, the device/media will be turned into the ISO for final disposition.

Original data collected on non-digital storage media, such as audio tapes, will be maintained in accordance with VA RCS-10-01.

We will use REDCap electronic data capture tools hosted at the Department of Veterans Affairs. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Through REDCap, participants are able to respond to survey items electronically and additionally research study staff can manually enter responses. All study software and licensing, such as SPSS IBM (which will be used for data analyses) will be managed by PVAMC IT and IRM.

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