Group CBT for PTSD: A RCT with veterans

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Project Narrative

A. Specific Aims:

Considerable attention has focused recently on the treatment of PTSD. At present, strong empirical evidence exists to support the efficacy of Cognitive Behavioral Treatments (CBT) when used in an individual format to treat PTSD following trauma. However, the development and testing of group treatment approaches for PTSD has lagged. Recently, Dr. Gayle Beck (a Co-I of this proposal) completed a treatment development grant (R21 MH64777) that designed and provided preliminary support for a Group CBT (GCBT) to treat PTSD. Pilot data suggested strong initial support for this treatment with survivors of serious motor vehicle accidents diagnosed with PTSD. The overall objective of this proposal is to test this GCBT with veterans. The proposed project encompasses **two specific aims**.

The project will consist of a randomized controlled trial with 196 cases, in which participants will be randomly assigned to (a) Group CBT (GCBT, *n*= 98) or (b) *Supportive Group Psychotherapy (SGP, n = 98)*. Outcome data will be collected at pre-treatment, mid-treatment, post-treatment, and *three times* during a 12-month follow-up. This application is a hybrid efficacy-effectiveness trial, in keeping with current translational emphasis on producing information about treatment outcomes that generalize to "real life" settings.

The primary specific aim is to examine if GCBT produces significant reductions in PTSD relative to the *SGP* condition, and to determine if these changes are durable across a *12 -month* follow-up interval. Two hypotheses are proposed:

Hypothesis 1. Patients with PTSD who receive GCBT will show greater reductions in PTSD-related symptoms, relative to patients who receive *SGP*, at post-treatment assessment, a between-group difference that will persist through *3 and 6 month follow-up*.

Hypothesis 2. Reductions in PTSD symptom severity will be maintained in the GCBT group at *12-month* follow-up.

The secondary specific aim is to examine the generalizing effects of both GCBT and *SGP* on distress, impairment, and co-morbid conditions (particularly generalized anxiety, depression, and substance use). Because most trials in the PTSD literature do not include a thorough assessment of treatment generalization, it is unknown whether available treatments only address PTSD or whether gains generalize to other domains. Three hypotheses are proposed:

Hypothesis 3. For veterans who are diagnosed with co-morbid Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and/or Alcohol abuse prior to treatment, GCBT will produce significantly larger symptom reductions for these conditions, relative to *SGP* at post-treatment assessment and these generalized changes will show stability at *6* -month follow-up.

Hypothesis 4. Patients who receive GCBT will report less distress and impairment, relative to patients who receive *SGP*, at post-treatment assessment, a between-group difference that will persist through 3 *month* follow-up.

Hypothesis 5. Gains in these domains (distress and impairment) will be maintained in the GCBT group at the *12-month* follow-up.

Overview

The proposal requests funding for, "Group CBT for Chronic PTSD." The project will involve a randomized controlled trial with 196 cases, in which veterans with chronic post-traumatic stress disorder (PTSD) will be randomly assigned to (a) Group CBT (GCBT, *n*= 98) or (b) *a supportive group psychotherapy (SGP; n = 98).* Outcome data will be collected at pre-treatment, mid-treatment, post-treatment, *three times during a 12* month follow-up (3-, 6-, and 12-months). This application is a hybrid efficacy-effectiveness trial, in keeping with current translational emphasis on producing information about treatment outcomes that generalize to "real life" settings.

There are several salient veteran health concerns that underlie this application. **First**, PTSD is the most prevalent mental health condition for which veterans seek mental health services (Desai et al., 2009). Surprisingly, the majority of veterans seeking PTSD treatment services are presenting for treatment for the first time despite some of these veterans having served in combat over 40 years ago. The number of veterans presenting for PTSD services represents an enormous case burden within the VA system. Clinicians' caseloads cannot accommodate individual-format treatment for all, which has resulted in VA healthcare sites developing their own group-based interventions, with little to no data to support their efficacy. **Second**, there are very few RCTs that have targeted PTSD in veterans (Bradley et al., 2005; Institute of Medicine, 2007). The study that is proposed here builds on this literature by testing a GCBT, composed of components that have each been shown empirically to be effective. The current application will address an important need in the VA Healthcare System, PTSD group treatment for veterans with chronic PTSD.

Rationale for a multi-site study: The involvement of multiple sites is required for several reasons. First, given the study sample, two VA medical centers are required in order to enroll a sufficiently large sample to test our primary hypotheses. The VA Boston/National Center for PTSD (Dr. Sloan, PI) and the VA Providence (Dr. Unger, PI) are supportive environments for this RCT, with considerable experience in clinical trial research. Data collection will occur at these two sites. In addition to accruing a sufficiently large sample, inclusion of two data collection sites will facilitate better representation of racial and ethnic minorities. Second, the developer of GCBT is located at the University of Memphis (Dr. Beck, Co-I) and is integral to the success of this project.

Between-site coordination/communication: Communication is an essential component of between-site coordination. We will follow rigorous, specified procedures for training, certification, and monitoring of all staff. The Boston site will enroll 112 and the Providence site will enroll 84 male veterans with PTSD, using the same recruitment and screening procedures, identical inclusion and exclusion criteria, standardized administration of semi- structured interview measures and self-report questionnaires, and manual-driven therapy procedures. Data entry at both sites will include double-entry procedures, to ensure accuracy, and standardized software which will detect and flag aberrations in data entry. This software will

also track scheduled visits, permitting careful patient tracking during the follow-up interval. The software will reside on a secured server, behind the VA firewall, accessible only to personnel of the study. We will follow state-of-the-art practices for the design and conduct of a multi-site study, with two recruiting sites following identical protocols, a Steering Committee (Drs. Sloan, Unger and Beck) that is in frequent (i.e., weekly) contact with one another, consistent statistical support throughout the duration of the trial, and a data safety and monitoring board that is in close contact with the trial. Minutes will be maintained for each conference call, to facilitate between-site coordination.

B. Background and Significance:

B.1. Public health significance of this application: This application targets male veterans with chronic combat-related PTSD, a target sample with enormous public health significance. **First**, the largest proportion of veterans presenting for mental health services at the VA have a diagnosis of PTSD (over 40%, R. Desai, personal communication, July 28, 2011). Although the media has focused on mental health needs of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans, other combat veterans continue to represent the majority of veterans presenting for PTSD treatment in the VA system. Indeed, of the 122,150 veterans who presented to the VA healthcare system in 2008 for PTSD treatment services**,** only 38% were OEF/OIF veterans (Desai et al., 2009). Strikingly, 19% of veterans seeking PTSD services have had previous specialized PTSD treatment (Desai et al., 2009). Thus, most of these veterans were presenting for PTSD treatment for the first time despite some of them having served in combat over 40 years ago. Moreover, the number of veterans presenting for PTSD services has substantially increased in recent years.

Second, early on in the trauma literature, some authors believed that specific treatments needed to be devised for survivors of specific traumatic events. Over time, it has become increasingly clear that similar types of treatment are effective for diverse trauma populations. Unfortunately, there are very few randomized controlled trials (RCTs) that have targeted veterans with PTSD (Bradley et al., 2005; Institute of Medicine, 2007). The proposed study builds on this growing literature by testing a GCBT, composed of exposure, cognitive interventions, and stress management, each which has been shown empirically to be effective in the treatment of PTSD (e.g., Bradley et al., 2005).

B. 2. Findings from the Literature on CBT for PTSD - Data on the Treatment of Groups: Several different types of group treatments for PTSD exist, including supportive treatment (e.g., Tutty et al., 1993), psychodynamic treatment (e.g., Ganzarian, 2000), and cognitive-behavioral treatment (e.g., Resick & Schnicke, 1992). Conceptually and practically, these approaches have different goals. However, as discussed by Shea et al. (2009), these approaches share some features, including provision of a supportive environment, validation and normalization of the trauma experience and its sequella, and encouragement of positive change efforts. Group-based treatment represents a valuable intervention as it offers the additional benefits of social support and group validation to the trauma survivor. Within the VA healthcare system (the largest provider of PTSD treatment in the world), group interventions are highly prevalent (Institute of Medicine, 2007; Rosen et al., 2004) and often preferred by patients with chronic PTSD (Resick, Monson, & Gutner, 2007). In addition, the veteran

population continues to grow, particularly given the country's current war efforts. The need for PTSD treatment services within the VA healthcare system is enormous and some VA sites are only able to offer group-based PTSD treatment in order to best accommodate the large number of veterans seeking such services. This has resulted in group treatment as the most frequently used PTSD treatment in the VA system (Institute of Medicine; 2007; Rosen et al., 2004). Data culled from the Austin Data Outpatient System indicate that 86,192 veterans received group therapy services between October, 2006 and June, 2007 within the VA system (A. Spence, personal communication, August 30, 2009), reflecting the wide-scale usage of group treatment within this healthcare environment. Unfortunately, this high demand for PTSD group treatments is problematic given the relatively sparse empirical literature on the efficacy and effectiveness of group-based PTSD treatment.

Traditionally, group-based CBT (GCBT) for PTSD has involved ET, CT, and relapse prevention training components (e.g., Foy et al., 2000; Shea et al., 2009). Group sizes have ranged from 2 to 8 members and treatment duration has ranged from 6 to 30 sessions. As summarized by Shea et al. (2009) and Sloan, Bovin, and Schnurr (in press), studies have examined GCBT with trauma populations including adult women who experienced childhood sexual abuse, combat veterans, female survivors of sexual or multiple other traumas, and dyads involving mothers and their sexually-abused children. Although not as developed as the individual CBT literature, these studies indicate that GCBT on average has a 0.68 effect size (Hedges' unbiased estimator, range .24 to 1.09). Unfortunately, this literature has methodological limitations, including lack of randomization to treatment/control conditions, an absence of control groups, treatments that were not manualized, and lack of monitoring of therapist adherence and competence. While recognizing these concerns as well as the apparent diversity among available interventions (with respect to group size, length, and content), Foy et al. (2000) drew three conclusions: 1) group therapy shows efficacy for PTSD, although the number of studies involving male patients is limited, 2) methodological limitations reduce the strength of conclusions that can be made about GCBT in general (an opinion shared by Shea et al., 2009 and Sloan, Bovin, and Schnurr, in press), and 3) Foy et al. and Shea et al. highlight the importance of expanding research on group therapy into applied settings, to merge efficacy and effectiveness research in an effort to increase the utility of group treatment. Some of these issues can be addressed via a well-controlled RCT, involving manualized treatment, an appropriate comparison condition, use of experienced therapists, inclusion of therapist adherence and competency checks, and the use of independent assessors, features that are included in this proposal.

In keeping with the recommendations of Foy and colleagues, Schnurr et al. (2003) examined the impact of Trauma-focused Group Therapy (TFGT) with 360 Vietnam veterans within the VA system (VA Cooperative 420 Study). TFGT involved groups of 6 male patients who met weekly for 30 weeks, followed by 5 booster sessions. Importantly, TFGT began ET slowly, waiting to introduce the technique until session 12. ET was conducted and shared within the group format (each group member listened to each others' exposure items). TFGT was compared with a Present-Centered Group Treatment (PCGT) that focused on current problems and avoided a trauma focus. Results indicated that patients in both treatment conditions showed improvements (average of 40% showing clinically significant change), although no difference was noted between the two interventions. Narrowing the analyses to veterans who had received

an adequate dose of treatment (at least 24 sessions) indicated that TFGT was marginally more efficacious in reducing avoidance and numbing symptoms and possibly overall PTSD symptom severity (p = .06). Schnurr et al. (2003) discuss the role of in-session exposure in these outcomes, indicating that perhaps the "dosage" of ET was not sufficient in TFGT. In considering TFGT, it is notable that this treatment program is fairly long (30 sessions) and requires some degree of distress tolerance from veterans, given that ET was conducted within the group. Recently, Ready et al. (2008) presented data from an uncontrolled trial of Group Exposure Therapy, which is somewhat similar to TFGT; the pre-to-post effect size was 1.20 in a sample of veterans with combat-related PTSD. Although promising, these studies suggest that group-based treatments for PTSD warrant continued study.

Dr. Beck (Co-I of this study) completed a treatment development effort designed to develop and pilot test a manualized GCBT that contains an adequate dose of ET while reducing in-session distress created by sharing specific exposure exercises. Efforts were made to limit the length of treatment in keeping with current models of care within public sector health settings, with the resulting GCBT involving 14, 2-hour sessions co-led by two therapists. As discussed more thoroughly within Section C "Preliminary Studies", 88.3% of patients receiving GCBT did not satisfy criteria for PTSD following treatment, relative to 31.3% of the comparison group (using assessors who were unaware of treatment condition & assessment point). Using several different metrics of end-state functioning, GCBT produced good outcomes. Stability of gains was noted at 3-month follow-up. Participants were individuals who had experienced serious motor vehicle accidents (MVA). Importantly, results were comparable with data from two trials involving MVA-related PTSD patients using a similar CBT program within an individual treatment format (Blanchard et al., 2003). Taken together, these data are very encouraging as they support the efficacy of the GCBT, which was developed in part because of the high need for group-based PTSD treatments. This need is especially great with the veteran population.

As presented in Section C.2, we have adapted the GCBT manual to be appropriate for combat-related PTSD in veterans and collected encouraging pilot data. In addition to establishing initial efficacy, the veteran participants were enthusiastic and positive about the material presented in GCBT, found the treatment useful, and indicated they would recommend this intervention to other veterans diagnosed with PTSD. Relative to a psychoeducation group, veterans in GCBT showed significant reductions in PTSD symptoms and depression. In addition to the data we have collected, group CBT interventions have been shown to be effective in addressing PTSD in two related studies involving chronic PTSD patients with multiple problems. Falsetti et al. (2003) demonstrated that a Group CBT protocol (involving exposure and cognitive therapy) was significantly more effective at reducing PTSD in a small sample of women who had experienced an average of 6-7 traumas, relative to a wait-list control condition. Likewise, Sikkema et al. (2007) examined the efficacy of a group CBT intervention with a sample of 199 individuals who were coping with HIV/AIDS and had experienced childhood sexual abuse. In Sikkema et al., relative to a wait list comparison condition, the 15 week group CBT program produced significantly greater reductions in intrusive trauma symptoms; compared to a general support group, the group CBT program produced significantly greater reductions in avoidant trauma symptoms. Although not directly examining combat-related PTSD in veterans, these two reports involved samples that experienced chronic PTSD and reported multiple other problems;

as such these reports document that this type of patient (whose problems are severe and chronic) can and does respond to CBT when administered within a group setting. Thus, we believe that our veteran pilot data, in conjunction with the reports from Falsetti et al. and Sikkema et al., suggest that it is scientifically appropriate to take the step proposed in this report, namely a RCT comparing GCBT with a plausible comparison condition with a sample of veterans experiencing chronic, combat-related PTSD.

In adapting the GCBT manual for veterans with combat-related PTSD, we made several minor revisions. First, the exposure-based components of treatment are conducted as homework assignments that take place outside of the group sessions. The men who participated in our pilot groups reported that this type of exposure was much more tolerable than prolonged in-session exposure and therefore, they were more likely to engage in the exposures. The group environment was frequently mentioned as important in providing motivation for exposure, given built-in social support within the group. Second, we increased emphasis on in-vivo exposure (and modified use of imaginal exposure), based on feedback from group members. Thus, members' exposure homework focused on in-vivo experiences with current trauma cues and trauma writing focusing on specific events that occurred in combat. Third, combat-related PTSD can be unique from other trauma-related PTSD in the degree of guilt and related emotions that are present among veterans. We modified some of the cognitive intervention components to recognize affect beyond anxiety. Fourth, with combat-related PTSD, the trauma events are not discrete, as they are for MVA survivors and some assault survivors. Identification of trauma cues for exposure sessions can therefore be particularly difficult for combat-related PTSD Veterans. Recognizing this, we expanded the use of handouts, based on feedback from the pilot groups we conducted. These initial modifications represent "fine-tuning" more than extensive modification of the GCBT, as it was initially developed. As such, we are confident that any remaining modifications similarly will be relatively minor and straight-forward.

B.3. Considerations involved in Selecting between Group versus Individual Treatment formats: Numerous authors (e.g., Miller & Magruder, 1999) have recognized that individual format treatments, while effective for reducing or ameliorating symptoms, are not cost-effective. Group treatments offer the possibility to help considerably more patients at once, reduce the workload on any given therapist, and cost less. Given current issues pertaining to health-care reimbursement, as a field we need to pay greater attention to developing empirically based group treatments, if we are to continue to provide viable services. Although group treatments may be difficult to schedule within private practice settings, they are the first-line treatment within most public sector mental health settings, particularly the VA Healthcare System (Institute of Medicine, 2007; Rosen et al, 2004; Sloan, Marx, & Keane, in press). This reflects a combination of limited therapist availability as well as high patient demand. Thus, outside of the private sector, group treatments are normative. At present, most group treatments for PTSD that are used in these settings are **not empirically based** and thus, are of unknown efficacy. Without well-controlled research on group treatment for PTSD, this situation will not change.

An additional issue is salient in this application. Because many VA therapists have been trained to use ET with PTSD patients (Sloan, Marx, Keane, 2011), the availability of a manualized Group CBT will permit more veterans to be treated by maximizing available therapist resources in VA

healthcare settings. As noted, there is a specific need for effective group PTSD treatments within the VA healthcare system given that the large number of veterans who present for PTSD treatment services far outweighs the available number of mental healthcare providers to treat these veterans. The development of effective group CBTs has lagged, in part owing to emphasis on individual treatment formats within the research community. With recognition that treatment formats need to be more efficient, it is imperative that we develop and test GCBTs with the veteran population.

As well, although the current state of research on group treatments for PTSD has lagged behind similar work on individual treatments, there is emerging evidence to suggest that group treatment can be effective. Given current demands within agencies that serve veteran populations, it is timely and important to test a recently-developed group CBT program, which is based on an empirically-supported individual treatment. Following suggestions from Foy et al. (2000), this project proposes an applied setting, in order to merge efficacy and effectiveness research. The proposed project includes refined methodology, appropriate experimental controls, and considerable attention to issues involving validity and reliability. Importantly, we have provided pilot data suggesting that this treatment can be effective with the veteran population. In particular, the current application targets veterans with chronic PTSD who will be recruited within a VA environment.

B. 4. Significance of the Proposed Research

As noted, the mental health needs of veterans within the VA Healthcare System are notable and the VA system is straining to accommodate these needs, relying heavily on group-based treatments of unknown efficacy. This project will take the next step in research on group psychotherapy for PTSD, by examining a Group CBT program with promising pilot support. We will test this treatment with a hybrid efficacy-effectiveness trial, to provide data that are applicable to "real world" settings. The proposed project has applicability to a large population of men with chronic PTSD relating to their combat experience. Ultimately, the information provided by the proposed project would benefit VA clinicians by providing clinicians with an empirically supported group-based treatment protocol for treating veterans with PTSD.

C. Preliminary Studies:

C. 1. Investigator Experience:

PI: Denise M. Sloan, Ph.D. (Associate Director, Behavioral Science Division, National Center for PTSD at VA Boston Healthcare System & Associate Professor, Boston University School of Medicine) is an expert in anxiety psychopathology, particularly physiological reactivity, fear activation and habituation, and development of a brief exposure-based intervention for PTSD (Sloan et al., 2010; R03 MH068223; R34MH077658). She has also conducted funded work investigating the similarity and distinction of depression and anxiety disorders. At the National Center for PTSD, Dr. Sloan served as PI of a recently completed clinical trial investigating the efficacy of a brief narrative exposure treatment for PTSD. She serves as Co-I on a study developing a measure of function impairment associated with PTSD, and Co-I on a study developing a registry of OEF/OIF veterans. Dr. Sloan also serves as a VA career development mentor. Dr. Sloan remains active in clinical activities within the PTSD clinic at VA Boston and

directs the training programs housed in the Behavioral Science Division (e.g., internship rotation, T32 fellowship program, clinical fellowship program and practicum). As PI, she brings considerable research and clinical expertise to the proposed project. Her knowledge and experience working with combat-related PTSD will be an additional asset to the proposed project.

PI, Providence Site: William Unger, Ph.D. (Chief, Posttraumatic Stress Disorder Clinic, VA Providence Healthcare System) is highly experienced in the treatment of chronic PTSD within veteran populations. He has been recognized numerous times for the quality of his clinical care, through awards for outstanding service, teaching recognition awards, and in 2006, was cited as the Outstanding VA Doctor. Dr. Unger has participated in several VA Cooperative studies, including the 420 Study that examined group PTSD treatment with a similar patient population as proposed here, and included Present Centered Group treatment as the supportive group psychotherapy comparison condition. He currently serves as Site PI for a smoking cessation study, illustrating that he truly personifies the scientist practitioner model. As PI of this proposal Dr. Unger brings considerable clinical research expertise to the proposed project. Dr. Unger has also collaborated with Drs. Sloan and Beck to adapt the GCBT protocol for the veteran population and has participated in the pilot work testing GCBT in the veteran population.

Co-Investigator: J. Gayle Beck, Ph.D. (Chair of Excellence, University of Memphis) is experienced in both basic behavioral research on psychopathology in the anxiety disorders and treatment outcome studies, with a wide range of patient samples. She has conducted several large-scale treatment outcome studies. As former Editor of *Behavior Therapy*, she is well-versed in research methodology, design, statistics, and presentation. As previously described, Dr. Beck recently completed a treatment development effort which serves as the preliminary support for the current application. Dr. Beck brings considerable expertise to the proposed project and is integral to the project given her role in the development of the GCBT protocol.

Table 1: ***Means (Standard deviations) for GCBT from MVA and Minimum Contact Comparison conditions at PRE, POST, and FU, with effect sizes for Completer analyses***

	GCBT (*n* = 17)			**MCC (*n* = 16)**		**Effect size at Post (Hedge's *g*)**
	Pre-treatment	Post-treatment	3 Month Follow-up	Pre-treatment	Post-treatment	
CAPS-Total	57.3 (15.5)	28.9 (19.9)	19.7 (18.8)	57.8 (14.9)	49.4 (27.0)	.84
CAPS Re-experiencing	17.2 (7.2)	8.4 (7.3)	5.2 (5.7)	19.0 (8.0)	15.4 (8.5)	.87

CAPS Avoid/ Numbing	22.8 (6.7)	11.1 (8.6)	7.2 (7.6)	21.9 (7.5)	20.9 (12.6)	.89
CAPS Phy. Hyper.	17.4 (6.5)	9.5 (7.9)	7.3 (7.7)	16.9 (5.7)	13.1 (8.0)	.43
# patients PTSD +	17/17 (100%)	2/17 (11.7%)	1/15 (6.7%)	16/16 (100%)	11/16 (68.7%)	
IES-R Intrusion	1.8 (0.8)	0.9 (0.9)	0.7 (0.7)	2.2 (0.9)	1.9 (1.2)	1.04
IES-R Avoidance	1.5 (0.8)	0.7 (0.8)	0.6 (0.8)	1.8 (0.9)	1.5 (1.0)	.83
IES-R Phy. Hyper.	1.8 (0.9)	1.3 (1.2)	0.9 (0.8)	2.5 (1.0)	2.3 (1.1)	.83

C. 2. <u>Preliminary Studies:</u> This investigative team has experience with research focusing on psycho-pathology, assessment, and treatment of PTSD. The work that is particularly germane to this application stems from a development grant from NIMH (R21 MH64777, PI Beck) that provided preliminary support for a GCBT to treat PTSD. The initial part of this grant developed the GCBT protocol, including writing the manual devising instruments to assess therapist adherence and competence, and testing the treatment with several groups of patients (Beck & Coffey, 2005). The second part of this grant included the conduct of a small RCT (Beck, Coffey, Foy, Keane, & Blanchard, 2008). Individuals (N = 45) with chronic PTSD related to a serious MVA were randomly assigned to either GCBT or a minimum contact comparison group (MCC) in which patients were repeatedly contacted by phone, to assess current functioning and symptomatology.

As reported in **Table 1**, compared with the MCC participants, individuals who received GCBT showed significant reductions in PTSD symptoms, whether assessed using clinical interview (using assessors who were unaware of treatment status & assessment point) or self-report measures. Following treatment, 88.3% of GCBT participants did not satisfy criteria for PTSD, relative to 31.3% of the MCC participants. Examination of anxiety and depression measures did not show a unique advantage of GCBT, although reduced power from the small sample size is relevant here. Treatment-related gains were maintained over a 3-month follow-up interval. Patients reported satisfaction with GCBT and attrition from this treatment was comparable with other individual-format CBT's (see also Beck et al., 2009).

Although the results of this pilot study are promising, there are several limitations that need to be addressed in the design of a larger RCT, as proposed here. Among these limitations is the fact that the sample size was small and so, analyses could not account for the natural clustering of patients within treatment groups in the GCBT arm. The statistical power also is lower than desired, given the sample size. Even in the face of these limitations, these pilot data suggest that GCBT may be an effective format for the treatment of PTSD and support the current application.

Importantly, we (Drs. Sloan, Beck and Unger) modified the GCBT manual to be appropriate to the treatment of PTSD in Veterans and collected pilot data from two treatment groups. We retained the basic format of the GCBT (14 sessions, 2 hours per session, 2 therapists) and the

content was largely unchanged. The exposure-based components of GCBT were modified based on input from these groups; specifically, we increased emphasis on in-vivo exposure and modified imaginal exposure to focus on events that occurred in combat, using narrative writing to guide exposure.

Thus, exposure homework focuses on in-vivo experiences with current trauma cues and trauma writing about specific events relating to combat. Because the exposure components of treatment are conducted as homework assignments that take place outside of group sessions, the men who participated in the two pilot groups reported that this type of exposure was much more tolerable than prolonged exposure. The group environment was frequently mentioned as important in providing motivation for exposure, given the built-in social support. Additionally, we modified some of the cognitive intervention components to recognize affect other than anxiety. Importantly, we modified all patient handouts, therapist outlines, and template sessions notes, in order to test this GCBT with veterans. These modifications represent "fine-tuning" more than extensive modification of the GCBT, as it was initially developed. As such, we are confident that any remaining modifications similarly will be relatively minor and straight-forward, particularly given our experience with two pilot groups.

Two pilot groups have been run using the revised manual for use with veterans (one group each at VA Boston and VA Providence). Both groups included 6 men, each diagnosed with chronic combat-related PTSD. Average age was 60.8 (*SD* 2.3) and most men reported multiple co-morbid disorders (83% were diagnosed with co-morbid disorders, primarily major depressive disorder, alcohol abuse, and generalized anxiety disorder). They varied considerably with respect to length of involvement with mental health care (range < 1 year to 11 years). These data are consistent with the average demographics of veterans presenting for PTSD services in the VA system (Desai et al., 2010). Thus, the pilot sample is representative of the proposed sample. Each group was led by two, VA Staff Psychologists with considerable PTSD experience. Given limited resources, our assessment battery involved self-report scales, specifically the PTSD Checklist-Military version (PCL-M), the Beck Depression Inventory – II (BDI-II), and three subscales of the Short-Form Health Survey, specifically the Role Limitations due to Physical Problems (Role-physical), Role Limitations due to Emotional Problems (Role-emotional), and

Table 2	Group CBT *N* = 11			Non-equivalent control group (Psychoeducation) *N* = 12	
	Pre-TX	Post-TX	Effect size (g) for **GCBT (pre-to post-TX)**	Pre-Tx	Post-Tx
PTSD Checklist –Military	63.82 (8.39)	49.82 (13.82)	1.36	63.58 10.35)	66.42 (8.78)
Beck Depression Inventory – II	32.09 (10.24)	25.76 (14.58)	0.56	29.67 (7.95)	32.08 (7.20)
SF-36: Role-physical subscale	23.75 (24.96)	40.00 (29.78)	0.44		
SF-36: Role-emotional	15.90 (17.66)	45.45 (34.43)	0.70		
SF 36: Social functioning	32.95 (16.07)	48.86 (29.29)	0.48		

Social Functioning scales. All Veterans completed the 14-week GCBT, although one did not complete the post-treatment assessment (final $N = 11$). Outcome data are shown in **Table 2**. As noted, a significant pre-to-post treatment reduction (p=.001) in mean PCL-M score was observed, which reflects a large effect size ($g = 1.35$). Participants reported notable improvements in role limitations due to emotional problems (pre-to-post $p = .025$, $g = .76$). A trend in reduced levels of depression (pre-to-post $p = .075$, $g = .56$) was noted.

Because we collected these data without external support, we were unable to randomize individuals into a control condition. However, in keeping with Kazdin's (2003) recommendations, a nonequivalent (or patched-up) control group can help to examine the plausibility of threats to validity such as history, maturation, and testing. We provide such data in **Table 2**, drawn from Veterans with diagnosed PTSD who participated in an 8-week psychoeducation group at the VA Boston PTSD clinic. This intervention is run by two Staff Psychologists, has 6-9 patients in each group, and meets for 90 minutes each session. Data are available for PCL-M and BDI-II. A Group (2:GCBT v Psychoeducation) by Time (2:Pre v Post) ANOVA for PCL-M revealed a significant interaction ($F(1,21)= 10.64$, $p = .004$), indicating a significant Pre-to-Post change for GCBT alone (and a significantly lower score for GCBT in comparison with the control group at post-treatment). A Group (2) by Time (2) ANOVA for BDI-II revealed a significant interaction as well ($F(1,21) = 8.54$, $p = .008$), indicating a significant Pre-to-Post <u>increase</u> for the control condition, a significant Pre-to-Post <u>decrease</u> for GCBT, and a significantly lower score for GCBT in comparison with the control group at post-treatment.

Importantly, comparison of the PCL-M effect size obtained with GCBT ($d = 1.43$) with a recent published trial of Cognitive Processing Therapy for veterans with combat- related PTSD (individual treatment format; Monson et al., 2006, $d = 2.16$) is quite favorable. Both d's are considered large within Cohen's framework. These data provide supportive and convincing pilot data that the GCBT, with minor modifications, can be effective with the veteran population. In particular, although these veterans reported severe levels of PTSD symptom severity, multiple co-morbidities, and considerable chronicity, the 14-week program produced significant changes in PTSD, role functioning, and to a lesser extent, depression. The veterans were enthusiastic about GCBT, found it helpful, and were encouraging of the introduction of this treatment into available care within the VA. Importantly, there were <u>no treatment drop-outs</u> from these two groups. On the Client Satisfaction Questionnaire (see Treatment Process Measures, Section D.4), the average score was 27.3 (max score on this scale = 32), reflecting high levels of patient satisfaction.

<u>As such, we believe that it is appropriate to take the next step in this line of research, namely to conduct a well-controlled RCT, comparing GCBT with a credible comparison therapy, in a sample of veterans with chronic combat-related PTSD.</u> The proposed research takes the next step to broaden research on group treatment of PTSD for veterans, in order to make this approach more applicable for dissemination within the VA healthcare system. Preliminary pilot data support the application of this treatment within a sample of veterans with chronic combat-related PTSD. The proposed project takes the next step, testing this treatment in a hybrid efficacy-effectiveness RCT using state-of-the-art methodology.

<u>D. Research Design and Methods:-</u>

Overview: This is a 5-year study designed to support a RCT that compares a new treatment, GCBT, with *SGP*. Two aims are involved in this project. The **first specific aim** is to examine if GCBT produces significant reductions in PTSD relative to the *SGP* condition and

to determine if these changes are durable across a 12 month follow-up interval. **The second specific aim** is to examine the generalizing effects of both GCBT and *SGP* on co-morbid conditions (depression, generalized anxiety, and alcohol abuse), distress, and impairment. Staff training, data-base construction, and preparation of materials will facilitate project integrity during the initial months of the proposed project. The RCT will involve 60 months, in which 196 male veterans with combat-related PTSD will be randomly assigned to GCBT (*n*= 98) or *SGP* (*n* =98) to determine efficacy in a naturalistic care environment. Outcome data will be collected pre-treatment, mid-treatment, post-treatment, and , 3-, 6-, and 12-month follow-up (see **Table 3**).

D. 1. Study Participants:

Study Criteria: Participants will include 196 male veterans. The participant must: (1) currently meet DSM-IV (American Psychiatric Association, 2000) criteria for chronic, PTSD (symptoms lasting 3 months or more) and (2) be free of psychosis and impaired cognitive function caused by traumatic brain injury or dementia. Exclusion criteria include: (1) a current diagnosis of substance dependence or unstable bipolar disorder, (2) currently involved in active treatment (individual or group) for PTSD, (3) substantial cognitive impairment that would negatively impact ability to engage in group PTSD treatment. The Clinician Administered PTSD - 5 Scale (CAPS-5;) will be used to establish DSM-IV diagnosis of current PTSD. The Structured Clinical Interview for DSM-IV (SCID, Spitzer, Williams, Gibbons, & First, 1994) will be used to evaluate psychosis, substance dependence, and bipolar disorder, as well as to assess for additional co-morbid anxiety and depressive disorders. The Wide Range Achievement Test (WRAT) reading subscale will be used to assess reading level. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) will be used to assess cognitive function. The MoCA is a relatively new instrument and was selected because it appears to be considerably more sensitive and specific with mild cognitive impairment. A cut-off score of 20 in combination with clinical judgment will be used to determine cognitive impairment (and exclusion from participation; Nasreddine et al., 2005). Information about current participation in psychological therapy will be obtained during the initial screening and from chart review.

Medication: Participants will be asked to maintain stable levels of psychotropic and pain-relieving medication throughout their participation. Although one could argue that participants should be removed from psychotropic medication, this choice (although methodologically sound) would pose considerable risks from a human subjects' perspective. Some of the men who will participate in this trial have required psychotropic medication for many years, given chronicity of their conditions. Medication discontinuation could increase distress in these men to an unacceptably high level. From a scientific standpoint, maintaining a stable medication regimen during treatment mirrors typical clinical practice and ensures that the results of this trial can be generalized to practice. As such, we will address this issue by asking participants to maintain a stable dosage of medication throughout their participation and will secure permission to inform the prescribing physicians about our treatment program and this request.

Participants will be required to meet psychotropic medication stabilization criteria for the periods preceding and overlapping with the diagnostic assessment and treatment. Patients using anxiolytics and beta-blockers will be required to maintain the same dosage for at least 1 month. Patients on antidepressants (tricyclics, SSRIs, MAO inhibitors) need to have maintained a stable dosage for at least 3 months. If a patient is in the process of stopping his medication when he requests to be in the study, the medication wash-out period (i.e., period since medication discontinuation) will be 1 month for all medications. Those individuals who are using prescription medication will be asked to maintain written records of their use, including any changes that occur. In the event that we have a substantial number of individuals who change their medication during the course of treatment (despite the request not to), we will examine potential differences in treatment outcome between individuals whose medications remain stable versus changed using descriptive statistics.

Diagnostic Procedures, including Training and determination of reliability: The CAPS-5 and the SCID will be used to establish current PTSD diagnosis, to characterize current co-morbid psychiatric problems, and to rule out current psychosis, unstable bipolar disorder and substance dependence. Doctoral-level staff will be trained in the administration of these instruments, following the procedures outlined by DiNardo et al. (1993). These procedures include successfully matching criterion diagnoses for 3 of 5 training tapes, as well as demonstrating competency in administering interviews. Dr. Sloan will oversee assessor training at the two sites. Additionally, all assessors will rate standardized diagnostic interviews (once every 3 months) to prevent rater drift. Assessors will be certified to administer the CAPS and SCID when they match criterion diagnoses and competently administer these instruments during a supervised interview. Throughout the trial, all interviews will be recorded and 25% will be selected at random for review by an Independent Reliability Evaluator. This individual will watch the recorded interview and provide a diagnostic profile. S/he will remain unaware as to participants' group assignment or the assessment time-point, in order to permit objective assessment of diagnostic reliability. Discrepancies between the Independent Reliability Evaluator's and the independent assessor's ratings will be resolved through consultation with the PI.

Assessors will be blinded to treatment condition assignment. We will protect assessors from knowing the treatment condition assignment using several methods. First, we are hiring assessors for this trial on a fee for service basis. Thus, they will not be staff specifically hired for this project and will therefore have limited information regarding the project and they will not have access to the study research database. In addition, assessors might know who the therapists are who are working on the proposed clinical trial, but they will not be told who the therapists are in each of the two treatment conditions. This will protect against the blind being broken if a participant mentioned the name of his therapist during the assessment. Assessors will be informed of the name of the veteran who they will be assessing but they will not be provided with any additional information, and the assessors will be instructed not to ask participant about their treatment experience in the study. Also, participants will be informed not to disclose any information about their treatment to the assessor. As all assessment sessions will be recorded we will conduct a random review of a portion of the assessment sessions to make sure that no information is disclosed during the assessment that would break the blind of

the assessor. If assessors believe information was obtained that breaks the blind to the treatment assignment of a participant, we will request that the assessor report this information to the project coordinator. We will track all such instances. One additional method by which we will ensure assessors are blinded to treatment condition is that assessors will all be supervised by Dr. Sloan. They will not receive any supervision from the therapy supervisors in the study.

CAPS: The CAPS is the gold standard interview for evaluating PTSD (Weathers et al., 2001) and includes ratings for each PTSD symptom, rated on 0-4 behaviorally-anchored scales. As APA has approved diagnostic criteria changes for upcoming DSM-5, we will use the CAPS-5 version for this study. Both PTSD diagnosis and PTSD symptom severity will be included as treatment outcome variables in this study.

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

In the event that the DSM-V is released prior to the start of the proposed project and CAPS and SCID are revised accordingly, we will use the versions of the instruments that correspond with the DSM-V.

Availability of Participants and Recruitment Process: Recognizing the multiple challenges of recruiting for a group clinical trial for PTSD, we have included two recruitment sites in the proposed project. Although the majority of recruitment will come from the PTSD clinics at the VA Boston (Jamaica Plain campus) and VA Providence sites, we will conduct additional recruitment efforts. These additional efforts will include community-based outpatient clinics, additional mental health clinics within the two VA sites (e.g., Brockton campus PTSD clinic at VA Boston, General Mental Health Clinic at JP and Brockton), and primary care clinics.

One challenge in recruiting from clinics is that clinicians may be aware of suitable participants. However, due to confidentiality, the clinicians cannot provide any information about potential veteran participants to the project staff. We are aware that other investigators at VA Boston Healthcare System have found that including the 10-5345 form has permitted research staff to more effectively reach veteran participants who express interest in the program but who may have not actively called study staff on their own, due to PTSD symptomatic avoidance reasons. Therefore, we will include the 10-5345 form in this study in order to more effectively reach potential participants. This form will be provided to veterans who express interest in the study during outreach presentations made veteran service events. This form also will be provided to all VHA clinicians from whom we recruit, in mental health clinics, PTSD clinics, and primary care clinics. The 10-5345 form will be presented to interested veterans during their clinical sessions. If the veteran expresses interest and consents to release contact information, the form

will be signed and dated. The clinician will then contact a research project staff member to state that a release has been signed. The 10-5345 form is included in this submission.

In addition to the above described recruitment strategies, we will also post flyers and brochures throughout the VA Boston Healthcare System announcing the research treatment study and providing a contact number for interested veterans to call and obtain additional information about the study.

Recruitment will involve several steps. First, interested veterans will speak with a project staff member who will provide detailed information about the research treatment study. If the veteran continues to express interest, a brief screen will be conducted. If the veteran appears eligible for the study based on the phone screen (see phone script included in this submission), an initial in person assessment will be scheduled. At the first in-person session, the veteran will again be provided with a thorough description of the project as part of the informed consent process. After providing informed consent, the veteran will complete a demographic form and basic health questionnaire, administration of the MoCA and WRAT and discussion of his willingness to adhere to the study conditions. Administration of the CAPS and SCID, as well as completion of the self-report battery will then take place.

Non-inclusion of Children, Adolescents, and Women in the Study Sample:
Individuals 18 and older will be eligible to participate in the study, however, we expect very few participants will be under the age of 21 give the available data on age of veterans presenting for PTSD services at VA clinics. This project will not include women for several reasons. First, the number of female veterans is considerably smaller than male veterans. Second, women veterans presenting with PTSD are more likely to have PTSD resulting from sexual trauma, relative to male veterans (approximately 71% among women compared with 4% for men; Fontana et al., 2007). Because of the different nature of trauma causing PTSD and the distinct needs of women veterans, the VA healthcare system has developed women only trauma specialty programs to better serve women veterans (e.g., locations in Boston, Madison, Albuquerque, and Palo Alto VA sites). The VA system has found that women are more likely to present for and participate in treatment if the clinic serves women only. Despite the development of these specialty clinics, 89% of veterans who present to the VA healthcare system for PTSD treatment are men (Desai et al., 2010). We considered running mixed male-female groups but recognized that the nature of the trauma exposure would likely be very different for male and female participants, which would require substantial revision to the GCBT program that is being tested here. In addition, women veterans with PTSD are very unlikely to participate in treatment groups that include male members. Given this, we felt that it was scientifically appropriate to start with single-sex (male) groups, which will require a small degree of treatment modification. Additionally, given that 89% of veterans presenting for PTSD treatment are men, it is very unlikely that we would be able to recruit sufficient number of women to run women only treatment groups. Taken together, for both scientific and clinical practice reasons, women will not be recruited in the proposed clinical trial.

D. 3. Procedures for conducting RCT: GCBT versus SGP

Recruitment and management of participants: One of the difficulties in conducting a study of any group treatment is that participants who have enrolled in the study must wait until

a sufficient number of participants have collected to form a cohort. We proposed two approaches to manage this difficulty. First, recruitment will occur in "waves," meaning that there will be 1-month intervals (every 3-4 months) where referrals will actively be sought. During these waves, efforts to screen and assess potential participants will be maximized, to concentrate resources on the formation of a cohort (14 participants). During the recruitment process, each participant will be made aware of the research requirements and have a chance to decline participation. Second, the project coordinator, with assistance from Dr. Sloan, will work with each participant as soon as he is enrolled in the study. The project coordinator will provide interim clinical care and remain in close contact with the participant while he is waiting for treatment to begin. As reported by Schnurr et al. (2001), this approach appeared successful in reducing attrition from the Cooperative 420 study, as only 3.7% of their PTSD veteran participants dropped out prior to randomization. As discussed in Section D.1, we will recruit 280 potential participants, for a final *n* of 196 to begin the trial (70% enrollment). Recruitment will occur in 7 waves (Year 01-1 wave, Year 02: 2 waves, Year 03: 2 waves, Year 04: 2 waves; Year 05: 0 waves); each wave will include 14 enrolled Veterans (20 to be screened to reach this target). The project coordinator will maintain close contact with each veteran throughout each step of the study.

Training therapists/Between-site coordination: A challenging aspect of a multi-site trial is implementation of procedures to ensure consistency across sites. In particular, consistency with respect to therapist delivery of GCBT and *SGP* is a paramount concern in this trial. In order to ensure that therapists at both sites are trained thoroughly and consistently, a *2-day* training will be scheduled at the start of the project. Because all project therapists will be experienced in treating combat-related PTSD in veterans, emphasis will be placed on mastery of the specific components of GCBT and *SGP*. Discussion will be included concerning expected, acceptable, and prohibited elements, in keeping with the design of this RCT. Additionally, therapists will meet weekly (by phone or in person) with the either Dr. Beck (GCBT) or Dr. Unger (*SGP*) for on-going supervision and discussion of adherence with the appropriate treatment manual.

Randomization: A methodological issue arises concerning randomization, which is intrinsic to studies involving group treatment. One should randomly assign each participant as they enter the study to a given treatment condition. Within a study examining group psychotherapy, randomization implies a brief wait for individual participants, which is necessary in order to collect enough participants who can then be randomized into one of the two group treatments. As noted in Section E.2, we will safeguard our participants during this wait interval preceding treatment through provision of contact and support from the project coordinator. The project coordinator will meet with each participant in order to assess current functioning and assist in problem-solving specific issues of daily-living. Greater details concerning these proposed procedures are found in section E.2. Additionally, from a methodological standpoint, it makes sense to stratify patients based upon pre-treatment CAPS severity score, if considerable variation exists in the sample's pre-treatment scores. Related research with this population suggests that the variability in CAPS total severity score will be fairly restricted and that eligible participants are likely to show severe levels of PTSD on the CAPS. For example, the pre-treatment CAPS Total scores in Monson et al. (2006) ranged from 76.7 to 79.1 with a SD of 2.6 to 3.5. These data indicate that we are likely to have insufficient variability in the sample for

stratification. However, in the event that considerable variability does occur, patients will be stratified based on their pre-treatment CAPS total score and randomly assigned to condition within strata. The project statistician will be responsible for randomization of participants.

Therapists: Background and assignment to condition: In this proposed study, we elected to nest therapists within condition for **three** reasons. **First**, we have no reason to suspect that study therapists will have particular enthusiasm for either treatment, as they have not been involved in the development of this project. **Second**, because these two treatments share some common features (e.g., facilitation of a supportive environment, provision of information about PTSD), we are concerned that therapists might become confused if counterbalanced. **Third**, therapists will be equivalent with respect to skill level, experience with veterans, and other factors that potentially could be confounds (e.g., sex).

Each treatment group at each site will be conducted by two therapists. Therapists will be doctoral level psychologists, who have a wealth of experience treating veterans with PTSD. The therapists also will have extensive experience delivering CBT and delivering group treatment. Therapists in the two treatment conditions will be matched for experience and demographic characteristics (e.g., race, sex). These procedures will ensure that any observed treatment condition differences are not due to therapist effects.

Treatment Procedures: The two treatments to be used in this study will be delivered using structured treatment manuals (as described in Section D.2; see Appendix). Each therapist team will meet with either Dr. Beck or Dr. Unger once per week for supervision. Each treatment session will be recorded to permit close supervision and assessment of treatment fidelity and integrity. Dr. Beck will serve as supervisor for GCBT and Dr. Unger will serve as supervisor for *SGP*.

Treatment fidelity and integrity will be assessed by two individuals who are otherwise unaffiliated with the project. These two individuals will be selected owing to their familiarity with either GCBT or *SGP* protocol. For each treatment condition, 20% of the treatment sessions will be randomly selected, reviewed and rated, using the adherence and competence form that was developed during R21 MH64777. This form will be modified to be appropriate for both GCBT and *SGP* (the original version of this form is included in the Appendix).

Care Path after Participation is Complete: Participants may have residual needs after participation. Because post-treatment and follow-up evaluations will include assessment of PTSD, depression, related anxiety problems, and substance use, we will be able to ascertain remaining treatment needs. If an individual continues to report significant distress or interference from a specific problem, he will be referred to appropriate services within the VA Boston. Where participants are referred will be determined based on their individuals needs. Referrals will always be made after discussion with the veteran.

D. 4. Measures

The hypotheses state that relative to participants who are assigned to the *SGP* condition, participants who receive GCBT will show greater reductions in PTSD symptoms, report less utilization of health-care resources, and report less distress and impairment, at post-treatment

and 3 and *6* month follow-up assessments. Additionally, for patients with co-morbid Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and/or Alcohol abuse prior to treatment, GCBT will produce significantly larger symptom reductions for these conditions, relative to *SGP* at post-treatment assessment and 3- and *6*- month follow up. As well, gains in PTSD symptoms, distress and impairment will be maintained in the GCBT group at *12*-month follow-up.

Measures selected to evaluate these hypotheses are described in the next section (see also Table 4).

Outcome variables:

Measures of PTSD symptoms will include the Clinician Administered PTSD Scale - 5 (CAPS -5) and the Posttraumatic Check List - 5 (PCL-S-5). The CAPS-5 has been discussed in Section D1 (Study Participants). The CAPS-5 will serve as the primary outcome measure for PTSD. Both measures derived from the CAPS-5 will be used (presence/absence of PTSD diagnosis and overall PTSD severity score

Other measures include:

- The PTSD Checklist-5 (PCL-5; Weathers, Litz, Huska, & Keane, 1994) is self-report measure of PTSD, that corresponds to the DSM-5 symptoms of PTSD. Like the CAPS, the PCL can be scored to yield an overall severity score (total score). Psychometric properties of the prior PCL are sound (Weathers et al., 1994). The proposed project will use the PCL-S-5, a version that requests individuals to state the index event for which they are rating symptoms. In addition to the assessment map provided in Table 4, the PCL5 will be administered weekly during treatment, in order to track participant risk. Greater details about how the PCL data will be used to assure participant safety can be found in Section E.2.

Measures of distress and impairment Three subscales of the Medical Outcomes Study Short-Form Health Survey (SF-36; Ware & Sherbourne, 1992) will be used to index objective role functioning/impairment. These scales are the Role Limitations due to Physical Problems (role-physical), Role Limitations due to Emotional Problems (role-emotional), and Social Functioning subscales which appear to be minimally confounded with psychopathology. All three of these subscales have shown factorial validity and discriminative validity (Ware & Sherbourne, 1992).

- **Health care utilization** will be examined as an exploratory aim to investigate the effect of PTSD group treatment on health care utilization. This measure will be evaluated via record tracking. Veterans may obtain medical care within or outside of the VA system. When men initially enroll in the project, we will ask the names of their medical providers. Physician records in the VA system can be electronically accessed using the CPRS system. For physicians outside of the VA system, we will seek a signed release of information, which will permit contact to track the number of visits. The Project Coordinator will keep monthly records of the number of medical visits (excluding wellness visits) for each participant.

Measures of comorbid anxiety, depression, and alcohol abuse will include the *Structured Clinical Interview for DSM-IV* (SCID, Spitzer, et al. 1994), the *Beck Anxiety Inventory*, the *Beck Depression Inventory* – II, and an amended version of the *Short Inventory of Problems*. The SCID has been discussed in Section D1 (Study Participants). Both measures derived from the SCID (presence/absence of each additional disorder and global Clinical Severity Rating for each disorder) will be used. The SCID will not be administered at mid-treatment assessment. Other measures are:

- The Beck Anxiety Inventory (BAI; Beck et al., 1988) will be administered as a continuous measure of anxiety. The BAI is a 21-item scale that assesses anxiety and is believed to avoid confounding anxiety with depression. The BAI has established psychometric properties (Beck & Steer, 1991).
- The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) will be administered as a continuous measure of depression. This 21-item questionnaire evaluates current depressive symptoms and has well-established reliability and validity (Beck et al., 1996).
- An amended version of the Drinkers Inventory of Consequences, named the Short Index of Problems (SIP; Miller et al., 1995) will be used to assess alcohol use and alcohol-related consequences. The SIP is a 15-item scale that includes five subscales: physical consequences, intrapersonal consequences, social responsibility consequences, interpersonal consequences, and impulse control consequences. The SIP possesses satisfactory psychometric properties (i.e., good internal consistency, good concurrent validity, good test retest reliability; (Forcehimes et al., 2007). The SIP will be supplemented with three questions that will assess how many days in the past 2 weeks the individual consumed alcohol, on average how many standard drinks were consumed on those days when he drank alcohol, and the number of days in the past 2 weeks on which 5 or more standard drinks were consumed. This assessment strategy was constructed in consultation with Dr. Gerard Connors, Research Institute for the Addictions, Buffalo, NY.
We have included a mid-treatment assessment period in our design; however, in order to reduce participant-burden we will not conduct the SCID diagnostic interview at the mid-treatment assessment time period.

The *Trauma Life Experience Questionnaire* self-report will be completed at baseline to obtain information on overall trauma exposure of the participants and will be used to identify the index event that will be referred to when completing CAPS-5 assessment.

The *Cognitive Emotion Regulation Questionnaire* is a brief, self-report measure of cognitive emotion regulation strategies. This measure will be completed to examine whether emotion regulation moderates or mediates treatment outcome. This measure will be administered every other week during treatment and at every assessment session.

Treatment Process Measures will be included as secondary measures. These four measures will be used in an exploratory fashion, to generate hypotheses about the impact of therapeutic process on outcome. These measures also will augment the ratings of therapist competence, by providing direct information about the group treatment experience from the group members themselves. The process measures will include:

- number of sessions attended;
- a widely-used measure of treatment credibility (Borkovec & Nau, 1972) to be administered at the conclusion of Session 1 (after the treatment rationale and specific procedures are explained). This measure asks patients to rate on a 10-point scale how logical

the treatment seems, their confidence in undergoing the treatment and recommending it to others, and their expectations for the treatment's success;

- The Client Satisfaction Questionnaire (Larsen, et al., 1979), a measure of participant satisfaction with treatment, will be administered at the last session of treatment. This 8-item measure assesses patients' satisfaction with treatment and has demonstrated concurrent validity;
- The California Group Psychotherapy Alliance Scales (CALPAS-P; Gaston,1991), a measure of therapeutic alliance, will be administered. The 24 items of the CALPAS load on 4 subscales: Patient working capacity, Patient commitment, Working strategy consensus, and Therapist understanding and involvement. The CALPAS (Patient version) shows good psychometric properties. This measure will be administered every other treatment session in order to evaluate patients' perceptions of the group and examine whether alliance serves as a mediator of treatment outcome;
- To assess homework compliance, we will use the homework compliance form; for GCBT, this form was developed during the treatment development project. For SGP, a parallel form will be created. Therapists will rate the percentage of each homework assignment that each participant completes each week and provide a rating of homework quality, following Primakoff et al. (1986) and successfully used in other RCTs (e.g., Leung & Heimberg, 1996).
- To qualitatively measure participants' experiences of the two different kinds of group formats, 7 open-ended questions about their experience will be asked at the 1-month post-treatment assessment. Answers to these questions will supplement quantitative data. Responding to these questions will take 3-5 minutes, and answers will be written, not recorded.

D.5. Follow-up: In designing this RCT, it was important to demonstrate durability of changes following GCBT and SGP and so, included a follow-up interval. The patients will be assessed three times during a 1-year follow up interval (at 3-, 6-, and 12 months).

D. 6. Between-site coordination: We (Drs. Beck, Sloan, and Unger) have worked effectively together over the past several years. Based on our collaborative work experience, we anticipate that our collaboration during the execution of the project will likewise be productive. We have collaboratively revised the GCBT treatment manual to be suitable for Veterans, organized the assessment battery to be used during pilot testing, and collected pilot data with two separate treatment groups. This section will delineate roles, including efforts designed to facilitate coordination between the PI's and the Co-I. In the initial months of the project, Drs. Sloan, Beck and Unger will write a procedures/operations manual. This manual will provide a detailed outline of each procedure, including recruitment procedures, each step in the assessment process, case management before and after treatment, specific procedures involved in treatment, and data management. The standardization of these procedures will ensure between-site coordination, as all personnel will have available a written set of directions to follow.

Importantly, all assessors and therapists will be trained at a common workshop. During the start-up phase of the project, an Assessment training workshop will be scheduled, led by Dr. Sloan. This workshop will focus on administration of the CAPS and the SCID, with particular attention to differential diagnosis and use of the 0-8 clinical severity rating. A therapy training workshop will be scheduled simultaneously, to train the study therapists. Dr. Sloan will coordinate the scheduling of these workshops. Dr. Unger will take responsibility for training

therapists in the SGP (present centered group treatment) protocol, and Dr. Beck will assume responsibility for training therapists in the GCBT protocol. These trainings will be digitally recorded so that they will be accessible throughout the project, which will allow consistency in training in the event that a staff member joins the project mid-way. Because the individuals who will fill these roles will have experience working with PTSD patients within a VA system, the two day training workshop will be conducted at an intermediate to advanced level.

Drs. Sloan and Unger will be responsible for the day-to-day operations at the Boston and Providence sites, respectively. In particular, Drs. Sloan and Unger will supervise recruitment of potential participants, and they will work closely with their project coordinators to ensure smooth operations of the proposed procedures. Drs. Sloan and Unger will also assist with case management during the interval prior to randomization to a treatment condition, as well as during the follow-up interval. Dr. Sloan will also maintain close contact with the project statistician, Dr. Lynda King. Dr. Beck will provide weekly supervision to therapists conducting GCBT and Dr. Unger will provide weekly supervision to therapists conducting the SGP treatment. Drs. Sloan, Beck and Unger will hold weekly conference calls for project planning and coordination, which will include discussion of recruitment efforts, issues that arise in case management, diagnostic reliability, and treatment fidelity.

Is this RCT adequately statistically powered? In the study design, several factors were involved in determination of sample size. **First**, we drew estimated effect sizes from the **two** pilot studies on GCBT and from a recent meta-analysis (Bradley et al., 2005). Within the MVA pilot study, which contrasted GCBT with a minimal contact comparison condition, effect sizes for PTSD measures ranged from .83 to 1.04 (Hedges's unbiased *g*, Hedges, 1981). Within our Vietnam veteran pilot data, the pre-post treatment effect size for the PCL-M was d = 1.43. Consulting the larger literature, Bradley et al. (2005) computed average effect sizes (Cohen's *d*) of .84 for contrasts between CBT versus supportive therapy conditions and 1.01 for contrasts between ET + cognitive therapy versus supportive therapy conditions. However, in RCTs involving veterans, effect sizes tend to be smaller, owing to the chronicity and severity of combat-related PTSD in this population. In computation of sample size for this trial, we have selected a relatively low value of *d* (.50); review of available studies (including our own pilot data) suggests effect sizes ranging from 0.84 to 1.43. Recognizing that effect sizes for contrasts between CBT and supportive psychotherapy tend to average *d* = .84 (Bradley et al., 2005), that data from samples with chronic PTSD tend to have smaller effects, relative to less severe samples, and that effect sizes drawn from relatively small samples can be unstable, we took a conservative stance in estimating the effect size for the GCBT versus SGP contrast to arrive at *d* = .50. **Second,** because treatment within both conditions of this RCT will occur in groups, the analytic plan must account for the cluster effect owing to the correlation of outcomes within groups (expressed as ρ, the intraclass correlation coefficient). There is one clustered variable in this design (individuals within groups) which will be adjusted for in determining sample size. Following guidelines provided by Hsieh (1988) and Diggle et al. (2002), we used an inflation factor that was driven by the ρ values from the MVA-related PTSD pilot data. In particular, the ρ estimate of 0.11 is a conservative assumption, based on the largest value obtained in the pilot MVA study. In the pilot MVA study (Beck et al., 2009), the ρ for the CAPS was 0.07, the ρ for the BDI-II was 0.03, and for the BAI, the ρ was 0.08. Within the Collaborative 420 study (Schnurr

et al., 2003), the ρ for the CAPS was 0.05. Thus, use of ρ = 0.11 in our power calculations is a conservative assumption. Larger values of the ρ can occur when the outcome measures (among patients) have a concrete connection to one another. In studies of physician behavior within a clinic, the ρ values are larger when the physician directly contributes to the assessment of the patient outcome measures. For example, Stedman et al. (2008) analyzed two such studies, one study of patients within selected clinics who were followed to determine if their clinic physician did or did not provide osteoporosis management, and a second study of patients within clinics to determine if physician education induced physicians to improve the quality of osteoporosis management. In each study the ρ = 0.12. The outcome measure for the patient was the level of disease management delivered by the physician, an outcome directly determined by the physician. In contrast, for our proposed study, the person who assesses patient outcomes should have little or no effect on the values of the patient measure outcome. In our study, the ρ captures a subtler effect, namely, potential assessor bias, a much smaller effect than the effect of physician practice patterns. With a proposed group size of 7, a maximum ρ of 0.11, and d = 0.50, we estimated a total n of 196, using $p<.05$. Although only two of 14 outcome variables in the pilot study exceeded ρ >.10 (see Beck et al., 2009), we felt it was preferable to be conservative regarding ρ levels in our power computations. **Third**, in computation of sample size, we relied on .80 power level, as is customary in power calculations for RCTs. Using these parameters, the total desired n will be 196 (n = 98 per condition); each treatment group will begin with 7 men. Thus, based on previous studies on Group CBT, as well as current data regarding ICC in the context of clinical trials, we have been appropriately conservative in our power calculations.

In addition to statistical significance, we were concerned about the potential clinical significance of these data. Presently, there is no agreed-upon effect size that is thought to be clinically significant. This is difficult to determine because effect sizes hinge on many variables (e.g., the size and nature of the sample, the amount of variance in the assessment strategy, the amount of variance in treatment administration). In our power calculations, we have relied on a .80 power level, to have a sufficient sample size for this RCT for statistical significance. Unfortunately, there is no consensus in the treatment literature regarding what constitutes a clinically significant effect size; Friedman and colleagues (2006) suggest that clinically meaningful differences between 2 active treatments would be illustrated by an effect equal to or greater than .30 (Cohen's d). Consultation with Dr. King (Project Statistician) thus indicates that the proposed n will be sufficient to determine whether GCBT produces clinically meaningful outcomes.

Analytic approach: Data from both sites will be combined prior to analyses. Dr. King, the Project Statistician, will work in close collaboration with Dr. Sloan to perform the analyses. Prior to testing hypotheses, the outcome data will be examined to assess if they meet the assumptions for the proposed statistics (Tabachnick & Fidell, 2001). If the assumptions are not met (e.g., the data depart from normality, multivariate outliers are present), appropriate data transformations will be used. Additionally, the GCBT and *SGP* groups will be examined for pre-treatment differences, to test for group equivalency. These analyses will involve a series of independent t-tests on each of the outcome measures as well as demographic variables. Pre-treatment differences between conditions will be incorporated into the models used to examine the primary hypotheses, as described below.

In any RCT, missing data are inevitable. Analysis of only complete cases is biased; likewise, values not missing at random can bias the results. Thus, analyses that impute missing data must accordingly increase standard errors. In designing this trial, we have included features that are intended to minimize attrition, such as the presence of a project coordinator (who will make regular contact with each patient before and after treatment). Even with these features, we expect some missing data. The analytic plan is designed to make maximum use of the data. In particular, we will use multilevel latent growth modeling (estimator = maximum likelihood [ML]) using Mplus software. Within this approach, missing data are handled with direct ML (cf. Allison, 2001), retaining an effective N = 196 for all analyses. In addition to fostering statistical power, modern missing data methods such as direct ML (and multiple imputation) provide accurate parameter estimates and standard errors (assuming that values are missing at random), unlike traditional methods such as restricting analyses to completers only or intent-to-treat (ITT) analyses. If we suspect that values are not missing at random, we will turn to methods discussed by Molenberghs and Kenward (2007), that are likelihood-based, intended for ITT studies, and tractable enough for standard statistical programs such as SAS. Potential bias due to attrition will be assessed by modeling 'missingness' patterns. In effect, these methods increase standard errors of the crucial study estimates thereby accounting for this source of uncertainty. If attrition occurs in a random manner (missing at random implies 'missingness' may depend on covariates but not on previous values of the outcome measure) then the mixed model produces unbiased estimates and conservative standard errors. Evaluations of potential bias, when attrition is not missing-at-random, requires cutting-edge statistical methodology (Daniels & Hogan, 2008). We will perform sensitivity analysis under various not-missing-at random assumptions following Daniels and Hogan's (2008) methodology.

The study analyses will include all cases that were randomized into the trial, including individuals who dropped out of treatment. Thus, the distinction between ITT and completer analyses becomes artificial. Greater detail about the proposed analytic approach is discussed in the next section. We intend to contact participants who voluntarily drop out of treatment during what would have been their mid, post- and follow-up assessments, in order to provide as complete a data set (and effect size estimates) as possible.

D.7.a Analyses to Test Specific Aims:

The **primary specific aim** of this project is to examine if GCBT produces significant reductions in PTSD relative to the *SGP* condition and to determine if these changes are durable across a *12* -month follow-up interval. Two hypotheses will be tested.

Hypothesis 1. Patients with PTSD who receive GCBT will show greater reductions in PTSD-related symptoms relative to patients who receive *SGP*, at post-treatment assessment, a between-group difference that will persist through *6* month follow-up. To test this hypothesis, we will use multilevel latent growth modeling. Whereas a traditional latent growth model approach would suffice in many instances (e.g., when patients are treated individually), as noted earlier, the delivery of treatment in group format is likely to result in the violation of the assumption of independent observations (i.e., within-group similarity on treatment outcomes and process variables; cf. Schnurr et al., 2001, 2003). In initial analyses, we will evaluate the

extent of dependency (i.e., clustering) by calculation of intraclass correlations (ICCs) using variance estimates from unconditional cell means models of key outcome variables (cluster = treatment group). Our proposed *N* of 196 will be clustered into 14 treatment groups per condition. Assuming non-zero ICCs, a multilevel approach will be incorporated into the latent growth framework in order to obtain correct standard errors, test statistics, and confidence intervals. In the traditional multilevel modeling, the design would be construed as a three-level model; i.e., repeated observations (Level 1) nested under individuals (Level 2), individuals nested under treatment groups (Level 3). However, because the first two levels are combined in the multivariate framework of latent growth modeling, this design can be characterized as a two-level model (i.e., latent growth factors are nested under treatment groups) where time-invariant covariates (i.e., dummy codes for treatment condition) are included to account for the within-group and between-group variability in initial status (pre-treatment) and symptom change (improvement over active treatment and follow-up). In the latent growth model portion of the models, the intercept will be centered on pre-treatment (i.e., first slope loading will be fixed to 0.0). Because there is no substantive interest in the form of the growth trajectory, intermittent time points (i.e., slope factor loadings) will be freely estimated and the final timepoint of interest (e.g., post-treatment) will have a corresponding factor loading fixed to 1.0. Accordingly, the mean and variance of the slope will convey the fixed (average) and random effects (individual differences) of change for the given time interval of interest. The Level 2 variables of treatment condition (single dummy code using *SGP* as reference group) will be included as predictors to account for individual differences in treatment response and variability in outcome across treatment groups. To examine pre-treatment differences between treatment conditions, the intercept (centered on pre-treatment) will be regressed onto the treatment covariates (i.e., significant paths are indicative of differences in pre-treatment levels as a function of treatment condition). Any pre-treatment differences will be accommodated into the interpretation of findings and in the parameterization of the models (e.g., regression of the slope onto the intercept, as well as covariates such as treatment condition). The dependent variable for this analysis is the CAPS total score. Additionally, PCL will be examined, using the same analytic approach, in order to examine respondent effects (interviewer-rated versus self-report).

Hypothesis 2. Reductions in PTSD symptom severity will be maintained in the GCBT group at *12*-month follow-up. Much as with Hypothesis 1, multilevel latent growth modeling will be used. In the analyses to examine *Hypothesis 2, we will not include the treatment condition covariate but will include the site dummy code, to examine potential site differences*. To test the prediction that the means of *6mos and 12mos* do not differ, the slope factor loadings corresponding to these two time points will be constrained to equality and compared to the fit of a latent growth model where the *6 mo* time point was freely estimated (e.g., Baseline model: 0 * * * 1; hypothesized model: 0 * * 1 1).

The **secondary aim** is to examine the generalizing effects of both GCBT and *SGP* on co-morbid conditions, distress and impairment. Because most trials in the PTSD literature do not include a thorough assessment of treatment generalization, it is unknown whether available treatments only address PTSD or whether gains generalize to related domains of functioning, including co-

morbid conditions such as depression, generalized anxiety, and alcohol use. Three hypotheses are proposed:

Hypothesis 3. For patients who are diagnosed with co-morbid Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and/or Alcohol abuse prior to treatment, GCBT will produce significantly larger symptom reductions for these conditions, relative to *SGP* at post-treatment assessment and these generalized changes will show stability at *6* mo follow-up (FU). To test this hypothesis, we will use multi-level analysis, as discussed for Hypothesis 1. For continuous variables (BAI, BDI-II, SIP), we will use the same approach as described for Hypothesis 1. Although latent growth modeling can accommodate categorical outcomes (e.g., MDD+, MDD-) with an appropriate estimator (e.g., robust weighted least squares, maximum likelihood with numerical integration), there is concern about the estimation failure resulting from low cell frequencies, particularly at post-treatment and follow-up. In the event that cell frequencies are too low, we will augment the analyses from the continuous variables with more descriptively oriented statistics showing the rates of comorbidity decline at each assessment point as a function of treatment condition.

Hypothesis 4. Patients who receive GCBT will report less distress and impairment, relative to patients who receive *SGP*, at post-treatment assessment, a between-group difference that will persist through *6* month follow-up. To test this hypothesis, we will use multi-level analysis, as discussed for Hypothesis 1. For continuous variables (SF-36 subscales), we will use the same approach as described for Hypothesis 1.

Hypothesis 5. Gains in these domains (distress and impairment) will be maintained in the GCBT group at *12-month* follow-up. To test this hypothesis, we will use multilevel latent growth modeling, using the same approach as discussed for Hypothesis 2.

D.7.d. Secondary data analyses: In addition to analyses designed to test these hypotheses, several secondary analyses will be conducted. **(1). Diagnostic and reliable change status**: In order to facilitate comparison with other RCTs, we will compute the percentage diagnosed with PTSD for both GCBT and *SGP* at post-treatment and , 3- and *6*- mo follow-up. To determine reliable change, we will follow guidelines outlined by Jacobson and Truax (1991). Specifically, the reliable change index utilizes both the reliability of measurement device, along with a confidence interval, to determine reliable change. We will utilize CAPS Total scores and a stringent confidence interval (95%) to determine reliable change scores within both the GCBT and *SGP* conditions, at post-treatment and 6 mo follow-up assessment.

(2). Examine the generalizing effects of both GCBT and SGP on healthcare utilization. We will examine the effect of PTSD group treatment on healthcare utilization. We expect that veterans who receive GCBT will display less health care utilization relative to veterans who receive SGP. We will use the same multilevel analysis approach described above (with number of health care visits as the continuous variable.

(3). Predictors of individual differences in outcome: Although the primary aims of this RCT do not include a focus on individual differences that may affect outcome, we propose analyses to look at select variables in this regard. Recognizing that these are exploratory, we propose to look at (1) the number of sessions attended, (2) group psychotherapy alliance (four

subscales of the CALPAS), (3) treatment credibility, and (4) homework compliance, defined as the percentage of homework that the veteran completes, as well as the quality of that homework as rated by the therapists. For analyses involving the number of sessions attended, group alliance, and treatment credibility, we will use data from both the GCBT and *SGP* conditions.

Number of sessions attended will range from 1-14 for patients in both conditions. For group psychotherapy alliance, the CALPAS will be used. For treatment credibility, the four items from the treatment credibility measure (administered following session 1) will be summed to form a composite score. These analyses will examine the direct and moderating effects of each of these variables on variation in treatment response using the CAPS Total score as the outcome. The same multilevel latent growth modeling approach described earlier will be used, bringing these variables into the analysis as additional predictors of within (individual) and between group (treatment groups) variability in symptom change. Of particular interest will be the possibility of significant interactions between each variable and treatment condition (e.g., a significant Treatment Condition x Alliance product term), which would indicate that the strength of effect of these variables on treatment outcome differs between the GCBT and *SGP* conditions (e.g., group alliance is more strongly related to treatment response in the *SGP* condition than the GCBT condition).

To examine the role of homework compliance, two composite variables will be formed: compliance between pre-and mid-treatment and compliance between mid-and post-treatment. The level of homework compliance may vary across the active treatment phase, and thus this variable will be treated as a time-varying covariate in the growth models. Specifically, it is expected that the mid- and post-treatment homework compliance variables will account for significant variance in the CAPS total score indicators that is unexplained by the underlying growth factors (i.e., latent intercept and slope) for the GCBT condition only. The same multilevel latent growth modeling approach described earlier will be employed, bringing these variables into the analysis as additional predictors of within (individual) and between group (treatment groups) variability in symptom change. Of particular interest will be the possibility of significant interactions between each variable and treatment condition, which would indicate that the strength of effect of these variables on treatment outcome differs between the GCBT and SGP conditions.

Treatment satisfaction data will not be examined analytically but will be used to determine consumer response in the event that GCBT has documented efficacy and is targeted for broad-scale dissemination.

E. Human Subjects Research

E.1. Risks to the Participants

a. Human subjects involvement and characteristics: The participant population is to be comprised of 196 male veterans who will be recruited on the basis of presence of a current PTSD diagnosis stemming from military-related trauma. These individuals will be recruited on a volunteer basis. As indicated in the Methods section, inclusion criteria are that participants have chronic PTSD, and that any psychotropic medications are stable. Participants will be required to meet psychotropic medication stabilization criteria for the periods preceding and overlapping

with the diagnostic assessment and treatment. Patients using anxiolytics and beta-blockers will be required to maintain the same dosage for at least 1 month. Patients on antidepressants (tricyclics, SSRIs, MAO inhibitors) will have to have maintained a stable dosage for at least 3 months. If a patient is in the process of stopping his medication when he requests to be in the study, the medication wash-out period (i.e., period since medication discontinuation) will be 1 month for all medications. With respect to involvement in other psychotherapy, we will ask participants to refrain from participating in any active PTSD treatments but other treatment engagement will be permitted.

Exclusion criteria include current suicide risk meriting crisis intervention. We recognize that numerous factors can adversely affect the validity of our data (e.g., neurocognitive deficits, difficulties stemming from using English as a second language, confabulation, extreme restlessness, irritability, threatening behavior, florid psychosis, sexually inappropriate behavior). Some of these dimensions will be formally assessed (e.g., mental status will be assessed using the MoCA, psychosis, current substance dependence, and current bipolar disorder will be assessed using the SCID). As well, we believe that there are other dimensions that might suggest that a participant would be inappropriate for this study (e.g., homicidal risk meriting crisis intervention, acute intoxication). It would be impractical for us to attempt to operationalize all of these dimensions. Instead, we propose to rely on the clinical judgment of the interviewer and the consensus of the research team to determine the validity of an assessment. If a participant is obviously unable to comprehend or conform to the study procedures, the interviewer will terminate the protocol. In less obvious cases where there are concerns about the validity of an assessment but the participant completes the protocol nonetheless, the research team will review the assessment recording and determine, through consensus judgment, if the case should be excluded from analysis. We will use statistical exclusion of outliers as a final level of protection against invalidity. Details about any such exclusion will be included in all final reports and study publications.

Only individuals who provide written informed consent may participate. A participant may withdraw his consent at any time and without prejudice. A clear and detailed explanation will precede all procedures. At the beginning of the first assessment session, participants will be fully informed that they may be asked to talk about very personal and distressing experiences for the assessment and if they are uncomfortable with this possibility, they should not continue in the study. Participants will also be informed that they are free to withdraw from the study at any time without any consequences. An in-depth debriefing will explain all procedures and answer any questions. The debriefing will be conducted at the conclusion of the follow-up session. Any participant withdrawing early from the study will be provided with a debriefing at the time of withdrawal.

Inclusion of Women and Minorities

This project will not include women for two reasons. First, the number of female veterans seeking treatment for PTSD in the VA is considerably smaller than male veterans (8% versus 92% for female and male veterans, respectively). Second, women veterans presenting for PTSD services are more likely to present with PTSD related to sexual trauma (Fontana & Rosenheck, 2002), while combat-related PTSD is very uncommon among women veterans. We considered

running mixed male-female groups but recognized that the nature of the trauma exposure would likely be very different for male and female participants, which would require substantial revision to the GCBT program that is being tested here. In addition, women veterans with PTSD are very unlikely to agree to enroll in group treatment that includes men, and the small number of women who present for PTSD treatment within the VA system would limit our ability to recruit sufficient number of women to run women only groups. Thus, for both scientific and clinical practice reasons, we are recruiting only males in the proposed study.

Minority representation is expected as shown on the targeted Enrollment Table. We expect a fairly racially diverse sample based on veterans presenting for PTSD treatment at the VA Boston and VA Providence sites and past enrollment with PTSD clinical trials conducted at these two sites.

b. Sources of research materials

All information pertaining to this project (e.g., screening forms, questionnaire data, interviews, digital recordings of assessment and treatment sessions) will be held in the strictest confidence, will be kept in a locked file (digital recordings will be held in a pass-word protected computer server), and will be available only to individuals directly involved with the project. Under no circumstances will individually identifiable data be released to anyone without written consent of the participant. Results will be published as group findings only. Assessment and treatment results will be discussed with the participant only.

Potential Risks

Treatment: Some risks are associated with the administration of any psychosocial treatment. In this study, the primary risk for both GCBT and SGP is the evocation of uncomfortable levels of anxiety or other emotions during the treatment sessions. Some patients may find sessions or assignments stressful and react to them with anxiety or anger. The GCBT carries an additional risk that exposure-based homework assignments may carry a likelihood of temporarily increasing PTSD symptoms. Recognizing this, the therapists assigned to this condition will alert participants to expect a possible increase in symptoms, to facilitate management of this should it occur. In addition, there will be a period of time between when participants are initially assessed and when there are a sufficient number of participants to randomize to a group treatment. We do not anticipate any adverse effects while participants are waiting for the group to begin. However, these individuals will be regularly monitored by the project coordinator and by Drs. Sloan and Unger at their respective sites.

Recording: Some participants may feel uncomfortable about the assessment and treatment sessions being recorded (necessary for supervision and treatment adherence checks). However, this will be a required procedure. The purpose of the recording will be explained, confidentiality will be respected, and both informed consent and authorization for recording will be obtained as per requirements put forth by the Healthcare Information Portability and Accountability Act (HIPAA). Digital recordings will be marked only by subject identification codes, stored on a secured server that is pass-word protected, and only available to study personnel. Adherence rating sheets will also be stored in a locked cabinet located within the project coordinator's office.

Diagnostic Interviews, Self-Report Measures and Assessor Ratings: Some discomfort associated with the recording may occur as well as some potential distress when discussing traumatic experiences during the assessment interviews. These situations will be handled as described above.

E. 2. Adequacy of protection against risks

Recruitment and Consent Procedures

Veterans will be recruited through the various clinics at the VA Boston and VA Providence sites. Given that we are recruiting at two sites that are relatively large and have demonstrated past successful recruitment for multiple PTSD clinical trials, we anticipate no problems recruiting the targeted sample size.

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

Participants will also be informed that if suicidal or homicidal intentions are disclosed, confidentiality may be broken in order for protective measures to be taken. Although there will be no questions asked in the assessments regarding children or geriatric persons, if a participant were to disclose child or elder abuse, appropriate agencies would be contacted and participants will be so informed in the consent form. See the Data Safety and Monitoring Plan (Section E.5 below) for specific information on assessment of suicidal information and at what point action(s) would be taken.

Protection against risk

We will carefully screen to identify individuals whose risk for potential adverse outcomes is elevated were they to participate in the proposed research. Such individuals will be excluded from the study. As an example, an actively suicidal person would be excluded from study participation and appropriate clinical care and referrals will be provided. The exact nature of "appropriate clinical care" will be determined by the judgment of clinicians and supervisors familiar with the specific participant and that person's access to community resources, and may include cognitive-behavioral treatment, other psychotherapy, referral to inpatient treatment or referral for medication treatment.

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

All personnel proposed for this project will have the required ethics, human subjects, and confidentiality training, which include information about maintaining data integrity and security.

Careful monitoring of participants during the pretreatment period and all phases of study participation will be conducted by the project staff. Each participant will see the same clinicians for each of their treatment visits. While waiting for a group to begin and during the follow-up interval, each participant will receive regular check-ins from the project coordinator. The project coordinator will be a Ph.D. level therapist who is trained to provide supportive services, as well as recognize if a participant is so distressed as to warrant exclusion from the trial. In particular, during the interval preceding the start of treatment as well as during the follow-up interval, the project coordinator will contact each participant once every 3-4 weeks, in order to determine how he is feeling and functioning (see below for further discussion of this choice). Veterans will be told to contact the project coordinator in case of emergencies or the respective VA after hours call line, which provides psychiatry on call service.

Explicit criterion for exclusion during the course of the trial are as follows:

1. Reporting of psychotic symptoms
2. Actively suicidal or homicidal (with intent)
3. Displaying repeated disruptive behavior within the group treatment setting (examples include being sarcastic towards therapists or other group members, routinely arriving late by 30 minutes or more, hi-jacking the scheduled group content in order to direct attention to his own agenda). If there is a question about an individual's behavior during group, Dr. Sloan will review the treatment recording and determine, in consultation with the other investigators on this application, if the veteran should be dropped from the trial.

Participants will be instructed to contact study personnel at any time (including during the follow-up interval) in the event of worsening of symptoms or relapse. Participants whose clinical condition has deteriorated will be removed from the study and given appropriate clinical care.

Participants failing to benefit from the study treatments will be provided with, or referred to, appropriate clinical care. Participants who begin treatment and experience adverse outcomes sufficient to require removal from the study will receive appropriate clinical care.

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

E. 3. Potential Benefits of the Proposed Research to the Subjects and to Others.

a. Potential Benefits

The direct benefit to participants who enter this study will be to obtain relief from PTSD symptoms, decreased avoidance, decreased disability, and increased quality of life. For many participants, PTSD has greatly impeded their social, vocational, and family functioning.

E. 4. Importance of the Knowledge to be gained

PTSD is a chronic and debilitating disorder and is particularly prevalent in the veteran population. Although we now have a number of first line treatments available, all of these first-line treatments are delivered in an individual format. This is unfortunate as there is a great need for group treatments. As is true for many medical centers, the VA Healthcare System does not have sufficient providers to provide individual services to all of the veterans who present for PTSD treatment. Thus, it is imperative that we identify efficacious group-based treatments for PTSD in order to be able to adequately serve those in need of PTSD treatment. The primary aim of the study proposed here is to examine the efficacy of a group-based cognitive-behavioral treatment for PTSD that has been shown to be efficacious in a sample of participants with PTSD resulting from a motor vehicle accident.

E. 5. Data Safety and Monitoring Plan (DSMP)

The VA's Centralized Data Monitoring Committee (DMC) will monitor this study. The DMC focuses on participant safety and accrual as well as on statistical issues. In general, the DMC will serve as an oversight committee, reviewing any modifications to the research design and conduct of the study and making recommendations.

Regarding the safety of participants, the DMC will review new risk management protocols and modifications to risk management protocols. The DMC will also review procedures and decisions regarding the adequate protection of specific participants when investigators move into risk management protocols because of adverse events or clinical deterioration. When appropriate, the DMC will serve as final arbiters of whether individual participants should be removed from the protocol.

The DMC will be in contact at least once per year with the PI and Co-I's in order to review progress reports and discuss issues relevant to study safety. Following each meeting, a summary of the board's review will be provided to the research team. They will also be available to review emerging data (in the study or the literature) which may alter the risk/benefit ratio and will be empowered to decide upon continuation, discontinuation, or termination of the study. In addition, study enrollment data will be submitted to the DMC on a quarterly basis in order for the DMC to monitor recruitment success on the project.

Data Monitoring Plan. Data will be collected using standardized forms and will only be identified using the participants ID number (no names or identifying information will be on the forms). The codes that link the names of participants and their ID numbers will be kept confidential by the site PI's in a secured, locked cabinet located within their office. These data will only be accessible to the site PI's and staff directly working with the study. All data will be entered on-line, with 100% review by the project coordinator in those instances where a

discrepancy occurs during double entry. Data will be double-entered by trained staff member, and data entry discrepancies will be corrected by the Project Coordinator, based on source documents. The quality of the data will be monitored on an ongoing basis.

Data quality will be monitored by inspection of the completed forms by a research assistant and any problems detected will be discussed with the PI. Interviewer reliability will be assessed using digital recordings of diagnostic assessments. Adherence to the intervention will be monitored using digital recordings of sessions and weekly supervision. If diagnostic and/or intervention drift is observed, staff will be retrained until acceptable reliability is reached.

Safety Monitoring Plan. During the first in-person screening, potential participants will undergo a comprehensive screening to determine their eligibility for, and safety for, their participation in the study, following the provision of informed consent. Attention will be placed on current suicidal risk. Individuals who are judged to be at risk for suicide will be excluded from participation in the study and will be provided with appropriate clinical referrals. Should suicidal risk increase during treatment, the therapists will consult with the PIs to determine whether the increased suicidal ideation can be managed within the clinical protocol or whether other steps will need to be taken to protect the participant.

If a participant is assessed to be at risk for suicide, treatment staff will immediately locate the site PI, who are both licensed psychologist and maintain clinical credentials at their respective medical centers, and will be on-site when assessment sessions are conducted. At that point, the site PI will intervene by a) following up with direct questions about suicidal behaviors, b) assess mental status by asking about psychotic symptoms, mood symptoms and drug and alcohol use, c) schedule extra contacts if necessary, emphasizing problem solving, d) help the participant generate short-term objectives, and e) negotiate an action plan. The action plan will be collaboratively generated by Dr. Sloan and the participant. The plan will address what actions need to be taken in the succeeding days to solve the problems that precipitated suicidal behavior. The plan will also address the use of voluntary or involuntary hospitalization, if necessary. The suicidal management plan that will be followed has substantial empirical support for its efficacy (Chiles & Strosahl, 2005) and is the plan that is recommended for use by the American Psychiatric Association.

In the proposed study we will use the FDA definition of adverse events (AE) and serious adverse events (SAE). Any SAE, whether or not related to study intervention, will be reported immediately to both the IRB and VA Centralized DMC and will be followed by an additional letter detailing the nature of the SAE. In the event that a participant either withdraws from the study or the site PI's (with consultation of the DMC) decide to discontinue a participant due to a SAE, the participant will be monitored by the site PI via ongoing status assessment until (a) a resolution is reached (e.g., the problem has resolved or stabilized with no further change expected), (b) the SAE is determined to be clearly unrelated to the study intervention, or (c) the SAE results in death. Outcomes of SAEs will be regularly reported to VA Centralized DMC (and the VA Boston and VA Providence IRB). A summary of the SAEs that occurred during the previous year will be included in the annual progress report as well as in the annual IRB renewal. Suicidal ideation and AEs will be formally assessed immediately after treatment and referrals for further care will be made as needed.

Under the arrangement to conduct the study on site at the VA Boston and VA Providence, the VA agrees to provide emergency services to anyone who participates in this project. We will have specifically outlined in the Informed Consent Form the availability of emergency services to veterans who may seek them during and after normal working hours. In the Informed Consent Form, we will provide specific information about emergency contacts. Participants are instructed to contact either Dr. Sloan (VA Boston) or Dr. Unger (VA Providence) or their study therapist during business hours. If they have problems after hours, they are instructed to page the psychiatry on call service; the psychiatrist on call will then respond immediately to their call. This is the policy of the VA Boston and VA Providence for conduct of clinical trials at their sites. Veterans will also be provided with the phone number for the VA National Suicide Hotline.

Resources

VA Boston Healthcare System – Primary site

The National Center for PTSD, Behavioral Science Division (BSD) at VA Boston Healthcare System is the primary site for the proposed project, and represents one of two recruitment sites for the study. The National Center for PTSD is mandated by public law 98-528 as a specialized center within the Department of Veterans Affairs devoted to research and training in all aspects of PTSD. The BSD is located in the Jamaica Plain campus of the VA Boston Healthcare System and is integrated with the PTSD outpatient clinic at the Jamaica Plain campus. The Jamaica Plain campus is conveniently located, with several public transportation alternatives (train and bus lines) that have stops either directly at the medical center or within a few blocks from the medical center. In addition, parking at the medical center is free to visitors. Shuttle service runs between the Jamaica Plain VA campus and the other VA Boston campuses, including the Brockton campus and the community based outpatient clinics. In addition, shuttle buses transport veterans from community based outpatient clinics in the surrounding area (e.g., Worcester) to the Jamaica Plain campus. Thus, the Jamaica Plain campus is easily accessible to veterans residing in the greater Boston area.

The BSD staff is comprised of 14 doctoral-level clinical psychologists with a broad range of expertise in the area of posttraumatic stress who work closely together within a collaborative center. In addition to the BSD staff, the PTSD Clinic has 6 Staff Psychologists. BSD also houses 8 or more post-doctoral fellows, 2 pre-doctoral interns, 2 full-time LAN administrator/programmers, 1 administrative officer, 1 full-time clerk for scheduling appointments, and approximately 15 full-time research assistants.

The BSD occupies two vertically adjacent floors in one wing of the main building on the Jamaica Plain Campus of VA Boston Healthcare System. BSD space comprises over 3200 square feet and includes over 30 offices, 4 conference rooms, 5 laboratory rooms, 2 computer rooms, multiple testing/therapy rooms, storage areas, and two staff kitchens. The division also controls 1700 linear feet of securely enclosed, track-mounted storage, located in the basement of the building, which is used for long-term retention of raw research data.

Staff working on this study will be housed in office space within BSD.

Other Resources:

Dr. Terence Keane, Associate Chief of Staff for Research, at the VA Boston Healthcare System and Director of BSD, is a Principal Investigator on a T32 training grant funded by NIMH that provides for post-doctoral clinical research training in PTSD to four fellows on a bi-annual basis. Dr. Sloan (Primary PI on this proposal) serves as Director of this fellowship program. The four post-doctoral fellows are very engaged in all aspects of ongoing research projects in BSD, and often assist with the conduct of assessments for study protocols.

Windows-compatible software of various types is available to all BSD staff via the network. Specific examples of the software include MS Word and WordPerfect for word processing, Excel for spreadsheets, Access and SQL Server for databases, PowerPoint for graphics applications, Adobe Illustrator and Photoshop for digital image manipulation, Adobe Acrobat for PDF file manipulation, and SPSS, S-Plus, LISREL, M-Plus, EQS, AMOS, HLM, and Solas for statistical analysis. Teleform software is used to create customized scannable forms for data collection and automated data entry, and Alchemy software is used for electronic archiving of research forms.

The BSD subscribes to the PsycInfo service for literature searches, and to the PsycArticles service for full text electronic access to journals published by the American Psychological Association. Both of these can be accessed directly from the LAN and remotely. In addition, through the BSD's affiliation with Boston University School of Medicine, there is electronic and physical access to journal articles, books, and databases. Commercial software is available for functions such as creating and searching customized bibliographic databases, statistical power calculations, and modem and fax communication.

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