Study Title: Group Cognitive Behavioral Therapy for Anger and Aggression in Veterans with PTSD

Clinical Trials Identifier: NCT02233517

Protocol and Statistical Analysis Plan

Research Protocol

Group Cognitive Behavioral Therapy for Anger and Aggression in Veterans with PTSD

Summary & Purpose

Posttraumatic stress disorder (PTSD) robustly predicts anger and aggression (Olatunji, Ciesielski, & Tolin, 2010), and U.S. Iraq/Afghanistan-era Veterans report that controlling anger and aggressive urges are primary readjustment concerns (Sayer et al., 2010). Anger interferes with recovery in therapy for PTSD (Foa, Riggs, Massie, & Yarczower, 1995; Forbes et al., 2008); as such, the DOD/VA Clinical Guidelines for the Treatment of PTSD recommend that Veterans with anger problems be specifically referred to anger management treatment. While anger management groups are offered at most VA hospitals, CBOCs, and Vet Centers, the virtual absence of established empirically supported treatments for PTSD-related anger and aggression leaves VA clinicians unclear as to how to most effectively treat these pervasive and disabling problems (Elbogen et al., 2010).

The proposed research project is a pilot study of the efficacy of Cognitive-Behavioral Therapy for Anger and Aggression in Combat Veterans with PTSD (CBT-A). CBT-A is a 12-week manualized group treatment protocol that is grounded in current research, and that has been designed to specifically address the cognitive, affective, and behavioral components of combat PTSD-related aggression. Specifically, this project will be a pilot 2-arm, randomized clinical trial comparing group CBT-A to group Present Centered Therapy (PCT), an active therapy control condition commonly used in PTSD efficacy studies.

The proposed pilot study has two Specific Aims: 1) to evaluate the feasibility of a full-scale RCT evaluating the efficacy of Cognitive Behavioral Therapy for Anger and Aggression (CBT-A) in combat Veterans with PTSD, and 2) to characterize the differences in effects of CBT-A and PCT on anger, aggression, and anger/aggression related functional impairment and quality of life in combat Veterans with PTSD. Specific objectives have been identified for each of these aims.

Aim 1: Evaluate study feasibility and treatment delivery procedures of a RCT comparing CBT-A to a PCT comparison condition.

Specific Objectives for Aim 1:

1. *Evaluate response rate to recruitment efforts and rate of accrual into the study.*
2. *Evaluate group drop-out rates.*
3. *Evaluate participant retention through the 6-month follow-up assessment.*
4. *Evaluate success of the randomization procedure, including the association of potential stratification variables with feasibility variables and treatment outcome*.
5. *Evaluate therapist treatment fidelity.*
6. *Assess adverse event frequency and severity.*
7. *Assess treatment adherence and participant engagement in treatment.*

Aim 2: Characterize the difference between the CBT-A intervention and the PCT comparison condition in effects on PTSD-related anger and aggression, anger and aggression-related functional impairments, and quality of life.

Specific Objectives for Aim 2:

1. *Examine the effects of the CBT-A intervention on reducing aggression and violence.*
2. *Examine the effects of CBT-A on managing PTSD-related anger; diminishing the negative impact of anger and aggression on functional life domains; and diminishing the negative impact of anger and aggression on quality of life.*
3. *Other outcomes of interest include: changes in PTSD symptoms and incidence and severity of substance misuse.*

Background and Significance

Anger and aggression are positively associated with PTSD with medium to large effect sizes, particularly in military and Veteran samples (Andrews & Brewin, 2012; Orth & Wieland, 2006), and U.S. Iraq and Afghanistan-era combat Veterans report controlling anger and aggressive urges as primary readjustment concerns. In a sample of 754 help-seeking Iraq and Afghanistan combat Veterans, 57% reported problems

controlling anger within the past 30 days, and 35% endorsed thoughts of hurting someone or dangerous driving over the same time period (Sayer, et al., 2010). In many cases these problems appear to worsen over time: In two longitudinal studies of Iraq War Veterans, self-reported aggressive behaviors (Thomas et al., 2010) and concerns about interpersonal conflict (Milliken, Auchterlonie, & Hoge, 2007) significantly increased from 3 to 12 months post-deployment. Further, research with Vietnam Veterans has suggested that functional impairment associated with PTSD-related anger can persist for decades (Novaco & Chemtob, 2002). For example, more than 20 years after the end of the Vietnam War, combat Veterans, their spouses, and clinicians continue to identify problems with anger as the highest priority among several potential psychiatric concerns including depression, anxiety, and alcohol problems (Biddle, Elliott, Creamer, Forbes, & Devilly, 2002).

Several meta-analyses and reviews of the literature suggest that therapy can be effective in treating anger problems and reducing aggression (Del Vecchio & O'Leary, 2004; DiGiuseppe & Tafrate, 2003), but that there is considerable variance in outcomes depending upon the patient population. Unfortunately, very little work has been done to examine the effectiveness of treatments to address anger problems and aggression in Veterans. In fact, only one randomized clinical trial has ever been published regarding the effectiveness of an anger management therapy for Veterans with PTSD (Chemtob, Novaco, Hamada, & Gross, 1997). This study, published in 1997, reported on the efficacy of a cognitive-behavioral treatment implemented in an individual format. Though there was a high (46%) drop-out rate, improvements were found in anger control at post-treatment and 18-month follow-up. Only three studies have been published specifically examining the effects of group anger management therapy for Veterans with PTSD, and none of these has included a comparison control group. All three studies examined cognitive-behavioral therapeutic approaches, and all reported significant drops in anger outcomes from pre- to post-treatment (Gerlock, 1994; Marshall et al., 2010; Morland et al., 2010).

Based on emerging empirical evidence that supports the unique relationship among PTSD, anger and aggression in combat Veterans (Forbes, et al., 2008; Kuhn, Drescher, Ruzek, & Rosen, 2010; Orth & Wieland, 2006; Prigerson, Maciejewski, & Rosenheck, 2002), we have developed a model of trauma-induced deficits in self-regulation that may prime combat Veterans with PTSD to react aggressively to perceived provocation (Beckham, Feldman, Kirby, Hertzberg, & Moore, 1997; Chemtob, Novaco, Hamada, Gross, & Smith, 1997). The primary components of this model are presented in Figure 1. Briefly, the model suggests that cognitive, affective, physiological, and behavioral biases fostering aggression have been developed and/or reinforced in the context of military training, combat, and combat trauma. These biases contribute to a distinctive affective style (Davidson, 1998) that serves to restrict the range of behavioral options available to combat Veterans with PTSD. Based on this model, treatment involves expanding cognitive, affective, and behavioral repertoires to provide Veterans with alternatives to overlearned aggressive scripts, thereby increasing their effectiveness across functional domains.

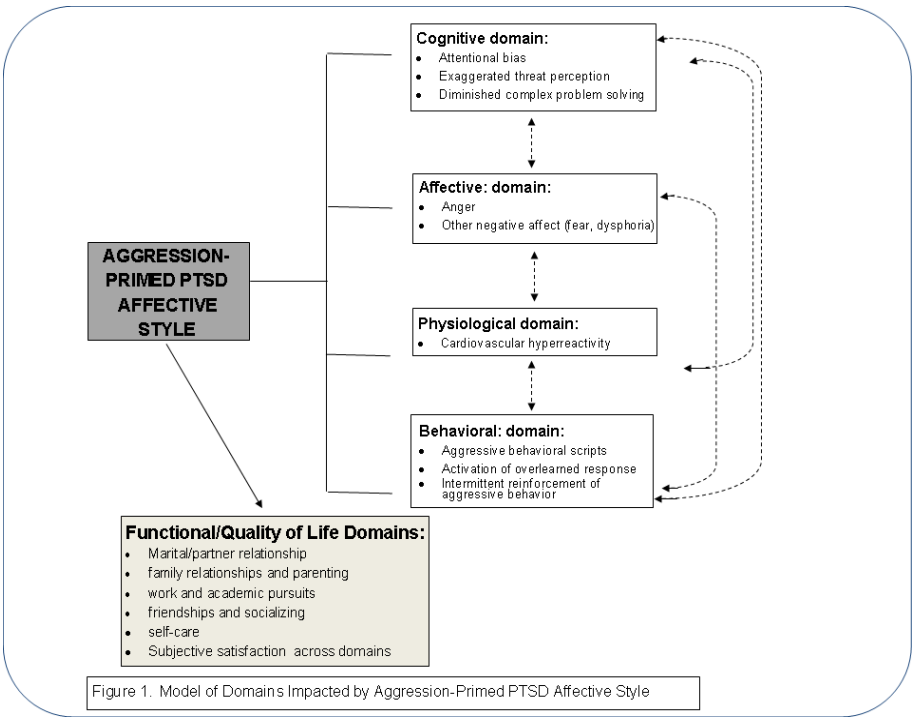


Figure 1. Model of Domains Impacted by Aggression-Primed PTSD Affective Style

In summary, treatment for anger and aggression in Veterans with PTSD is in high demand in the VA, and VA service providers are currently in the position of having to provide treatment for these impairing problems with little empirical guidance.

Given that there is mounting evidence that anger in PTSD may be unique and may therefore require a tailored treatment approach (Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003; Olatunji, et al., 2010; Teten et al., 2010), this study seeks to fill an important need by testing a group therapy protocol that specifically address the cognitive, affective, physiological, and behavioral aspects of PTSD-related anger and aggression.

Anger and aggression in combat Veterans with PTSD are associated with diminished quality of life and functional impairments across domains (Thomas et al., 2010), including problems with domestic violence, ineffective parenting, unsafe driving, employment, and social alienation (Rodriguez et. al., 2012). Anger has been found to mediate the association between PTSD and partner physical and psychological abuse (Taft et al., 2007), as well as between PTSD and family functioning (Evans et al., 2003). Compared to Veterans without PTSD, Veterans with PTSD reported greater parenting problems, and their spouses reported more frequent and severe behavioral problems in their children (Jordan et al., 1992). Functional impairment associated with PTSD-related anger and aggression in combat Veterans can persist for decades (Biddle et al., 2002; Koenen et al., 2003; Novaco & Chemtob, 2002). For example, a relatively recent study found that Vietnam Veterans, their spouses, and clinicians identified problems with anger as the highest priority among several potential psychiatric concerns, including anxiety, depression, and alcohol problems (Biddle et al., 2002).

Though anger and aggression lead to functional impairment and diminished quality of life in Veterans with PTSD, they may also play an important role in how Veterans cope with their PTSD symptoms. A core facet of PTSD is avoidance of others because of the possibility of encountering conflict; feeling vulnerable; or experiencing sadness, guilt, or fear. As such, Veterans with PTSD may use anger or aggression 1) to distract themselves from other negative affect such as fear, guilt, sadness, or vulnerability by fostering a sense of power and control (Foa et al., 1995; Gerlock, 1994); 2) to control others' behavior through instilling fear; and 3)to keep others at bay, allowing for the use of behavioral and emotional avoidance to cope. Because these behaviors are used by Veterans with PTSD to distance themselves from others, it may be difficult for them to accurately report the negative effects they are having on those closest to them. To accurately measure the effect of the intervention on functioning, therefore, it is important to collect information from collateral sources. Unfortunately the few studies of anger and aggression interventions in Veteran have typically not incorporated collateral reports of anger and aggression, leaving a significant gap in our ability to accurately evaluate the effectiveness of the intervention.

The proposed study is a 2-arm, randomized clinical trial comparing group CBT-A to group PCT. Thirty-six (12 female, 24 male) eligible Veterans who agree to participate will be randomized to one of two group conditions: CBT-A (n = 18; 6 female, 12 male) or PCT (n = 18; 6 female; 12 male). Each of the 3 CBT-A and 3 PCT groups will consist of 5-6 members.

Please note that in some correspondence with participants and/or recruitment materials, this study may be referred to by the acronym **CALM**, **C**ognitive Behavioral Therapy for **A**ggression and Anger **L**evel **M**anagement.

Methods

Selection of Subjects

The following inclusion and exclusion criteria were developed to adhere to recommendations for the early stages of research on an intervention while appropriately representing the target clinical population (US Department of Veterans Affairs Office of Research & Development., 2008). In the early phases of this project, we had a large number of women screen out during the telephone screening process because they were not deployed to a combat zone. However, most of them have reported that they have PTSD from other traumatic events, and that they experience significant functional impairment related to their anger. Because of this difficulty recruiting female combat Veterans, we will plan to expand inclusion criteria for this feasibility trial to include all women who have served in the military and who have PTSD, regardless of deployment history. As we have successfully completed recruitment with male Veterans, we will not change the deployment criterion for men.

Inclusion criteria:

- (If potential participant is a male Veteran) have deployed to serve in or near a war zone (including the Balkans, Iraq, Kuwait, Afghanistan, etc.);
- meet criteria for current PTSD based on the Clinician-Administered PTSD Scale;
- can speak and write fluent conversational English;
- are at least 18 years of age; and
- report problems with irritability, anger, or difficulty controlling aggressive urges within the past month.

Exclusion criteria:

- expected to be unstable on their medication regimen during the study;
- active substance use during study participation;
- currently meet criteria for manic episode or a primary psychotic disorder, as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID);
- are receiving anger-management psychotherapy at the time of study entry;
- are receiving psychotherapy for PTSD (or plan to begin) during treatment phase of study (see explanation below); or
- are determined to have moderate or severe impairment related to traumatic brain injury.

Eligibility for research participation is not contingent on eligibility or enrollment for VA care. This is important for this study because there is a subset of Veterans with PTSD who are unlikely to voluntarily seek treatment in the VA (see Spoont et al., 2014). Any Veteran who is not enrolled for care within VA will be offered a Notice of Privacy Practices, and we will document the receipt thereof. This study does not involve procedures that are likely to cause any risk to pregnant women or unborn children. Therefore, pregnant women will not be excluded from participation in the study.

In order to maximize the data for understanding whether CBT-A may assist in reducing aggression, the treatment will be administered independent of concurrent other PTSD psychotherapies. To evaluate the relationship between treatment for PTSD and treatment for anger and aggression we will collect information about participation in therapy for PTSD prior to study participation or during the follow-up assessment phase; however, endorsement of therapy for PTSD prior to or after the study treatment phase will not be exclusionary. If a participant expresses interest in therapy for PTSD during the treatment component of the study, the participant will be offered a referral for treatment within the VA (i.e. CPT or PE). Participants who receive such referrals will be informed that if they plan to initiate treatment for PTSD immediately they will no longer be eligible for participation in the study but will be compensated for their partial participation, and that if they are interested in being screened again after completing therapy for PTSD they will be eligible to do so. Participants

will continue to be eligible for participation in the current study if they plan to initiate treatment during the 6-month post-treatment assessment phase.

It is important to acknowledge that the proposed intervention does not address PTSD symptoms other than anger and aggression, and that participation in this research study should not be seen as a substitute or alternative to receiving empirically-supported treatment (EST) for PTSD. In fact, among the rationales for providing the proposed treatment to individuals with PTSD is that reductions in anger and aggression might increase the likelihood of seeking, benefiting from, and completing EST for PTSD.

The VA is committed to disseminating empirically-supported treatments for PTSD including PE and CPT. The VISN-6 MIRECC has a close relationship with the Durham VA OEF/OIF/OND Clinic, and research clinicians routinely do "warm hand-offs" of Veterans interested in treatment for PTSD by taking them directly to the Clinic and introducing them to the staff. With Veterans' consent, MIRECC clinicians also enter consults for Veterans directly into CPRS, thereby facilitating clinical assessment and treatment for PTSD and other psychiatric or medical problems.

Consistent with routine procedure within the VISN-6 MIRECC, throughout the screening, treatment, and assessment process of the proposed study Veteran participants will be educated about PTSD and about CPT and PE; will be provided with resources for accessing these treatments; and will be encouraged to participate in one of these empirically-supported therapies. Participants will be informed that while they cannot participate in this study while receiving psychotherapy for PTSD, they are free to discontinue participation in the study at any time if they wish to initiate specific treatment for PTSD. They will also be provided with information about the OEF/OIF/OND Clinic or other appropriate resources and about PE and CPT at screening, and they will be encouraged to follow up with EST for PTSD either immediately or upon completion of participation in this study. Finally, PE and CPT will be discussed throughout the group sessions. PE and CPT will specifically be a focus of discussion in the 1st session during the review of the history of PTSD; during the 8th session when we review the principles behind trauma-focused therapy; and during the last session when follow-up treatment options and referrals are discussed.

Subject Recruitment

The recruitment site for this study will be the Durham VAMC. This region is heavily populated by active duty, National Guard, and Reservist military personnel. There are currently over 9,000 Afghanistan/Iraq-era Veterans enrolled at the Durham VAMC.

Our planned recruitment activities involve several strategies. First, potentially eligible Veterans will be identified through a data pull using the VAMC's Fileman system and/or the Corporate Data Warehouse. Second, the Durham VAMC is the primary site for the VISN 6 Mental Illness Research, Education, and Clinical Center (MIRECC), which focuses on Post-Deployment Mental Health of OEF/OIF/OND-era Veterans. As of February 2013, over 2,500 Afghanistan/Iraq era Veterans have participated in the VISN 6 MIRECC's study, the Study of Post-Deployment Mental Health (IRB# 00933). A majority of those Veterans have agreed to be re-contacted regarding participation in future research studies regarding post-deployment issues as part of their enrollment in the Re-Contact Database of the VISN 6 MIRECC Post-Deployment Mental Health Data Repository (IRB# 01706). Application to recruit from the Re-Contact Database of the VISN 6 MIRECC Post-Deployment Mental Health Data Repository will be made to the VISN 6 MIRECC Director (Dr. John Fairbank) in accordance with IRB and R&D approved data repository procedures.

Drs. Van Voorhees and Dr. Calhoun (co-Investigator) perform clinical work in the PTSD Clinic, and as such, have access to the PTSD Clinic's database summarizing results of clinical evaluations. As part of these clinical evaluations, Veterans complete several measures that include indices of anger and angry behavior, including the PTSD Checklist, Conflict Tactics Scale, Clinician-Administered PTSD Scale, and Cook-Medley Hostility Scale. We would like to use the PTSD Clinic database results to identify potentially eligible Veterans and target recruitment to them by sending IRB-approved recruitment letters to them (just as we do for those Veterans we identify through Fileman/CPRS).

In addition to these targeted mail outs, we will place flyers and brochures that have been approved by DVAMC's Institutional Review Board (IRB) on research bulletin boards, at program offices, in clinic areas (including Vet Centers and CBOCs), and in the community in places such as grocery stores, restaurants, etc. We will also advertise via the closed circuit television system within the VA Medical Center and in local newspapers and online classified services such as www.craigslist.com. Upon approval by the DVAMC's Public Affairs officer, we will also post information about the study on the DVAMC's Facebook page. Also, upon approval from the Public Affairs officer, we will host informational tables in the medical center. At these informational tables, IRB-approved recruitment materials from the study (and from other studies run in the

Traumatic Stress and Health Research Laboratory) will be made available to interested veterans, and study staff members may be on site to answer questions about the research studies. No participants will be consented or screened at these public locations.

We plan to recruit OEF/OIF/OND-era Veterans from the VISN 6 MIRECC Repository and from the VAMC's Fileman system and/or Corporate Data Warehouse using a recruitment letter (see Appendix A for attached recruitment letter). For repository recruitment we will request that the VISN 6 MIRECC provide the name and mailing address of Veterans who are likely to meet the inclusion/exclusion criteria outlined above. The letter will inform potential participants that they will be called regarding participation unless they call a toll free number to refuse participation. Seven business days after the mailing, Veterans who have not called the toll free number to decline participation will be called by a research assistant (see telephone script).

If we are unable to recruit a sufficient number of participants for the study through mailing Veterans a single recruitment letter as outlined above, as a second course of action we will implement procedures recommended by Dillman, Smith, and Christian (2009). The recommended contact strategy includes sending a series of four letters to potentially eligible Veterans. Based on social exchange theory, Dillman and colleagues recommend that the second letter be sent with a small token of appreciation. This token incentive serves two functions – it will encourage respondents to respond based on the principles of social exchange theory, and more importantly, it will bring additional attention to the request for participation so that it will be more readily considered. As recommended, letter two will be sent with a small selection (i.e., monetary value less than $2) of commemorative stamps. The token of appreciation included in the second letter was written into the protocol after careful consideration of the ethical principles involved. As stated previously, the stamps are in place with the intention that they will facilitate more patients to consider enrolling in the study and seek more information about it. Because there is minimal risk associated with contacting a study coordinator, beneficence is not drastically affected by inclusion of stamps in the second letter. The potential ethical concerns are undue influence of the stamps. In considering whether the stamps would be an undue influence, we noted that the provision of stamps are not contingent on participation or even contacting study staff, as they are provided to everyone as a token of appreciation. In addition, the stamps were specified at a monetary value of less than $2 so that the value would be too small to unduly influence potential participants.

Clinicians and case managers in the North Carolina National Guard Integrated Behavioral Health System (IBHS) have indicated that they would like to refer Veterans to the research study. Clinicians and/or case managers in this program are required to document whether a referred Veteran is eligible for and/or attends treatment to which he/she is referred. Therefore, they have requested that we provide them with information regarding attendance, such as alerting them to no-shows, screen-outs, treatment drop-outs, etc. Potential participants referred by IBHS are informed that data re: ineligibility, treatment drop out, withdrawal, or losses to contact for any Veteran participant who is referred directly by the IBHS will be shared with his/her referring counselor or case manager. We will not share this information for any Veteran who refuses to provide consent. If any Veteran indicates that he/she does not wish to sign consent, we will ask him/her to contact his/her IBHS counselor or case manager so that a different treatment can be recommended, but no study staff member will contact the IBHS staff member if the ICF and HIPAA authorization aren't signed.

There is a subset of Veterans with PTSD who are unlikely to voluntarily seek treatment in the VA (Spoont et al., 2014). Reaching this hidden population of Veterans who do not seek treatment in order to provide them treatment for anger management is an important goal. In order to reach Veterans who may not be enrolled for care in the VA system, we will plan to use a recruitment method referred to as respondent-driven sampling, or "seed recruitment" (Christina Meade, Ph.D., personal communication). Seed recruitment is suitable for sampling "hidden populations" of participants who are best known by their own peers (Heckathorn, 1997). It includes providing incentives to participants for referral of other eligible participants. In our model, each participant, or seed, will receive two coupons to recruit other Veterans in his/her social networks. The recruitment coupons will provide a brief description of the survey and a phone number for contacting the study coordinator. The coupon will be marked with a unique identification number (not the study identification number) so that when the coupons are returned to us, the ID number can be used to provide a small payment ($5) to the participant who made the referral. The key connecting the participant's study ID number with the seed ID number will be kept in a database separate from other PHI, creating two layers of separation between the seed ID and the already-participating Veterans' identifying information. Any Veteran who does not wish to recruit in this manner will not be required to do so.

It is estimated that 60 potential participants (20 women, 40 men) will be consented and screened, and 36 will be randomized to a study condition. Considering drop-out rates in pilot groups of CBT-A, in studies in the

Traumatic Stress and Health Laboratory more broadly, and in previously published studies of anger management in Veterans, we will assume a 15% drop-out rate, for a final sample of 30 individuals with PTSD that will complete the interventions. Because the planned full RCT will employ an intent-to-treat analysis using a mixed-models repeated measures statistical approach, we will include all 36 randomized participants in all analyses.

Recruitment of Women: Though the majority of research on the association between PTSD and aggression has been conducted with men, at least one study has found that PTSD significantly increases the odds of both interpersonal and general violence in women with PTSD (Kirby et al., 2012). In an ongoing longitudinal study of Iraq and Afghanistan era Veterans conducted by Drs. Elbogen and Beckham, we found that 33% of female Veterans reported engaging in at least one violent act over the past year, and that there were no significant differences between males and females in rates of aggression. These data suggest that there is a need for effective treatment for anger problems and aggression in both genders.

On the other hand, previous researchers and clinicians have observed that much of the anger expressed by males in anger management groups is directed at women (Gerlock, 1994), and inclusion of women with sexual trauma histories in groups with males is contraindicated (Chard, 2010). For these reasons, one group of each treatment arm of the proposed study will be exclusively women, and two groups of each treatment arm will be exclusively men. As such 1/3 of the total sample in the pilot study (n=12) will be women Veterans. Though this will not allow for meaningful gender comparisons in this pilot data, important information will be collected regarding feasibility, recruitment, treatment tolerability, retention, and estimate effect sizes. These findings will inform the development of a larger RCT in which gender issues can be more effectively considered.

Consent Process

Veteran Participants: We are applying for a waiver of informed consent/HIPPA authorization to obtain the names of individuals who may be eligible for the study from the Re-Contact Database of the VISN 6 MIRECC Post-Deployment Mental Health Data Repository (IRB# 01706) and from the VAMC's Fileman system and/or the Corporate Data Warehouse, and so that we can conduct pre-screening with potential participants over the telephone. Informed consent will be sought at the beginning of the in-person screening session. Before participants provide informed consent, a study coordinator will explain the study in detail, provide the participant with a written document explaining the procedures and risks, and answer any questions. Participants will be informed that they may withdraw their participation from the study at any time without penalty. They will be given numbers to call if they have additional questions about the consent form or the research, if they have any problems during the study, or they have general questions about participating in research studies. The informed consent document will then be signed by the participant and the study coordinator. Participants will be given a copy of the informed consent form for their records.

Collateral Reporters: If the veteran agrees to the study, the interviewer will obtain consent from a collateral reporter to participate in the study. Collateral reporters will be chosen using a systematic decision-making tree. Specifically, we will first request collateral information from a spouse if one is living with the veteran. If not, we will request information from another family member living with the veteran. If the veteran lives alone, we will request that the family member the veteran sees most often provide information. Finally, in the unlikely event that the veteran has not identified potential family members, we will request that a friend or roommate who knows the veteran best be considered to be a collateral reporter on the study. The family or a friend will then be contacted and a research assistant will explain the nature and the purpose of the research, study procedures, standard protections for human subjects, and risks and benefits of the study.

Any participant who cannot or chooses not to identify a collateral reporter to participate alongside him/her will still be allowed to participate in the other portions of the study. Once a collateral reporter has been identified by the participant (see Collateral Informant Contact Information Sheet), the study coordinator will contact him/her regarding participation in the study. He/she will be asked to attend an in-person session in which he/she will provide informed consent, sign HIPAA authorization, and complete study questionnaires. If the study coordinator is not able to reach the identified friend or family member, the participant may be asked to provide the name and contact information of another potential collateral reporter. If the family member or companion who consents in session one is unable to attend session two, the veteran will be asked to identify another family member or companion, who will be consented prior to beginning session two. Any time a collateral reporter chooses to withdraw from the study, this will not impact the participation of the main study

participant. The Traumatic Stress and Health Research Laboratory has extensive experience conducting studies asking veterans and their family members to describe violence and has had a very low rate of refusal to participate from family members.

Screening Procedures

Potential participants will undergo a brief telephone screen, followed by an in-person screening session at the Durham VA Medical Center (DVAMC). At the beginning of the in-person screening session participants will be provided with greater detail about the group requirements and procedures, as well as about randomization to one of the two treatment conditions. In an effort to diminish attrition rates, the screener will discuss with the participant his or her ability and willingness to adhere to the study conditions. The screener will encourage the participant to identify potential barriers to group attendance and treatment adherence, and will assist him or her in brainstorming solutions to these barriers.

Each potential participant will be administered the CAPS to evaluate for current PTSD; the SCID to assess for the presence of comorbid disorders; the Brief Traumatic Brain Injury Screen. Upon determination of eligibility, participants will complete the pre-intervention measures.

Group treatment sessions will take place at DVAMC, the Raleigh Vet Center, Raleigh II CBOC, or Hillandale II, depending on space availability and/or participant preference. Participants are asked to attend each group session free from alcohol and drugs. If any participant endorses recent consumption of alcohol or drugs, the appointment will be rescheduled or the participant will be asked to attend the next group therapy session. The participant will be reminded not to consume drugs or alcohol in the hours prior to the appointment. If the participant has driven to the appointment, we will advise the participant not to drive home. We will encourage the participant to use the local bus system, the Disabled American Veterans transportation system (if available), call for someone to pick him/her up, or call a taxi. We will help the participant arrange transportation home, but we will not pay for this transportation. If a study participant attends group while under the influence of substances or cannot participate in group therapy sessions for other reasons, he/she may be withdrawn from the study.

Participants will be asked to attend a total of 14 study sessions including one screening and pre-treatment session, 12 treatment sessions, and a post-treatment assessment and feedback session. Collateral reporters will be asked to attend one in person study session, and they will be mailed packets of questionnaires at post-treatment, and 3- and 6-months post-treatment. Packets of questionnaires will be mailed to participants at 3- and 6-months post-treatment. Questionnaires completed and mailed will include only the following identifiers: the study identification code and a place for participants to enter the date that questionnaires were completed. Questionnaires will be returned to study staff in a self-addressed stamped envelope that is provided to the participant. Any participant who wishes to come to the medical center to complete the study questionnaires in person will be allowed to do so.

In order to enhance participant retention during the 6-month follow-up period, we will use strategies recommended by Wisniewski and colleagues (Wisniewski et al., 2006). Specifically, we will maintain frequent participant contact throughout the evaluation period. For example, we will make intermittent phone calls to participants to check on their status, and, where relevant, send birthday and holiday cards and study newsletters to encourage a sense of community and ownership of the study. We will also employ methods we have successfully used in Dr. Elbogen's large longitudinal study of Afghanistan/Iraq-era Veterans (i.e. Elbogen, 2012), including mailing reminders 16 days after follow-up materials are sent either thanking them for participating in the assessment, or encouraging them to do so.

Please see Table 1 for timing of administration of all assessments.

Optimal randomization of participants to group would require us to enroll 12 eligible participants prior to group assignment, resulting in significant delays between screening and the initiation of treatment (Schnurr, Friedman, Lavori, & Hsieh, 2001). However, requiring participants to wait for several months between study enrollment and treatment for anger and aggression may be ethically questionable, and may also increase the likelihood that a high percentage would drop out of the study prior to the first session to seek treatment elsewhere. As a result, we will begin a group immediately upon enrollment of 6 participants, and will alternate the initiation of CBT-A and PCT groups through the implementation process. Participants will not be stratified to group in this pilot study. Instead, randomization effectiveness will be evaluated through an examination of pre-treatment variables including PTSD severity, anger severity, and level of aggression. If there is evidence of randomization failure, this will be addressed through the use of covariates in analyses of the pilot data, and

will be used to evaluate the need for alternative randomization procedure or the use of stratification variables in future studies (US Department of Veterans Affairs Office of Research & Development, NIMH, & DoD, 2008).

Measures

Demographic Information

We will collect demographic information including name, age, birth date, phone numbers, address, email address, military position, rank, dates of service, locations of service, military occupation, number of deployments, and information on degree of combat exposure. If consent is provided for re-contacting for future studies, we will collect phone numbers and address. Collateral reporters will also be asked for demographic information including name, age, phone numbers, address, and whether or not they are Veterans themselves. We will collect social security number as required for informed consent and HIPAA authorization. If necessary to compensate participants (i.e. through electronic funds transfer), we will collect bank account numbers.

Table 1. Study Measures

Instruments for Veteran Interviews/Self-Report	Time (mins)	Screening/ Pre-treatment	Treat-ment sessions	Post-treatment	3 months	6 months
Clinician Administered PTSD Scale (CAPS)	60	●				
Structured Clinical Interview of Diagnosis (SCID) (selected modules)	60	●				
Brief Traumatic Brain Injury Screen	1	●				
Traumatic Life Events Questionnaire (TLEQ)	10	●				
Deployment Risk and Resilience Inventory (DRRI) (specific scales)	15	●				
Self-Appraisal Questionnaire (SAQ)	15	●				
WHO Disability Assessment Schedule 2.0 (WHODAS)	5	●	●	●	●	●
Inventory of Psychosocial Functioning (IPF)	5	●		●	●	●
Community Reintegration of Service Members (CRIS)	10	●		●	●	●
McMaster Family Assessment Device (FAD)	10	●		●	●	●
Connor-Davidson Resilience Scale (CD-RISC)	3	●		●	●	●
Conflict Tactics Scale (CTS)	5	●		●	●	●
Aggressive Driving Questions	5	●		●	●	●
Novaco Anger Scale (NAS)	10	●		●	●	●
Dimensions of Anger Reactions (DAR)	5	●	●	●	●	●
Cook-Medley Hostility Scale	5	●		●	●	●
The Drug Abuse Screening Test (DAST)	5	●		●	●	●
Alcohol Use Disorders Identification Test (AUDIT)	3	●		●	●	●
PTSD Checklist (PCL)	10		●	●	●	●
Helping Alliance Questionnaire	5			●		
Posttraumatic Cognitions Inventory (PTCI)	5	●		●	●	●
Pittsburg Sleep Quality Index (PSQI-A)	5	●		●	●	●
Instruments for Collateral Reporters						
McMaster Family Assessment Device (FAD)	10	●		●	●	●
Conflict Tactics Scale (CTS)	5	●		●	●	●

Diagnostic Assessment

1. ***The Clinician-Administered PTSD Scale [CAPS; Weathers, Blake et al., 2013]*** is a semi-structured interview to assess PTSD. The CAPS has been extensively used with Veterans, and its strong evidence of reliability and validity have established it as the "gold standard" for PTSD assessment. A randomly selected 10% of the assessments will be randomly chosen to be observed by an independent rater to check the inter-rater reliability of diagnostic determinations. Inter-rater reliability for diagnoses based on videotapes of patient interviews across previous studies has been high, kappa = .96.
2. ***The Structured Clinical Interview for DSM-IV Diagnosis [SCID; (First, Gibbon, Williams, & Spitzer, 1997)]*** **(selected modules)** will be administered to assess other Axis I disorders, using standardized prompts determined by computerized algorithms. If a participant endorses any items on the computerized screening, the appropriate SCID module will be administered to determine whether the participant meets current or lifetime criteria for the respective disorder. Diagnostic raters will be trained using SCID and CAPS standardized training, which includes review of interview manuals,

training videotapes, and co-rating training with an experienced rater. Inter-rater reliability based on videotapes of patient interviews for Axis I diagnoses across previous studies has been excellent (kappa = .96).

3. ***The Brief Traumatic Brain Injury Screen (Schwab et al., 2007)*** is a three-item self-report questionnaire that will be administered to identify Veterans with the requisite event that triggers further examination by a clinician. If participants screen positive for TBI, we will review available medical records. In those cases in which available medical records are not thorough regarding the severity of the TBI, we will seek further information from current VA treatment providers regarding severity. If a Veteran has a non-VA provider that it will be necessary to contact, we will request a release of information from the Veteran to speak with that provider. Veterans determined to have mild severity will be enrolled in the trial, and those determined to have moderate or severe TBI will be excluded. In those cases in which we are unable to determine severity, those participants will be excluded from participation.
4. ***Self-report measures*.** Self-report scales will be administered to gather information about trauma exposure, risk and resilience factors, and participants' capacity to self-assess their own risk for future violence.
    a. *The Traumatic Life Events Questionnaire* [TLEQ; (Kubany et al., 2000)] is a brief self-report inventory that asks about exposure to 21 kinds of potentially traumatic events from natural disasters to sexual abuse. The TLEQ provides a 7-point response format to indicate frequency of occurrence. Consistent with DSM-IV diagnostic criteria, follow-up probes ask whether respondents felt fear, helplessness, or horror during any event experienced. This instrument allows for detailed assessment of trauma exposure, prior to military service, during military service, and following military service. The TLEQ results in trauma exposure summary categories of combat, childhood sexual assault, childhood violence, adult sexual assault, attack, illness and accident.
    b. *The Deployment Risk and Resilience Inventory [DRRI* (Vogt, Proctor, King, King, & Vasterling, 2008)] is a 201-item self-report measure assessing 14 risk and resilience factors associated with post-deployment health and well-being of Veterans. Factors include pre-deployment/pre-war factors; deployment/war-zone factors; and post-deployment/post-war factors.
    c. *The Self-Appraisal Questionnaire* [SAQ] is a 72-item self-report measure designed to predict violent and nonviolent recidivism among adults. The SAQ will be administered to evaluate how Veterans' self-appraisal of violence risk may be used to develop tailored treatment strategies. We will use six of the eight subscales: Validity, Conduct Problems, Antisocial Personality Problems, Criminal Tendencies, Criminal History, and Antisocial Associates. The information from Anger and Alcohol and Drug Abuse subscales will be gathered by measures describes in section 2.A.3.10.1 [AUD, DAST, Novaco Anger Scale, and Cook Medley], because these measures have stronger empirical normative values. Research has demonstrated that the SAQ has sound psychometric properties, acceptable reliability, and concurrent validity for assessing recidivism across cultures.

Primary Outcome Measures

1. ***Standard Family Violence Index (SFVI) of the Conflict-Tactics Scale (CTS)***. The SFVI (Straus, 1979) index includes 18 items measuring behaviors of throwing something at someone, pushing, grabbing, shoving, slapping, kicking, biting, hitting, beating up, threatening with a gun or knife, or using a gun or knife on someone. First, participants answer how often these behaviors were perpetrated against them in the last six months and then answer how often they themselves have perpetrated aggressive behaviors: 0 (never); 1 (once); 2 (twice); 3 (3-5 times); 4 (6-10 times); 5 (11-20 times); 6 (more than 20 times). In each instance of aggression, the perpetrator and victim will be identified. Consistent with previous studies on Veterans and violence (Beckham, et al., 1997), the original SFVI instructions will be modified in 2 ways to more appropriately reflect the goals of this study: 1) the target of the behavior will be expanded from "partner" to "anyone"; and 2) the time frame of the response will be reduced from one year to one month to detect potential changes associated with treatment. Coefficient alpha for this subscale of the CTS has been found to range from .62 to .88, with good evidence of construct validity. Separate scores will be calculated for severe and less severe violence. The CTS will be completed by both Veteran participants and collateral reporters.

2. ***Aggressive driving questions.*** Two studies have assessed aggressive driving in Veterans through single items on self-report questionnaires designed specifically for the study described (Kuhn, et al., 2010; Strom et al., 2012). Based on these studies, respondents will be asked to rate the frequency of occurrence of the following 5 items on a 5-point scale ranging from 0 (never) to 5 (very often): 1) Verbal outbursts or angry hand gestures while driving; 2) tailgating or intentionally cutting off another driver; 3) chasing another driver; 4) intentionally driving a car into another object (i.e. a tree, another car, etc.); and 5) driving after drinking or taking a psychoactive drug.

Secondary Outcome Measures

1. ***Novaco Anger Scale (NAS).*** The NAS (Novaco, Swanson, Gonzalez, Gahm, & Reger, 2012) will be administered to measure anger and coping. The measure contains 85 items, and displays convergent validity with other anger measures. The four subscales are Cognitive, Arousal, Behavior, and Anger Regulation.
2. ***Dimensions of Anger Reactions (DAR).*** The DAR (Novaco, et al., 2012) is a 7-item scale measuring the frequency, duration, and behavioral response to anger, and anger-related functional impairment on social relationships, health, and work. It was found to have concurrent and discriminant validity, and to correlate highly with measures of functional impairment, in a large sample of treatment-seeking soldiers who had served in Iraq or Afghanistan.
3. ***Cook-Medley Hostility Scales, short form (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989).*** A short form of the Cook-Medley Hostility Scales (Barefoot, et al., 1989) contains 27 items derived from rational and empirical analysis. The three subscales are cynicism, hostile affect, and aggressive responding. The Cook-Medley scale has shown high test-test reliability and a number of studies have supported its construct validity as a measure of hostility.
4. ***Community Reintegration of Service Members Computer Adaptive Test (CRIS-CAT)*** **(**Resnik et al., 2011; Resnik et al., 2012). The CRIS-CAT is a computer-administered interview based on item response theory that was developed specifically to assess the ICF domain of Participation in Veterans. CRIS-CAT questions target areas of functioning particularly salient for Veterans with PTSD. The CRIS-CAT has three sub-scales, each measuring a different dimension of participation. The Perceived Limitations to Participation subscale assesses Veterans' perceived limitations in participation, and includes items such as "I felt that I easily lost control of my feelings". The Extent of Participation subscale assesses how often Veterans experience a challenge in participation, and includes items such as "How often did you get together with friends?" The Satisfaction with Participation subscale assesses Veterans' level of satisfaction with participation, and includes items such as "How satisfied were you with your daily accomplishments?" The computer adapted testing (CAT) version allows for brief administration (i.e., 10-15 minutes for all 3 scales) facilitated by software that selects specific items based on Veterans' responses to previous items. The CAT will be administered on a free-standing, non-networked computer stored in the Traumatic Stress and Health Research Laboratory. The CRIS-CAT demonstrates good reliability and construct and predictive validity in samples of Iraq and Afghanistan war-era Veterans (Resnik et al., 2011; Resnik et al., 2012). The fixed-form (paper) CRIS will be used for the mailed questionnaires at 3- and 6-month follow-ups.
5. ***Inventory of Psychosocial Functioning (IPF) (Rodriguez, Holowka, & Marx, 2012).*** The IPF is an 80-item self-report measure that assesses functioning over the past 30 days in the following domains: romantic relationships; family relationships; work; friendships and socializing; parenting; academic pursuits; and self-care. The measure was developed using a Veteran sample, and in a validation sample of 457 Veterans it was found to have very good internal consistency of both the total scale (Chronbach alpha = .90) and for the subscales (Chronbach alphas between .80 and .90). With respect to validity, the measure correlated well with other well-established scales of quality of life and of specific domains of functioning (i.e. Quality of Life Inventory; Sheehan Disability Scale); as well as with measures of PTSD and depression.
6. ***The McMaster Family Assessment Device (FAD).*** The FAD (Epstein, Baldwin, & Bishop, 1983) is a 60-item scale that consists of statements about families to which respondents indicated agreement or disagreement on a 4-point scale. It yields a General Functioning (GF) score, as well as indices of 6 areas of family activity: problem solving, communication, roles, affective responses, affective involvement, and behavioral control. Internal reliability of the scales has been demonstrated with Chronbach alphas ranging from .74 to .92, and the scale has been found to have adequate test-retest

reliability, and low correlations with social desirability. Collateral reporters will be asked to complete this measure.

7. ***World Health Organization Disability Assessment Schedule, Version 2.0 (WHO-DAS 2.0)*** (WHO, 2001). The 36-item, self-report version of the WHO-DAS 2.0 will be administered to assess the impact of anger and aggression on broad functioning, as well as across six ICF functioning domains of mobility, self-care, getting along, life activities (household and work) and participation. Responses on this measure can be weighted according to difficulty and severity, and a summary disability factor score can be calculated using an SPSS algorithm developed by WHO. Population-based norms are available for this measure. The WHO-DAS requires less time to administer than the CRIS-CAT, so it will be administered weekly to collect exploratory information about Veterans' perceptions of how their overall functioning changes over the course of the group.
8. ***The Connor-Davidson Resilience Scale (CD-RISC)*** is a reliable and valid 25-item self-report measure of resilience that has been found to be responsive to treatment for PTSD over time (Green, Calhoun, Dennis, MIRREC, & Beckham, 2010).
9. ***PTSD Checklist (PCL).*** On the PCL (Weathers et al., 2013), participants first report an autobiographical narrative of a trauma, and subsequently rate symptom frequency (0 [not at all] – 4 [everyday]) and severity (0 [not at all distressing] – 4 [extremely distressing]) for all DSM5 PTSD symptoms within the past week. The PCL has high reliability and validity across trauma populations.
10. ***The Alcohol Use Disorder Identification Test (AUDIT) (Bradley, Bush, McDonell, Malone, & Fihn, 1998)*** contains 10 multiple choice questions about behavior and symptoms related to alcohol consumption.
11. ***The Drug Abuse Screening Test (DAST) (Skinner, 1982)*** contains 20 "yes/no" questions about behavior and symptoms pertaining to substance use. Both the AUDIT and the DAST have shown excellent psychometric properties in studies of Veterans.
12. ***Helping Alliance Questionnaire (HAQ)*** includes 19 questions designed to measure participant alliance with the therapy and the therapist. Therapeutic alliance has been shown to be an important construct that predicts positive outcome in therapy (Horvath & Luborsky, 1993).
13. ***Posttraumatic Cognitions Inventory (PTCI)*** includes 36 items designed to evaluate trauma-related cognitions including self-blame and negative cognitions about self and the world. The PTCI has good test-retest reliability and is internally consistent (Foa et al., 1999).
14. ***Pittsburg Sleep Quality Inventory with PTSD Addendum (PSQI-A)*** will be used to evaluate sleep quality and sleep problems (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; Germain, Hall, Krakow, Shear, & Buysse, 2005).

Other Optional Study Procedures: With participants' written consent, contact information containing identifying information such as name, address, phone number along with diagnostic information will be added into a "Contact Database". This "Contact Database" is a database included in IRB protocol # 01080, "Management of Two Databases in the Nicotine Lab." The purpose of this database is to re-contact potential subjects about future studies for which they may qualify. Potential participants will only be contacted about future studies in the Traumatic Stress and Health Research Laboratory. Only IRB #1080's PI, Dr. Beckham, other co-investigators, and the research staff will have access to this database, which will be housed on the VA Network's S:\ Drive (S:\Nicotine Research\Study Information\Study Databases). Collateral reporters will not be asked to participate in the contact database.

Also, with participants' express permission, diagnostic, demographic, and questionnaire data and other information collected as part of this study will be added to a larger database entitled 'Trauma Database.' This "Trauma Database" is a database included in IRB protocol # 01080, "Management of Two Databases in the Nicotine Lab." Inclusion of all subject information in the "Trauma Database" will be accomplished in a three-step process. First, information from this study will be coded and will only be linked by an assigned random study number. Second, information collected from other protocols run by Dr. Beckham will also be coded. Lastly, the information will be merged into the larger "Trauma Database," which will be used for future research. Information collected from many study participants (1000 or more) from different studies will then be examined to inform researchers about the topic they are trying to learn more about. Topics of research change over time and for that reason, the development of a combined research database is particularly useful. Only IRB #1080's PI, Dr. Beckham, other co-investigators, and the research staff will have access to this database, which is stored on the VA Network's S:\ Drive (S:\Nicotine Research).

Subjects who were recruited through the VISN 6 MIRECC's Post-Deployment Mental Health Data Repository Re-Contact Database will be asked to allow their current contact information (e.g., phone number and address) to be updated in the Re-Contact Database. In addition, subjects recruited through the VISN 6 MIRECC'S Post-Deployment Mental Health Repository will also be asked if the data collected as part of their participation in the current study may be added to the Post-Deployment Database in the MIRECC's data repository (IRB # 01706). This written permission will be sought through the ICF. The purpose of feeding data back into the data repository is to increase the data available with which to answer future, unique research questions pertaining to post-deployment mental health and is part of the purpose of the creation of the VISN 6 MIRECC Post-Deployment Mental Health data repository.

Study Interventions

Intervention Description: Cognitive-Behavioral Therapy for Anger and Aggression in Combat Veterans

Cognitive-Behavioral Therapy for Anger and Aggression in Veterans with PTSD (CBT-A) is a 12-week manualized group treatment protocol that is grounded in up-to-date research, and that has been designed to specifically address the cognitive, affective, physiological arousal, and behavioral components of combat PTSD-related anger and aggression. Sessions last 120 minutes. All participants will be asked to come to sessions about 15 minutes early so that they can complete weekly assessment measures. The first session orients participants to the structure and philosophy of the program, provides a historical overview of PTSD, and introduces the model of how a PTSD-related affective style contributes to problems managing anger and aggression. The remaining 11 sessions follow a standard format: 1) practice relaxation training (15-20 minutes); 2) review homework, introduce new material, and engage in group activities focused on implementing new skills and behaviors (70-80 minutes); and 3) review problems or concerns of group members. Appendix C presents a table summarizing each session, how sessions have been tailored for combat Veterans with PTSD, and references supporting these unique components of the intervention.

Description of Active Comparison Condition: Present Centered Therapy

Present Centered Therapy (PCT) was developed to provide an active, manualized treatment comparison condition for psychotherapy trials. PCT is designed to control for nonspecific factors of therapy such as contact with a trained therapist, rationale for treatment, and instillation of expectancy for therapeutic gains. The therapeutic approach was drawn from Yalom's group therapy model, which utilizes interpersonal process, supportive techniques, identification of response options, encouragement of adaptive reactions, and focus on the "here-and-now." Previous large-scale randomized clinical trials of Veterans with PTSD have found reduced PTSD symptoms in the PCT comparison condition(Schnurr et al., 2003), and a survey of practice patterns within the VA suggests that similar present-focused approaches are routinely employed by VA mental health providers(Rosen et al., 2004). Consistent with recommendations in the PCT manual, training will emphasize the approach rather than specific interventions.

Treatment Fidelity Ratings for Interventions

In order to examine treatment fidelity and counselor competence, we will videotape all counseling sessions using a VA-approved videorecording device, the Toshiba Camileo x200. This camera is not moved off site, as the groups are held at the Durham VA Medical Center's main campus. The recordings will then be reviewed by another trained study staff member using the Yale Adherence and Competence Scale system [YACS; (Carroll, 2000)]. Because of the nature of group therapy, we believe it would be less confusing for the reviewer to be able to see the participants (e.g., to determine who is talking). For this reason, we will videotape the sessions rather than audiotape, and it is likely that participants' voices and faces will be captured on the recordings. Study participants are informed during the informed consent process that they will not be allowed to participate in the treatment if they are not willing to be recorded. Because this study uses an informed consent form and HIPAA authorization, and videotaping is described fully therein, we will not require that form 10-3203 be signed. Recordings will be moved from the camera to the VA shared drive, S:\Nicotine Research\Study Information\Study Logbooks\gCBT for An.Agg\Therapy Recordings. Recordings will be retained as per VA Records Control requirements.

Justification for Inclusion of Non-Veteran Collateral Reporters

Non-veterans may be enrolled as collateral reporters for study procedures. It is presumed that many of the collateral reporters identified by participants to participate in that portion of the study will be non-veterans. It would likely not be possible to identify only collateral reporters who are veterans for each study participant. For this reason, we plan to enroll non-veterans as collateral reporters. All non-veteran participants will be provided with the VA's Notice of Privacy Practices.

Risk/Benefit Assessment

The risks of participation in this research protocol are minimal. Risks are expected to be similar to what would be expected when participating in psychotherapy for PTSD in the VA.

Potential Risks

The clinical interview to establish diagnosis can cause some psychological distress in the form of a temporary increase in anxiety or PTSD symptoms, but any ensuing distress is usually well-tolerated. There is a risk of temporary exacerbation of PTSD symptoms early during PTSD treatment. There are no known psychological hazards or risks associated with completing questionnaires. There is a risk associated with the potential loss of confidentiality of study data.

Therapeutic Risk

VA treatment guidelines require that patients diagnosed with PTSD have access to treatment for the disorder. The treatments employed as part of the proposed intervention are grounded in evidence-based research. CBT-A, for example, was specifically designed to address components of combat PTSD-related aggression. In the treatment, Veterans are provided with tools to decrease anxiety inherent in PTSD treatment. The PCT condition also employs an established treatment of PTSD that has been used in previous psychotherapy trials with acceptable levels of safety. The risks associated with these interventions are of the type and severity expected in the treatments the VA promotes for PTSD.

Research Risk

To complete study procedures, participants will complete diagnostic interviews that might not otherwise be used in the course of clinical treatment. Participation in research always presents additional risk of disclosure of protected health information. However, the procedures described in the "Protection Against Risk" section will be used to minimize these risks.

Protection Against Risk

Potential risks to participants will be minimized by carefully screening participants according to the inclusion/exclusion criteria and closely monitoring symptom levels. All project staff will complete educational units required by the Durham VAMC Human Subjects Committee. To ensure confidentiality of data, all records will be identified by a study identification number assigned to the participant, not by name. All raw hard copy data will be kept in locked file cabinets in a locked room. Electronic data files will be stored in a password-protected file on a secure, password-protected networked drive behind the VA firewall. Only study personnel will have access to data files.

All adverse events, including reports of suicide intent or attempt, will be closely monitored by the Principal Investigator (PI). Any serious adverse events will be promptly reported to the DVAMC Institutional Review Board as required.

The Traumatic Stress and Health Research Laboratory (TSHRL) has established, IRB-approved standards of practice for the evaluation of risk of suicide and homicide. The policy includes a thorough risk assessment including evaluation of risk factors and protective factors associated with both suicide and homicide. Also included in the policy are differential recommendations for action based on determinations of low, moderate, or high risk. Any staff member conducting an interview in which moderate or high risk is determined will contact a senior staff person with clinical expertise in risk assessment (including the PI, co-investigator(s), and/or the DVAMC's Psychiatric Emergency Clinic or Emergency Room). Also, the TSHRL has established standards of practice for reporting potential abuse and/or neglect of a child, elderly person, or person with a disability. These standards are based on VHA guidelines and North Carolina and Virginia law. These standards will be used in this study.

Potential Benefits of the Proposed Research to the Subjects and Others

While participants may benefit from receiving treatment for PTSD-related anger and aggression, there are no guaranteed benefits to the individual participant and no immediate benefits of the proposed research to others. The information and treatment generated by this project could be helpful in identifying a more tailored treatment for anger and aggression in Veterans with PTSD.

Importance of the Knowledge to be Gained

If it is shown to be effective, the proposed treatment would provide immense benefit to Veterans with PTSD. Veterans with PTSD report that anger and aggression are among their primary concerns, and the empirical evidence for treatments that are currently provided is lacking. It is critical to devote efforts to develop novel, empirically-based treatments for PTSD-related anger and aggression.

Adverse Events

Dr. Van Voorhees will monitor serious adverse events, adverse events, and unexpected problems from the study. Aside from those adverse events previously mentioned as potential risks of study participation, other adverse events for participants in this project are not expected. Regardless, we will minimize potential risk by careful screening of potential participants (see “Screening Procedure” under “Selection of Subjects” above), and by careful monitoring of enrolled participants.

The PI and primary mentor (Dr. Jean Beckham) will oversee monitoring activities. There will be several ongoing mechanisms for monitoring and reporting of adverse events: 1) ongoing participant contact via study personnel, 2) a phone number provided to participants to report concerns related to study participation, 3) weekly meetings between the PI and study personnel.

Any adverse events will be reviewed and patients evaluated as necessary by the PI and the primary mentor to determine whether the AE is study related. In addition, study staff will provide patients with any applicable referral numbers. The project manager will follow up with participants within 48 hours of any study-related adverse event to ensure that the event has been resolved and document actions taken. The Durham VAMC IRB serious adverse events report form will be used to document and report any serious adverse events, whether they occur during study visits or are reported over the phone.

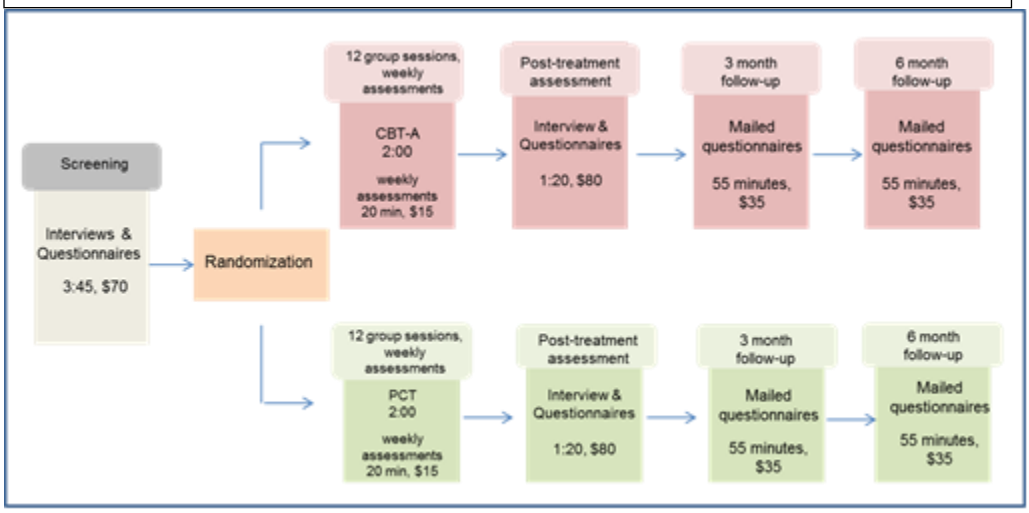
The PI will meet at least weekly with study personnel to discuss participants' reactions to the intervention, proper delivery of the intervention, and any adverse events. Monthly meetings between the investigators and the project manager will allow for ongoing progress reports, including the number of participants currently involved in the study groups, attrition rates, and scheduled data collection from participants, as well as notification and review of any adverse events. The investigative team will classify adverse events as "health threatening" or "non-health threatening" events and "possibly attributable" or "non-attributable" to the intervention. All adverse events will be reported to the PI within 72 hours of occurrence and those considered serious adverse events, including increases in suicidal ideation, will be communicated to the PI within 24 hours. All adverse events will be reported to the IRB in accordance with the Durham VA’s Human Research Protection Program.

Over the course of screening, pre-intervention assessment, treatment, and post-intervention assessment it is possible that we will encounter some participants with suicidal or homicidal ideation. If a participant indicates that he or she may be imminently dangerous to self or others, further assessment will be undertaken by the PI or by another senior staff member with a graduate degree in clinical psychology, psychiatry, or social work who has appropriate training in the assessment of homicidality and suicidality. As appropriate, the Veteran will be referred to urgent clinical intervention at the Durham VAMC.

Cost and/or Payment to Subjects

Participants will be paid $400 for their complete participation. Participants who drop out will receive partial reimbursement for the time they donate. Payment for study visit assessments is to compensate patients for completing assessments and travel, as patients who would normally receive travel reimbursement are ineligible for this reimbursement when attending research appointments (See Figure 2). Upon request, we will plan to provide local bus tickets to those Veterans who use public transportation.

Figure 2. Timeline of Study Procedures, Time Commitment, and Payment Schedule



Collateral reporters will be paid up to $65 for participation in the study. These participants are paid $35 for the initial, in-person visit, and $10 for returning questionnaires by mail at three time points – post-treatment, 3-month follow-up, and 6-month follow-up.

Privacy and Confidentiality

Except when required by law, approved through a separate IRB protocol, or authorized by a HIPAA authorization or other approved mechanism (e.g., limited dataset, data use agreement, etc.), we will not identify participants by name, social security number, address, telephone number, or any other personal identifier in study records disclosed outside the DVAMC. The keys linking the random code back to the participant will be maintained in a secure database on the VA network behind the VA firewall. The study results will be retained in participants' research records per the VA Records and Retention schedule.

Information describing the study's confidentiality limitations is included in the informed consent document. Confidentiality will be limited in situations where the participant is assessed to be at risk for threat and/or harm to self or others (see Adverse Events section).

Data Storage and Information Security

For the current study, data will be stored in a study database to which only Dr. Van Voorhees and her research staff have access. The database will be housed on a VA Network password-protected shared drive, at S:\Nicotine Research\Study Information\Study Databases\gCBT for An.Agg. In addition to being housed on this protected drive, the database will be password-protected, and only Dr. Van Voorhees' research staff will have access to the password.

Subjects' identifying data (e.g., name or phone number) will only be available to those research staff personnel who are employed and/or WOC at the VA Medical Center. A study identification number will be assigned to each participant's research study data, and this study data (e.g., answers to questionnaires) will not include any of the 18 individual identifiers under the Privacy Rule. Information that would allow re-linking/re-identifying of research data (e.g., answers to study questions) with personal health information such as name or phone number will be kept in a separate, password-protected database on the VA Network password-protected shared drive, at S:\Nicotine Research\Study Information\Study Logbooks\gCBT for An.Agg. The key to seed recruitment coupons that connects the participant's study ID number with the seed ID number will be kept in a database separate from other PHI, creating two layers of separation between the seed ID and the already-participating Veterans' identifying information.

Study data that are gathered during the sessions include coded pen-and-paper measures and video recordings of therapy sessions. Video recordings include PHI (i.e., full face images). Given the sensitive nature of the data, we have arranged protections for data that are being transferred from any therapy site external to DVAMC back to the primary data storage sites at DVAMC. All data, including video recordings, will be

personally transported from the therapy site to DVAMC by Dr. Van Voorhees, another therapist on the study staff listing, or her study coordinator. Data will be moved directly from the therapy site to DVAMC; no stops will be allowed during transport. For example, the study coordinator would not be allowed to take the data home in the evening to avoid a trip back to DVAMC. The study staff member will be required to store the study data in the back of his/her vehicle, and where available, a locked car trunk. All data will be transported in a lockable briefcase to which only Dr. Van Voorhees and her study staff have access. Only study staff members will be given the combination for the briefcase lock(s). The briefcase will be labeled with the following notice:

NOTICE!!!

1. Access to these records is limited to: AUTHORIZED PERSONS ONLY.
2. Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164.
3. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

In addition, we will execute an "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" memorandum for each person who will carry PHI between facilities prior to their being allowed to transport PHI between facilities.

One study measure that is completed at baseline, the CRIS-CAT, is a computerized measure. Because the Traumatic Stress and Health Research Laboratory does not have VA networked computers that allow patients to complete questionnaires directly (e.g., "patient-facing" kiosks), we plan to use a free-standing computer that does not connect to any network for this purpose. The computer to be used for this purpose is owned by Duke University Medical Center, but is not connected to Duke networks or Duke shared drives. Data collected via the CRIS-CAT will be coded, and it will be stored temporarily on the hard drive of this computer, which is stored in a locked office suite (C10006) that houses the laboratory. Scores from this task will be recorded on hard copy and placed in the medical record. Data from the CRIS-CAT will be backed up at regular intervals (approximately once per month) using a VA-owned, FIPS 140-2 compliant, and Sanctuary exempt thumb drive that is operated by a study staff member.

Data will be analyzed using Statistical Applications Software (SAS) or the Statistical Package for the Social Sciences (SPSS). If software is not available locally, coded data (the code being the participant's study ID number) will be housed at VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx) in order to access their data analysis software. The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Our researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN). VINCI will be used primarily to provide our investigators with the opportunity to use statistical software packages that are not available locally.

Staff members who leave the research project will have access to all research data removed immediately (e.g., permissions to the research folders on the shared drive revoked). Any issues involving potential privacy or confidentiality violations or problems will be reported to the facility's Information Security Officer(s) and Privacy Officer immediately.

With regards to the videorecordings taken during treatment sessions, we will videotape all counseling sessions using a VA-approved videorecording device, the Toshiba Camileo x200. Recordings will be moved from the camera to the VA shared drive, S:\Nicotine Research\Study Information\Study Logbooks\gCBT for An.Agg\Therapy Recordings. These recordings will be retained according to the VA Records Control Schedule.

Data Analysis and Statistical Considerations

Intention-to-treat random-effects mixed regression models will be used to analyze treatment effects. Changes in aggression across time will be modeled as a function of treatment group (CBT-A vs. PCT), time

(within-subject repeated measures), and the interaction of group x time. Mixed effects models with random intercepts will account for subject effects and correlation of repeated measures over time. Models will be developed that include as independent variables the treatment group and baseline aggression score. The effect CBT-A (vs. PCT) will be assessed by examining the significance of the slope β_3 in the following model:

$$A_{ik} = \beta_0 + \beta_1 t_{ik} + \beta_2 x_i + \beta_3 (x_i \times t_{ik}) + v_{0i} + v_{1i} t_{ik} + \epsilon_{ik}$$

Where A_{ik} is the aggression score for the i^{th} participant at time point k; β_0 is the aggression score at baseline; x_i is the dummy-coded treatment group variable (x_i=0 for PCT and x_i=1 for CPT-A); β_1 is the linear effect of time for the PCT group; β_2 is the condition difference at baseline; β_3 is the condition difference in terms of the linear effect over time; v_{0i} and v_{1i} are subject-specific random effects representing the deviation of each subject from the group intercept and linear trend; and ϵ_{ik} is random residual effects(Hedeker & Gibbons, 1997).

Mixed models are able to handle missing data. Pattern mixture models can be used to describe the effects of missing data on outcome and to provide estimates by averaging over missing data(Hedeker & Gibbons, 1997); and Intent to Attend the next session data can be used to determine if participant drop-out or loss to follow-up meets the assumption of ignorable attrition(Leon, Demirtas, & Hedeker, 2007).

Power Analysis and Sample Size Determination

The paucity of studies examining outcomes of treatment for anger and aggression in Veterans with PTSD, and the inconsistency in measures used across studies, makes it difficult to estimate effect size for sample size estimations. One study reported pre- to post-treatment decreases in aggression with an effect size in the medium range(Marshall, et al., 2010). This is consistent with more general studies of anger management therapies, where effect sizes have been reported in the medium to large range depending upon the measure used and the population sampled(Del Vecchio & O'Leary, 2004; DiGiuseppe & Tafrate, 2003).

Effect sizes for sample size determination of the larger RCT will be calculated based on differences between pre-treatment and post-treatment scores on the measures of aggressive behavior. Comparisons will be made using a two-sample t-test. Because there is a risk of inaccurate estimation of effect sizes in pilot studies(Kraemer, 1992), we will employ recommended procedures for improved characterization of effect sizes derived from pilot studies. These include close consultation with clinicians who have used the treatment (i.e. Dr. Patrick Calhoun), and accounting for the effect size uncertainty by constructing confidence intervals around the observed effect sizes.

Group treatment research presents unique challenges with respect to consideration of sample size, because a portion of the variance in treatment effects has consistently been found to be accounted for by clustering of effects within a particular group(Schnurr, et al., 2001). Clustering of group effects can be measured by an intra-class correlation ρ, which is defined as the ratio of variance due to the clustering variable relative to the total variance (both the cluster and error) (Schnurr, et al., 2001). Once ρ has been determined, the adjusted sample size can be determined using the following formula:

$$m = n^*N/(1+(n-1)\rho)$$

where m is the effective number of independent observations after accounting for interclass correlation; n is the number of repeated measures per group; and N is the base sample size needed to detect the effect.

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