Medical University of South Carolina
Protocol Version 2 (September 24, 2013)

PI Name: Daniel Gros, Ph.D.

Study Title: **Transdiagnostic Psychotherapy for Veterans with Mood and Anxiety Disorders**

TABLE OF CONTENTS

A. SPECIFIC AIMS

Cognitive behavioral therapy (CBT) is robustly effective in treating patients with depressive and anxiety (depressive/anxiety) disorders. CBT also is brief, cost-effective, and provides protection against relapse. However, access to CBT by patients is limited, in part, because the sheer number of different CBT protocols for specific disorders limits the extent to which providers can deliver all of these interventions with a high level of fidelity and competence (Barlow et al., 2004). In addition, most CBT protocols are not designed to treat patients with comorbidity. Together, this state of affairs suggests that there are unique opportunities to enhance outcomes and recovery in Veterans within the Department of Veterans Affairs (DVA).

The primary goal of the proposed study is to improve outcomes in Veterans with depressive/anxiety disorders by testing a transdiagnostic CBT that distills the existing disorder-specific CBT protocols for emotional problems into a single, unified CBT protocol for all depressive/anxiety disorders. Currently, basic training in each of the disorder-specific CBT protocols requires lengthy direct trainings, supervision, and case consultation. Completing these requirements across each of depressive/anxiety disorders would require several years. In addition, training in CBT designed for specific disorders would likely fall far short of adequately addressing comorbidity, which is highly prevalent and difficult to treat, particularly in Veteran populations. A transdiagnostic CBT approach would reduce the complexity of treatments and dramatically reduce training time and cost, possibly resulting in better prepared providers to address comorbidity as well as improved access to high-quality care and related outcomes in DVA patients.

This study is designed to evaluate a transdiagnostic CBT specifically constructed to treat Veterans with depressive/anxiety disorders. The protocol includes both a primary transdiagnostic exposure component as well as supplementary disorder-specific modules to address ancillary symptoms. This transdiagnostic CBT has been investigated through focus groups with Veterans and two pilot demonstrations. This study will compare transdiagnostic CBT to an existing evidence-based version of CBT, behavioral activation therapy (BAT; psychotherapy control condition). A randomized controlled trial (RCT) of 96 DVA patients with depressive/anxiety disorders will be conducted to examine its efficacy, feasibility, and accessibility. Diagnostic interviews and self-

report symptom questionnaires will be completed at pre-treatment, immediate post-treatment, and 6-month follow-up assessment time points.

Research Primary Aim 1: To examine efficacy of transdiagnostic CBT on reducing transdiagnostic and disorder-specific mental health symptoms and improving quality of life at immediate post-treatment and 6-month follow-up.

Hypothesis 1: The transdiagnostic CBT will result in significantly greater reductions in symptomatology (for principal and comorbid diagnoses) and improvements in quality of life compared to the BAT control condition at immediate post-treatment and 6-month follow-up. Although limited specific symptoms may ultimately be comparable across treatments (e.g., depression), the transdiagnostic CBT will demonstrate significantly greater reductions in the majority of symptoms (e.g., anxiety, panic, fear, stress).

Research Primary Aim 2: To examine feasibility and acceptability of transdiagnostic CBT

Hypothesis 2: The transdiagnostic CBT will be well tolerated by DVA patients as demonstrated by improved attendance and dropout rates, patient satisfaction questionnaires, and positive feedback in post-treatment patient interviews as compared to the BAT control condition. This hypothesis is based on the predicted greater symptom improvement (hypothesis 1) as well as the flexibility and individual tailoring of the treatment approach incorporated within transdiagnostic CBT.

B. BACKGROUND AND SIGNIFICANCE

Between 2001 and 2010, nearly 1.9 million U.S. service members were deployed in Operations Enduring/Iraqi Freedom (OEF/OIF), many returning home with psychiatric disorders post-deployment. As a result, the DVA has witnessed a large influx of new Veterans seeking mental health services. It is the responsibility of the DVA to provide quick, effective, recovery-oriented treatments to Veterans to ensure that they can return to their civilian lives with minimal impairment. However, this volume of new patients is making it difficult for the DVA to provide high quality psychosocial treatments for mental health concerns.[11]

One priority area is the treatment of depressive/anxiety disorders, representing the most common psychiatric disorders in the United States (prevalence: 28% past year; 49% lifetime). Similar rates of depressive/anxiety disorders have been reported in Veterans. The category of depressive/anxiety disorders includes posttraumatic stress disorder (PTSD), panic disorder (PD), social phobia (SOC), specific phobia, generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), major depressive disorder (MDD), and dysthymic disorder (DD). Due to high rates of comorbidity within the depressive/anxiety disorders, the presence of one disorder typically is accompanied by several comorbid depressive/anxiety disorders, and the diagnostic (and hence treatment) distinction between disorders is not routinely reliable. In addition to severe occupational, educational, and social impairment, these disorders also are associated with elevated risk for cardiovascular disease, suicide, and substance use disorders in Veteran and civilian populations. Research also demonstrates high cost associated with depressive/anxiety disorders, including estimates that Veterans with depressive/anxiety disorders have 60% higher medical costs than their non-anxious/non-depressed Veteran counterparts. Together, these findings highlight the overwhelming burden associated with the these disorders and the daunting task of addressing them in the DVA.

CBT has demonstrated reliable efficacy in treating depressive/anxiety disorders. CBT involves several different evidence-based treatment components that are typically delivered over the course of 10-20 weeks. Although CBT is a short-term intervention, the benefits of CBT typically persist following the termination of treatment, with long term studies demonstrating maintenance of treatment effects at least two years after treatment ends. Another benefit of CBT is its impact on the financial burden associated with the depressive/anxiety disorders. Psychosocial interventions, including CBT, significantly reduce the long-term medical costs in patients with depressive/anxiety disorders. Together, these findings support the effectiveness of CBT as well as its many additional benefits in promoting long-term recovery in patients.

Despite its clear benefits, several limitations exist in the current delivery of CBT. One of the most significant limitations is the sheer number of different manualized CBT protocols, representing a major obstacle to providers through separate manuals and workbooks for each disorder, each with significant direct costs and time and training requirements. In addition, indirect costs also can be a significant hurdle for both providers and facilities (e.g., loss of revenue during training activities). Standard workshops for disorder-specific, evidence-based psychotherapies typically involve substantial commitment from providers. Only a small number of workshops are available per year and typically require out-of-town travel, representing a significant burden on providers,

especially if training is needed for more than one disorder (e.g., 6-12 month commitment per treatment per disorder), and these types of trainings are only available for specific disorders. In fact, Dr. David Barlow – one of the leaders in the development and dissemination of CBT – has argued that, "unless these treatments become more 'user-friendly' as recommended (by a recent NIMH task force), it is unlikely that most non-research clinicians will have a sufficient understanding of, or access to these empirically supported techniques for the depressive/anxiety disorders (Barlow et al., 2004)." This notion has been echoed by other CBT experts, suggesting less complicated treatments and related training requirements would be more easily disseminated.

In contrast to the lengthy training necessary for the disorder-specific CBT protocols, a shift to a transdiagnostic CBT protocol for depressive/anxiety disorders would eliminate much of the unnecessary procedures, time commitment, and financial burden from therapists and the DVA. Transdiagnostic treatments are based on the notion that various disorder-specific CBT protocols contain important but overlapping treatment components that can be distilled into a single treatment and therefore address the symptoms and comorbidities across all of the disorders at once (Norton, 2009). This notion is most true of the depressive/anxiety disorders in which a large number of overlapping symptoms and related components of CBT exist. The transdiagnostic approach to the depressive/anxiety disorders represents a major shift in philosophy regarding application of evidence-based psychotherapy to specific symptoms after decades of developing scores of disorder-specific treatments. This approach aims to simplify treatment of the depressive/anxiety disorders by combining the shared/overlapping treatment components into a single treatment for the entire class of disorders. Transdiagnostic treatments would greatly reduce the training burden on providers as only one protocol would be needed for the depressive/anxiety disorders, rather than separate protocols for each separate disorder. In addition, because transdiagnostic treatments are designed to address multiple depressive/anxiety disorders at once, they are fully able to address the needs of patients with comorbidities without requiring providers to successfully identify and implement multiple treatment protocols. This transdiagnostic approach to comorbidity is in contrast to disorder-specific treatments that focus solely on the treatment components designed for their specific disorder. Together, these findings suggest that developing, evaluating, and implementing transdiagnostic treatments for multiple depressive/anxiety disorders and comorbidities would greatly reduce the number of protocols, costs, and trainings necessary for providers, thereby improving their acceptability and availability to their patients and, importantly, improving outcomes in DVA patients.

A small number of transdiagnostic treatment approaches have been proposed for the depressive/anxiety disorders (Norton, 2009). Although still in development and preliminary evaluation, early outcomes suggest that transdiagnostic approaches can be delivered efficaciously across the depressive/anxiety disorders, with moderate-to-high effect sizes (Farchione et al., 2012; Norton, 2012; Schmidt et al., 2012). Because transdiagnostic CBT approaches have the potential to address numerous barriers to accessibility and delivery of evidence-based care as discussed earlier, these initial findings are very encouraging. However to date, no transdiagnostic CBT protocols have been developed for or studied in Veterans.

The proposed investigation seeks to study a transdiagnostic CBT protocol for Veterans with depressive/anxiety disorders. The current status of psychosocial treatment for the eight depressive/anxiety disorders targeted in this study necessitates that providers receive specific comprehensive training in eight or more distinct CBTs focused on specific disorders, rather than the more common comorbid presentations of the disorders. The transdiagnostic CBT proposed for evaluation in this study has the potential to reduce the training burden tremendously, and also has the potential to achieve superior outcomes with regard to comorbid depressive/anxiety disorders because the intervention is designed specifically to address the disorders with and without comorbidity. This integrated treatment incorporates evidence-based practices for each of the included disorders, tailoring treatment to Veterans through the completion of OEF/OIF Veteran focus groups and initial piloting in VAMC patients with depressive/anxiety disorders. The treatment aims to improve recovery of VAMC patients with depressive/anxiety disorders by reducing mental health symptoms and improving quality of life. If efficacious, this treatment will have the potential to reduce VAMC provider-training burden and associated costs and improve the quality of care provided to VAMC patients with depressive/anxiety disorders by improving access to CBT.

C. PRELIMINARY STUDIES

Initial Demonstration of Transdiagnostic Protocol

Fifteen VAMC patients were recruited over a 6-month period through the CBT Clinic at the Ralph H. Johnson (RHJ) VAMC to complete the treatment within standard clinical psychotherapeutic practices at the VAMC. All

participants referred to this clinic already have expressed interest in receiving psychotherapy; and, thus, none of the 15 invited participants refused to participate in treatment. All participants were diagnosed with multiple comorbid depressive/anxiety disorders and reported severe, pre-treatment symptoms of anxiety and depression. PTSD was the most common presenting problem (46.6% PTSD, 26.7% SOC, 26.7% PD, 7.1%) and MDD was the most common comorbid disorder (64.2% MDD, 14.3% SOC, 7.1% PTSD, 7.1% PD). In general, participants were stabilized on multiple psychotropic medications prior to beginning CBT. Twelve of the fifteen participants finished treatment (80.0%). Treatment completers attended an average of 11.5, 50-minute sessions. As presented in the table below, participants demonstrated significant improvements in symptoms of impairment/quality of life, depression, stress, anxiety, and PTSD across all disorders and comorbidities. These findings provide preliminary support for the feasibility of a structured, transdiagnostic CBT protocol for the depressive/anxiety disorders among VAMC patients.

Efficacy of Initial Transdiagnostic CBT in VAMC Patients

Scale (*n*)	Pre	Post	*t* (*p*)	Effect Size
IIRS-Impairment (12)	66.0 (14.9)	41.2 (19.8)	6.4 (< .001)	1.42
PTSD Checklist (7)	56.1 (13.1)	37.0 (14.0)	5.6 (< .01)	1.41
DASS-Depression (12)	26.2 (10.8)	10.3 (10.3)	5.3 (< .001)	1.51
DASS-Anxiety (12)	25.2 (10.7)	11.8 (9.1)	5.5 (< .001)	1.35
DASS-Stress (12)	26.3 (10.8)	15.7 (9.6)	3.6 (< .01)	1.04

Note. Sum scores reported as means (standard deviations). Cohen's *d*s used for effect sizes.

Focus Group with OEF/OIF Veterans

The second step of the development of the transdiagnostic CBT protocol involved focus groups with OEF/OIF Veterans. These focus groups were designed to assess Veterans' opinions and interests in CBT, transdiagnostic CBT, and online transdiagnostic CBT. Feedback was received from four focus groups with a total of 16 Veterans (15 males; 1 female) who were recruited through the RHJ VAMC. Feedback could be summarized in three primary themes. First, participants identified symptoms of depression, anxiety, and PTSD as the most relevant to OEF/OIF Veterans. Participants also identified several additional symptoms (e.g., anger, sleep, hypervigilance, drinking to cope) that they labeled as secondary to depression, anxiety, and PTSD. Second, participants suggested that brief, straight-forward approaches to treatment were needed with clear objectives, assignments, and feedback. Participants noted that the core components should be presented early in the treatment to facilitate faster improvements. Third, participants suggested that treatments should include components to address and improve patient motivation to improve participation and assignment completion. Although several of these findings were predicted from the previous literature, together, these findings provided additional support for the direction of the transdiagnostic CBT protocol and highlighted areas of further revision/improvement.

Demonstration of Revised Transdiagnostic Protocol

The results from the initial demonstration and OEF/OIEF Veteran focus groups were used to inform the revisions of the transdiagnostic CBT protocol. Once the revised protocol was complete, a demonstration of the revised transdiagnostic CBT protocol was initiated, once again, within standard clinical psychotherapeutic practices at the VAMC. The methods of the second demonstration were largely identical to the first demonstration. Thirty-one VAMC patients were recruited to complete the treatment. All participants were diagnosed with multiple comorbid depressive/anxiety disorders and reported severe pre-treatment symptoms. Among the twenty-three treatment completers, PTSD was the most common principal diagnoses (39.1% PTSD, 26.1% MDD, 21.7% PD, 8.7% SOC, and 4.3% OCD) and MDD was the most common comorbidity (43.5% MDD, 26.1% PTSD, 8.7% drug/alcohol abuse, 4.3% PD, 4.3% SOC). Treatment completers attended an average of 11.8, 45-60 minute sessions. As presented in the table below, participants demonstrated significant improvements in symptoms of impairment/quality of life, depression, stress, anxiety, and PTSD across all disorders and comorbidities. These findings provide additional support for the feasibility and likely efficacy of the transdiagnostic CBT protocol for the depressive/anxiety disorders among VAMC patients.

Efficacy of Revised Transdiagnostic CBT in VAMC Patients

Scale (*n*)	Pre	Post	t (p)	Effect Size
IIRS-Impairment (23)	64.3 (13.1)	37.3 (17.6)	7.3 (<.001)	1.74
PTSD Checklist (22)	56.5 (17.8)	33.7 (14.2)	7.2 (< .001)	1.42
DASS-Depression (23)	12.0 (6.1)	4.8 (4.3)	6.7 (< .001)	1.36
DASS-Anxiety (23)	10.9 (5.4)	5.0 (3.5)	6.2 (< .001)	1.30
DASS-Stress (23)	13.8 (5.1)	7.0 (3.9)	6.1 (< .001)	1.50

Note. Sum scores reported as means (standard deviations). Cohen's *d*s used for effect sizes.

D. RESEARCH DESIGN AND METHODS

Project Timeline

Project Component	Year	Timeframe
Preparing for RCT	Y01	month 01 – 06
Hiring staff	Y01	month 01 – 03
Training on procedures/protocols	Y01	month 03 – 06
Advertising upcoming trial for recruitment	Y01	month 03 – 06
Randomized controlled trial	Y01-Y04	month 06 – 54
Recruitment and active treatment		month 06 – 45
Ongoing data entry and integrity/fidelity reviews		month 09 – 42
Data analyses of post-treatment (follow-up)		month 24 – 54
Grant application(s) (e.g., DVA CSR&D Merit)	Y04-Y05	month 36 – 60
Dissemination of findings	Y05	month 54 – 60
Revision of manual based on findings/feedback	Y05	month 54 – 60

RCT of Transdiagnostic CBT

Objective

To evaluate the transdiagnostic CBT in a RCT of VAMC patients with depressive/anxiety disorders by investigating its preliminary efficacy in reducing symptomatology, comorbidity, and improving quality of life compared to BAT (psychotherapy control condition) at immediate post-treatment and 6-month follow-up. Patient satisfaction and predictors of feasibility (attendance and dropout) also will be assessed.

Recruitment Strategy

VAMC patients will be recruited through the Primary Care – Mental Health Integration program and CBT Clinic at the RHJ VAMC. Within these programs, all VAMC patients reporting symptoms of depression and anxiety meet with a mental health staff member to complete a diagnostic interview and self-report measures as part of their standard clinical practices. If VAMC patients endorse symptoms consistent with a depressive/anxiety disorder, the patient's interest in participating in research will be assessed and, if agreeable to research, patients will be put in contact with research staff (same day meeting and/or follow-up phone to schedule research assessment). A research assessment will be completed with the project staff to first complete consent documentation and then assess inclusion/exclusion criteria (with a targeted sample of 96 VAMC patients; $\geq$ 72 completers), including a semi-structured clinical interview and self-report questionnaires focused on the psychiatric symptoms and quality of life (described later). Participants who meet diagnostic criteria for the targeted disorders will be randomized into a study condition, and will be assigned to a project therapist. Because most VAMC patients who meet study criteria likely will present with multiple depressive/anxiety disorders, principal diagnosis, or the most impairing of

the diagnosable disorders, will be used to select patients for participation. To balance diagnoses across the two conditions, a stratified random assignment based on principal diagnosis will be used for the most common principal diagnoses (MDD, PTSD, and PD). Based on new patient consults at the RJH VAMC (i.e., nearly 1000 in 2011 with at least one-half presenting with symptoms of an depressive/anxiety disorder), it is expected that ≥50% of the recruited VAMC patients will have served in OEF/OIF and ≥33% will be representative of minority groups.

Eligibility Criteria

Inclusion criteria involve: 1) participants must be clearly competent to provide informed consent for research participation; 2) participants must meet DSM diagnostic criteria for a principal diagnosis of a depressive/anxiety disorder (PD, PTSD, SOC, OCD, GAD, specific phobia, MDD, or DD); and 3) participants must be 18 – 80 years old. **Exclusion criteria involve:** 1) recent history (≤ 2 months) of psychiatric hospitalization or a suicide attempt as documented in their medical record, 2) current diagnosis of substance dependence or abuse on the structured clinical interview, 3) acute, severe illness or medical condition that likely will require hospitalization and/or otherwise interfere with study procedures as documented in their medical record (e.g., active chemotherapy/radiation treatment for cancer, kidney dialysis, oxygen therapy for chronic obstructive pulmonary disease), 4) recent start of new psychiatric medication (≤ 4 weeks), 5) diagnosis of traumatic brain injury (TBI) in their medical record and/or endorsement of screener questionnaire regarding the symptoms of TBI modified from the Post-Deployment Health Assessment employed by the Department of Defense, or 6) diagnosis of schizophrenia, psychotic symptoms, personality disorder, and/or bipolar disorder. VAMC patients excluded due to these factors will be reconsidered for participation once the condition related to their exclusion is resolved or stabilized. Together, these inclusion/exclusion criteria should allow the vast majority of interested VAMC patients with depressive/anxiety disorders to be eligible to participate. Ineligible VAMC patients will be referred for non-study-related treatments within mental health at the RHJ VAMC.

Procedures

Eligible VAMC patients will be randomized into one of two treatment conditions: transdiagnostic CBT or an existing evidence-based version of CBT (BAT). Both treatment conditions will include 12-16 weekly 45-60-minute individual psychotherapy sessions. The total number of sessions will vary slightly depending on participant needs and progress during therapy, as is common in most CBT approaches to psychotherapy (and will serve as a covariate in the outcome analyses). The general format of sessions will involve: 1) brief check-in; 2) review of materials from previous sessions; 3) review of homework assignments; 4) overview of new materials and in-session exercises; and 5) assignment of homework for next session. Attendance and homework completion will be recorded. A full battery of self-report questionnaires and a diagnostic interview will be completed pre-treatment, post-treatment, and at the 6-month follow-up to track participants' progression through treatment and maintenance. Post-treatment participant interviews will be completed at immediate post-treatment and 6-month follow-up to collect feedback on participants' perspectives on the treatments.

Table of Procedures for Each Visit – Summarized Across Treatment Conditions

Week	Content	Assessment Summary
1	Pre-Treatment Assessment	Clinical interview & self-report battery (7 measures)
2	Session 1: Psychoeducation	Brief self-report battery (3 measures)
3	Session 2: Treatment planning	
4	Session 3: Introduction to behavior therapy	Brief self-report battery (3 measures)
5	Session 4: Behavior therapy	
6	Session 5: Behavior therapy	Brief self-report battery (3 measures)
7	Session 6: Behavior therapy	
8	Session 7: Behavior therapy	Brief self-report battery (3 measures)
9	Session 8: Behavior therapy	
10	Session 9: Behavior therapy	Brief self-report battery (3 measures)
11	Session 10: Behavior therapy	
12	Session 11: Behavior therapy	Brief self-report battery (3 measures)
13	Session 12: Behavior therapy	
14	Session 13: Behavior therapy (as needed)	Brief self-report battery (3 measures)
15	Session 14: Behavior therapy (as needed)	
16	Session 15: Behavior therapy (as needed)	Brief self-report battery (3 measures)
17	Session 16: Relapse prevention (as needed)	
~18	Post-Treatment Assessment	Clinical interview, immediate treatment interview, & self-report battery (7 measures), treatment satisfaction
~33	6-Month Follow-Up Assessment	Clinical interview, immediate treatment interview, & self-report battery (7 measures), treatment satisfaction

Note. Behavior therapy involves the introduction, teaching, in-session and between-session practice, and mastery of behavioral therapeutic techniques designed to improve symptoms of depression and anxiety, including behavioral activation (BAT group) as well as situational, physical, thought, and emotional exposures (transdiagnostic CBT group). Final treatment session will take place between sessions 12-16, as determined by provider and participants' collective decision. Final treatment session will involve relapse prevention content. Post-treatment assessment will be completed 1 week immediately after final treatment session. 6-month follow-up assessment will be completed 6-months after final treatment session.

Randomization Procedures

Participants will be randomly assigned (1:1) to one of the two study arms (n = 48 per arm) using a permuted block randomization procedure. Randomization will be stratified by principal diagnostic group and block size will be varied to minimize the likelihood of unmasking. After determining eligibility and completing consent and baseline assessment materials, enrolled participants will be assigned to treatment groups by the Project Research Assistant using a computer generated randomization scheme. Once a participant is randomized and attends the first session, they will be included in the intent-to-treat analysis. Randomization will occur at the participant level. As such, we will take the following steps to minimize contamination between the two arms of the study: 1) only one member of a household will be eligible for enrollment; and 2) other VAMC providers will be informed of their patients' participation in the study, but will be blinded to the treatment condition of their patients.

Transdiagnostic CBT Treatment Condition

As noted above in the Preliminary Studies section, a transdiagnostic CBT protocol was developed and revised through two demonstration studies and one focus group. The resulting protocol involves several primary components, including psychoeducation on the symptoms of depression and anxiety (session 1), assessment of motivation and setup of treatment plans (session 2), exposure therapy (sessions 3-15), and relapse prevention (final session). In addition to these primary components, optional modules are included to supplement exposure

therapy later in treatment to address secondary symptoms (e.g., anger, sleep, hypervigilance, drinking to cope). The goal of these modules is to allow providers to tailor treatment to specific symptoms that may be present in any single or set of diagnoses that may be reducing the effects from the primary exposure approach. Session will be weekly for 45-60 minutes with homework assignments to be completed between sessions.

BAT Control Condition

To provide an evidence-based comparison for the transdiagnostic CBT condition, a second group of participants will receive manualized BAT. BAT is a well-established form of CBT that is based on early behavioral models that suggest that decreases in positively reinforcing healthy behaviors are associated with the development of negative affect. In general, BAT involves teaching patients to monitor their mood and daily activities with the goal of increasing pleasant, reinforcing activities and reducing unpleasant events. BA is a brief treatment, can be administered in either individual or group formats, and has demonstrated reliable effectiveness across a wide range of university, community, civilian and Veteran clinical samples with depression. BAT also has been shown to be effective in the treatment of PTSD and other related depressive/anxiety disorders in Veterans. In the present study, the BAT condition will be manualized, following an existing protocol in the literature. BAT will be structurally equivalent to the transdiagnostic CBT with the same session length (45-60 minutes), frequency of sessions (weekly), duration of treatment (12-16 sessions), and amount of homework.

Treatment Training and Fidelity

All therapy will be delivered by a Project Masters-Level Therapist, trained and supervised by the Principal Investigator (Dr. Gros). Training of treatment staff will involve mastery of the two treatment protocols, completion of two practice participants for each protocol, and review of all practice sessions by Principal Investigator in order to assess/minimize therapist drift between the two protocols. Consistent with other well-designed treatment outcome studies, all treatment sessions will be audio recorded with 20% of sessions randomly selected for review for treatment integrity and fidelity. These integrity and fidelity reviews will focus on evaluating the match between the treatment manuals and the material covered in session (e.g., treatment components introduced/reviewed, in session exercise, and homework assigned). To evaluate adherence, rating forms will be developed by the Principal Investigator and based upon the treatment manuals to determine if the therapist appropriately covered the content of each session (i.e., demonstrated the particular behavior described in each item). These rating forms use 7-point Likert scale response formats, and are modeled after the therapist rating forms used in other studies of CBTs. Staff will be recruited and trained and then asked to rate the recordings independently to allow for the computation of inter-rater reliability. If participants request changes to their mental health medications at any time during the treatment, a medication consult will be completed with their existing providers within the RHJ VAMC (e.g., Dr. Steve Byrd for patients recruited from Primary Care Mental Health Integration program) with changes in medications recorded for inclusion in the analyses as a possible covariate.

Assessment of Mental Health Symptoms, Quality of Life, and Treatment Satisfaction

The full battery of self-report questionnaires and a diagnostic interview will be completed pre-treatment, immediate post-treatment, and at the 6-month follow-up to track participants' progression through treatment and maintenance. These time points for the assessments are consistent with CBT research with Veterans with depressive/anxiety disorders. To reduce the likelihood of missing data, all assessments will be scheduled separately from normal treatment sessions (intake appointment, one week following the final treatment session, and at 6-month follow-up). Additional staff training will be required prior to administration of the diagnostic interview. All assessments will be completed by the Project Research Assistant. All assessment staff will be required to observe the Principal Investigator administer the test twice and then administer the test twice themselves under the direct observation of the PI. All assessment staff will be blinded to treatment condition and supervised by the Principal Investigator. Assessments will be recorded to investigate inter-rater reliability. In addition to the pre- and post-treatment and follow-up assessments with the full battery, a brief assessment involving a few self-report measures (e.g., Depression Anxiety Stress Scales, Illness Intrusiveness Rating Scale, and State-Trait Inventory for Cognitive and Somatic Anxiety) will be completed biweekly to monitor symptoms during the course of treatment.

Albany Panic and Phobia Questionnaire (APPQ). The APPQ is a 27-item self-report measure that assesses agoraphobia, social anxiety, and interoceptive avoidance. Each subscale has been shown to have good internal consistency (αs > .85) and temporal stability (rs > .87).

Anxiety Disorder Interview Schedule-5 (ADIS-5). The ADIS-5 is a well-established, semi-structured interview designed to assess a wide range of Axis I disorders. The ADIS-5 assesses current and past diagnoses with DSM

diagnostic criteria, severity scores, and lists of feared and avoided situations for the anxiety disorders. The ADIS has demonstrated excellent inter-rater reliability and validity of depressive/anxiety disorder diagnoses.

Depression Anxiety Stress Scales 21-Item Version (DASS). The DASS is a 21-item measure with three subscales designed to assess dysphoric mood, fear and autonomic arousal, and tension and agitation. The factor structure, reliability, and validity of the subscales have been supported in the literature. The DASS scales also have demonstrated excellent convergence with similar measures of depression and anxiety and high internal consistency (α > .85).

Illness Intrusiveness Ratings Scale (IIRS). The IIRS is a 13-item questionnaire that assesses the extent to which a disease interferes with important domains of life, including health, diet, work, and several others. Each item is rated on a 7-point Likert scale, ranging from 1 to 7, and summed to compute the scale score. The IIRS has been shown to have high internal consistency in the previous literature and present study (α = .88).

Multidimensional Assessment of Social Anxiety (MASA). The MASA is a 38-item self-report measure that was designed to assess trait symptom dimensions consistent with the hybrid model of social anxiety. The psychometric properties of the MASA are supported in the literature, including its factor structure, convergent and discriminant validity, test-retest reliability, and internal consistency. The internal consistency was found to be acceptable for each of the scales in the present study (αs > .71).

Mini International Neuropsychiatric Interview (MINI). The MINI is a structured diagnostic interview designed to provide a brief, but accurate, assessment of a wide range of Diagnostic and Statistical Manual (DSM-IV) psychiatric disorders, including the mood disorders, anxiety disorders, and substance use disorders. The MINI has demonstrated adequate inter-rater and test-retest reliability across most disorders, and specifically has shown good inter-rater reliability with a GAD SCID diagnosis (κ = 0.7). DSM-IV diagnostic criteria, including hierarchy rules, were used to establish diagnoses.

PTSD Checklist (PCL). The PCL is a 17-item measure designed to assess PTSD symptom severity related to military/combat-related trauma. Respondents are presented with 17 specific symptoms of PTSD and asked to rate "how much you have been bothered by that problem in the last month" on a 5-point Likert scale, ranging from 1 (not at all) to 5 (extremely). The PCL has been shown to have excellent internal consistency in veterans, victims of motor vehicle accidents, and sexual assault survivors (αs > .94) and excellent test-retest reliability in veterans (r = .96). In addition, the PCL has demonstrated excellent convergent validity with alternative measures of PTSD (rs range from .77 to .93). Due to the PCL's focus on DSM-IV diagnostic criteria, a revised PCL for DSM-5 criteria will be included when made available by the authors.

Satisfaction with Therapy and Therapist Scale – Revised (STTS-R). The STTS-R assesses patients' level of satisfaction with their therapeutic experiences. The STTS-R contains 12 items that represent two subscales: satisfaction with therapy and satisfaction with therapist. The measure has been investigated in a large sample of patients receiving group CBT for depressive/anxiety disorders. The two subscales have demonstrated excellent internal consistency (αs > .88) and high positive correlations with indicators of successful treatment outcome.

State-Trait Inventory for Cognitive and Somatic Anxiety – Trait Version (STICSA-Trait). The STICSA-Trait is a 21-item measure that assesses trait cognitive and somatic anxiety. The cognitive and somatic subscales have been supported in the literature and both subscales have high internal consistency (αs > .87). In addition, the STICSA-Trait scale was found to remain stable over repeated administrations during several stress manipulations (rs > .65).

Veterans Short-Form Health Survey (V/SF-36). The V/SF-36 is a 36-item measure designed to assess functional health, well being, and quality of life in Veterans, and can be scored to produce two primary subscales for physical health and mental health. The V/SF-36 was adapted from the original SF-36, which has received extensive support in the literature.

Post-treatment Participant Interviews (immediate post-treatment & 6-month follow-up)

It is essential that the transdiagnostic CBT is agreeable to VAMC patients. Thus, structured interviews will be completed with participants at post-treatment and 6-month follow-up to evaluate the presentation, format, and active components of the treatment. The two time points will assess participants immediate (post-treatment) and

delayed (6-month follow-up) reactions to treatment. The interview methodology allows for the acquisition of data through open discussion of predetermined topics as facilitated by the interviewer. Interviews will be conducted by the Project Research Assistant and will follow pre-determined areas of discussion. The discussion will use open-ended questions, including follow-up probes and examples. These 30-60 minute interviews will be completed with all participants that completed the treatment in the transdiagnostic CBT condition. Interviews will be audio recorded for transcription and interviewers also will keep notes on the discussion.

The following are elicitation questions that will be discussed in the interviews:

1. What did you think about the treatment? What do you like about it? What don't you like?
2. What aspects of the treatment did you find to be most helpful and why?
3. Would you recommend this treatment to other Veterans with similar problems with anxiety/depression? If so (or if not), why?
4. Are there any additional things that should be included in the treatment that were not discussed?

At the completion of the interviews, all audio recordings and facilitator notes will be transcribed by the project staff. The overarching goal of the analysis of these data is to identify a set of thematic categories and to assign these categories to higher-order categories to provide a clear picture of the data. Multiple steps will be involved in the analysis of the data:

1. *Narrative descriptions.* Specific sections and quotes from the narratives will be carefully selected as exemplars of the content to characterize the general feel of the data.
2. *Content analysis.* This step involves the identification of relevant examples, themes, and patterns in the data. The data will be organized and reviewed by the project team to first develop thematic categories for the relevant quotes and then eventually come to consensus about the themes. The content analysis is based the expectation that important insights will emerge through the evaluation from several different perspectives.
3. *Inductive analysis.* The project team will further group the identified themes into categories that are based on information that was obtained from participants (indigenous typologies) and categories observed by the project staff, but not directly articulated by participants (analyst-constructed typologies).
4. *Logical analysis.* Cross-classification process/outcomes matrices will be developed from the categories developed in the previous steps.

Payment to Participant:
Participants will be compensated $10 for completing the self-report questionnaire packet and $10 for completing the interviews for each of the 3 assessment periods (pre-treatment, immediate post-treatment, 6-month post-treatment) for a total of $60. Payment is not contingent on completing the entire questionnaire packet and/or interview; rather, participants still will be compensated $10 if they begin either the questionnaire packet or the interviews but choose not to complete them fully. A check will be mailed to the address provided by participants after they complete each phase of the assessment (pre-treatment, immediate post-treatment, 6-month post-treatment). This process will likely take appropriately 30-60 days.

Data Entry and Management
All data collected for this study will be specifically collected for research purposes and will not be used for any other purpose. The study database will be maintained in a password-protected system with access limited to authorized members of the research team. Other authorized persons, such as regulatory authorities, also may have access to these records. Regarding security, data will be stored on computers that are password protected, on a secure VAMC server, behind the VAMC firewall, and access is logged. All privacy obligations under the Health Insurance Portability and Accountability Act (HIPAA) will be met. During assembly of the final research database, all participants will be given a study identification. Participant information always will be treated as confidential. The study database will be maintained in a password-protected system with access limited to the Principal Investigator and/or authorized members of the research team.

Our software (logical) security policy has three main components: 1) VAMC standard antiviral protection; 2) password policies; and 3) additional level of firewall protection. The National DVA maintains firewall protection. The backup schedule at the RHJ VAMC consists of fully-verified daily backups. The backup tapes, which are in current rotation, are stored locally.

All data will be entered into an SPSS database. The SPSS database will be created by the Principal Investigator and research assistant will be responsible for all data entry. Data quality and consistency checks (e.g., data range checks) will be integrated as part of the data entry procedure. Data quality will be monitored and assured in several ways: 1) as reported; and 2) as entered into the study database. For the former, all hardcopy data forms will be visually inspected by project staff prior to data entry. Furthermore, a manual comparison of randomly selected data hardcopy forms with data output generated from the SPSS database will be performed, and consistency checks will be generated as part of routine data cleaning procedures. All hardcopies of the data files will be stored in a locked file cabinet behind a locked door in the PI's office at the RHJ VAMC (B530). Hardcopies of the data will be destroyed/shredded at five years after the completion of the study.

Analysis Plan – Treatment Outcome Symptomatology and Feasibility

Preliminary Descriptive Analyses

Univariate descriptive statistics and frequency distributions will be calculated as appropriate for all relevant variables to identify potential departures from distributional assumptions of proposed analyses. If necessary, appropriate data transformations will be applied, or alternative analysis procedures (e.g., nonparametric) will be used. Baseline values for demographic and symptom variables will be described via frequency distributions for categorical variables, measures of central tendency (mean, median), and variability for the total sample and within race groups. The baseline variables will be compared between intervention groups using t-tests (or Wilcoxon rank sum tests) for continuous outcomes and chi-square (or Fisher's Exact Test) for categorical variables.

Missing Data

The full intent to treat (ITT) analysis set will comprise all randomized participants. Missing data in the full analysis set will occur if participants drop out prior to the end of the study. Participants will not be discontinued from the study because of non-adherence and all will remain in the study unless consent is withdrawn or if there are concerns regarding participant safety. Missing data for the ITT analysis set will be imputed using multiple imputation methods. The results of analyses using study completers and protocol adherers (completer and per-protocol analyses) will be compared with results using the ITT analysis set to test sensitivity of study conclusions to study drop-outs and protocol non-adherence. In addition, the information on dropout proportion will be used as one of the outcome measures of intervention feasibility.

Efficacy (Symptomatology & Quality of Life) Measures Analyses (Primary Aim 1)

The continuous measures of intervention efficacy and quality of life are APPQ, DASS, IIRS, MASA, PCL, STICSA, and V/SF-36. The primary outcome time point is at the end of the active intervention phase (immediate post-treatment) and the secondary time point is at the end of the naturalistic 6-month follow-up period. The difference in mean change from baseline to end-of-active intervention (effect sizes) for transdiagnostic CBT versus BAT control condition will be estimated via 95% CI. For the secondary time-point analyses, transdiagnostic CBT versus BAT control differences in change from immediate end-of-intervention to the 6-month follow-up will also be estimated using 95% CI. By assessing the magnitude of the between-intervention-group differences, as described by the CI, clinicians can judge whether the novel intervention provides sufficient improvement in these outcomes to suggest a clinically significant result that warrants further investigation.

In preliminary hypothesis testing, efficacy outcome variables will be compared using the generalized linear mixed models (GLMM) approach. This approach provides a general framework that accommodates a wide range of data types (continuous, ordinal, dichotomous, categorical, count) and distributional assumptions (e.g. Gaussian, Binomial, Poisson) and accommodates repeated measures, covariate structure among repeated observations, and missing data. In the first set of primary hypothesis testing analyses, immediate post-treatment scores for each outcome of interest will be used (separately) as the dependent variable in the model, intervention (transdiagnostic CBT versus BAT control) will be included as the primary independent variable, and pre-treatment scores for the outcome of interest will be added as covariates. When approximate normality is assumed, GLMM reduces to a general linear models (GLM) approach which, in the simplest case (intervention as the primary independent variable with baseline level of outcome variable as covariate), is equivalent to a comparison of change from baseline scores for transdiagnostic CBT versus BAT control using an independent sample t-test. Additional covariates (e.g. age, number of psychiatric comorbidities, race, sex, combat theatre, and number of treatment sessions) will be added to the model to adjust for putative confounding variables. If intervention differences in other baseline variables are found in initial descriptive analyses, these variables will be also be added to the multivariable model. In secondary analyses, the modeling procedure will be repeated for the period between immediate post-treatment and 6-month follow-up. Given that we are seeking preliminary evidence of treatment

efficacy (to justify the next step in this line of research), there will be no adjustment for multiple outcomes or time points to avoid an overly conservative approach at this preliminary stage.

Feasibility and Acceptability Analyses (Primary Aim 2)
Measures of feasibility and acceptability are dropout proportions (dropout y/n), proportion of sessions attended, proportion of homework assignments completed, and patient satisfaction scores on the STTS-R. 95% CI for proportions will be used to estimate the proportion of participants who exit the study prematurely (drop out) within each intervention group and the difference in dropout proportions between the intervention groups. For the treatment satisfaction and adherence outcomes (STTS-R, proportion of missed sessions or homework assignments), the median and mean responses will be obtained within and between each intervention group. 95% CI for difference in means will be used to estimate the between intervention differences in treatment satisfaction (mean STTS-R) and adherence (e.g. average proportion of missed sessions or homework assignments) for the transdiagnostic CBT versus BAT control conditions. Frequency distributions describing the participants' reasons for noncompliance and discontinuation of participation will be developed.

The GLMM modeling framework described for Primary Aim 1 will be used to compare the effect of transdiagnostic CBT versus BAT control on treatment satisfaction, retention (dropout), and treatment adherence (% missed sessions, % homework completion) . Dropout proportions (dichotomous outcome) and % of missed visits and % homework completion will be compared between the intervention groups using GLMM, with logistic/binomial regression analyses as special cases for dichotomous and percentage outcomes; STTS-R will be modeled as a continuous outcome using an appropriate link function. We also will model the longitudinal profile of adherence as a dichotomous outcome at each visit (e.g. attended/did not attend a given session). This will allow us to evaluate the trends in session attendance and to determine if the trends differ by intervention (e.g. whether the probability of missing visits is less/greater at earlier or later time points).

Exploratory Analyses – Diagnostic Groups
Exploratory analyses using GLMM modeling, as described above, will be carried out to determine if there is a preliminary suggestion that the effect of the intervention on efficacy and acceptability outcomes differ by principal diagnosis. For these analyses, a diagnosis by intervention group interaction term will be included in the model. Trends toward significance for the diagnosis by intervention interaction term would provide suggestive evidence of a possible differential diagnosis effect, suggesting that the change in the outcome variable is different for disorder groups (e.g., depressive disorders versus anxiety disorders) or between specific disorders (e.g., PTSD versus MDD). It is acknowledged that this study may not be powered to fully evaluate the statistical significance of the diagnostic comparisons; however, for this preliminary study, trends toward statistical significance are sought for future hypothesis-driven study in a larger adequately powered trial, rather than confirmation of a hypothesized differential diagnosis effect. Similar exploratory analyses will be completed for race and combat theatre.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Risks to the Subjects

Participants will include 96 VAMC patients in the mental health service. The inclusion criteria are that participants must: 1) be an adult (18 – 80 years old), 2) be competent to provide informed consent for research participation, 3) be diagnosed with an depressive/anxiety disorder as determined by a semi-structured diagnostic assessment (ADIS-5) at pre-treatment assessment, and 4) be able to commute to the RHJ VAMC for weekly appointments, immediate post-treatment assessment, and a follow-up assessment at 6-months post-treatment.

Several exclusion criteria exist for the proposed investigation, including 1) recent history ($\leq$ 2 months) of psychiatric hospitalization or a suicide attempt as documented in their medical record, 2) current diagnosis of substance dependence or abuse on the structured clinical interview, 3) acute, severe illness or medical condition that likely will require hospitalization and/or otherwise interfere with study procedures as documented in their medical record (e.g., active chemotherapy/radiation treatment for cancer, kidney dialysis, oxygen therapy for chronic obstructive pulmonary disease), 4) recent start of new psychiatric medication ($\leq$ 4 weeks), 5) diagnosis of traumatic brain injury in their medical record and/or endorsement of screener questionnaire regarding the symptoms of TBI modified from the Post-Deployment Health Assessment employed by the Department of Defense, or 6) diagnosis of schizophrenia, psychotic symptoms, personality disorder, and/or bipolar disorder.

VAMC patients excluded due to these factors will be reconsidered for participation once the condition related to their exclusion is resolved or stabilized.

Targeted/Planned Enrollment Table

Total Planned Enrollment 96

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	2	6	8
Not Hispanic or Latino	22	66	88
Ethnic Category: Total of All Subjects*	24	72	96
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	5	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	25	34
White	14	42	56
Racial Categories: Total of All Subjects*	24	72	96

b. Sources of Materials

All participants will randomized into either a transdiagnostic CBT psychosocial treatment for the depressive/anxiety disorders or the comparison evidence-based CBT, Behavioral Activation Treatment (BAT), control condition. The transdiagnostic CBT is a variation of pre-existing psychosocial treatments that are regularly administered at the VAMC and will involved 12-16 weekly 45-60-minute individual therapy appointments. The protocol for the BAT condition will be consistent with approaches that have been shown to be effective in the past literature. Throughout the course of treatment, a multi-method assessment of psychosocial factors and quality of life will be completed for all participants, involving 1) treatment credibility and satisfaction, 2) treatment retention and adherence, 3) clinical symptomatology including anxiety, depression, and impairment, and 4) general feedback on treatment process. Participants will be paid $10 for completing the self-report questionnaires and an additional $10 for the completion of the ADIS-5 for a possible combined total of $60. In addition to the pre-treatment, immediate post-treatment, and 6-month follow-up assessments with the full battery, a brief assessment involving a few self-report measures (e.g., DASS, IIRS, & STICSA) will be completed biweekly to monitor symptoms during the course of treatment.

1. *Demographic Information*: Age, race, sex, education, employment, and combat experience will be collected via a study specific demographic form.

2. *Albany Panic and Phobia Questionnaire.* The APPQ is a 27-item self-report measure that assesses agoraphobia, social anxiety, and interoceptive avoidance. Each subscale has been shown to have good internal consistency (αs > .85) and temporal stability (rs > .87).

3. *Anxiety Disorder Interview Schedule-5.* The ADIS-5 is a well-established, semi-structured interview designed to assess a wide range of Axis I disorders. The ADIS-5 assesses current and past diagnoses with DSM diagnostic criteria, severity scores, and lists of feared and avoided situations for the anxiety disorders. The ADIS has demonstrated excellent inter-rater reliability and validity of depressive/anxiety disorder diagnoses. The ADIS-5 is currently in press and so an editor's copy provided in the appendix (with editor's comments). The PHI (e.g., name, address, contact information, DOB) on the demographics cover page (page 1) will be removed in the study copy.

4. *Depression Anxiety Stress Scales 21-Item Version.* The DASS is a 21-item measure with three subscales designed to assess dysphoric mood, fear and autonomic arousal, and tension and agitation. The factor structure, reliability, and validity of the subscales have been supported in the literature. The DASS scales also

have demonstrated excellent convergence with similar measures of depression and anxiety and high internal consistency (α > .85).

5. *Illness Intrusiveness Ratings Scale.* The IIRS is a 13-item questionnaire that assesses the extent to which a disease interferes with important domains of life, including health, diet, work, and several others. Each item is rated on a 7-point Likert scale, ranging from 1 to 7, and summed to compute the scale score. The IIRS has been shown to have high internal consistency in the previous literature and present study (α = .88).

6. *Multidimensional Assessment of Social Anxiety*. The MASA is a 38-item self-report measure that was designed to assess trait symptom dimensions consistent with the hybrid model of social anxiety. The psychometric properties of the MASA are supported in the literature, including its factor structure, convergent and discriminant validity, test-retest reliability, and internal consistency. The internal consistency was found to be acceptable for each of the scales in the present study (αs > .71).

7. *Mini International Neuropsychiatric Interview.* The MINI is a structured diagnostic interview designed to provide a brief, but accurate, assessment of a wide range of Diagnostic and Statistical Manual (DSM-IV) psychiatric disorders, including the mood disorders, anxiety disorders, and substance use disorders. The MINI has demonstrated adequate inter-rater and test-retest reliability across most disorders, and specifically has shown good inter-rater reliability with a GAD SCID diagnosis (κ = 0.7). DSM-IV diagnostic criteria, including hierarchy rules, were used to establish diagnoses. The PHI (e.g., name and DOB) in the header will be removed in the study copy.

8. *PTSD Checklist*. The PCL is a 17-item measure designed to assess PTSD symptom severity related to military/combat-related trauma. Respondents are presented with 17 specific symptoms of PTSD and asked to rate "how much you have been bothered by that problem in the last month" on a 5-point Likert scale, ranging from 1 (not at all) to 5 (extremely). The PCL has been shown to have excellent internal consistency in veterans, victims of motor vehicle accidents, and sexual assault survivors (αs > .94) and excellent test-retest reliability in veterans (r = .96). In addition, the PCL has demonstrated excellent convergent validity with alternative measures of PTSD (rs range from .77 to .93). Due to the PCL's focus on DSM-IV diagnostic criteria, a revised PCL for DSM-5 criteria will be included when made available by the authors.

9. *Satisfaction with Therapy and Therapist Scale – Revised.* The STTS-R assesses patients' level of satisfaction with their therapeutic experiences. The STTS-R contains 12 items that represent two subscales: satisfaction with therapy and satisfaction with therapist. The measure has been investigated in a large sample of patients receiving group CBT for depressive/anxiety disorders. The two subscales have demonstrated excellent internal consistency (αs > .88) and high positive correlations with indicators of successful treatment outcome.

10. *State-Trait Inventory for Cognitive and Somatic Anxiety – Trait Version.* The STICSA-Trait is a 21-item measure that assesses trait cognitive and somatic anxiety. The cognitive and somatic subscales have been supported in the literature and both subscales have high internal consistency (αs > .87). In addition, the STICSA-Trait scale was found to remain stable over repeated administrations during several stress manipulations (rs > .65).

11. *Veterans Short-Form Health Survey.* The V/SF-36 is a 36-item measure designed to assess functional health, well being, and quality of life in Veterans, and can be scored to produce two primary subscales for physical health and mental health. The V/SF-36 was adapted from the original SF-36, which has received extensive support in the literature.

Participants will be asked to complete the assessment materials three times throughout the duration of treatment: pre-treatment, post-treatment and six-month follow-up.

c. Potential Risks

There is a potential psychological risk of emotional discomfort during the assessment and treatment procedures. Although this reaction is not uncommon in exposure-based treatments of anxiety and depression and typically is brief in its duration, there are several provisions to reduce and/or avoid it in the proposed study. First, the proposed treatment will be designed specifically to target the reduction of emotional distress, anxiety, and

avoidance. Second, if a participant expresses a desire to discontinue treatment due to distress and/or a study clinician determines that participation is counter-indicated, all research and treatment procedures will be terminated.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

VAMC patients will be recruited from within the Primary Care Mental Health Integration psychotherapy program and CBT Clinic at the RHJ VAMC. All eligible and willing VAMC patients will be required to meet with project staff to review the purpose of the study and review the consent documentation. VAMC patients will be given ample time to discuss the study and ask questions regarding the procedures. Upon thorough review of all documentation, VAMC patients will sign the informed consent document prior to participation in study procedures.

b. Protection against Risk

1. Participants will be made aware of the potential risks and benefits associated with participation and their right to withdraw from the study at any point without any negative impact on their care within the VAMC. Any participants expressing interest in withdrawing from the study will be referred for treatment within the VAMC.

2. Participants who appear unable to tolerate the assessment process will be offered a referral to the VAMC and terminated from the study procedures.

3. As a member of the mental health service at the VAMC, the Principal Investigator will maintain active collaborations and communications with other VAMC providers to ensure appropriate continuity of care and safeguard against any adverse events.

4. All assessors and treatment providers will be trained and supervised by the Principal Investigator, who is a licensed psychologist. At intake, participants identified by clinical interview with both suicidal ideation and acute intent will be excluded from the study and immediately offered emergency psychiatric care at the VAMC. During the duration of the study, the Principal Investigator immediately will contact the participant and assess suicide risk when any instance of suicide risk is identified. If suicidal ideation is present but not intent, the participant will be retained in the study and reassessed for suicide risk by the investigators in one week. In cases of acute suicidal intent, state law requires immediate hospitalization and these guidelines will be followed.

5. Treatment progress will be assessed throughout the active treatment phase through participant interactions with the project therapist as well as biweekly self-report measures of various psychiatric symptoms (e.g., DASS, IIRS, & STICSA). Participants who do not respond adequately to either treatment will be offered mental health treatment with an appropriate VAMC provider.

6. All adverse events associated will be reported to CSR&D program officers and relevant IRBs.

7. All participants will be informed if significant information is discovered about the treatment or if other more effective treatment interventions are discovered.

8. Published works or presentations will be limited to aggregate findings; individuals will not be mentioned or identified. All participants will be linked by their social security number and then assigned a research identification number to de-identify the master database for data analyses. Copies of research identification numbers and social security numbers will be stored separately as will consent documentation and assessment and treatment instruments. All paper materials will be stored in locked file cabinets. Access to all research records will be restricted to project staff.

9. All project staff will undergo training in the protection of human subjects, including the DVA's Good Clinical Practice and the Miami University CITI course.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There are several potential benefits of the proposed research. First and foremost, a large number of VAMC patients with depressive/anxiety disorders will participate in an evidence-based psychosocial treatment, resulting in reduced symptomatology and improved quality of life. Second and more broadly, a new transdiagnostic psychotherapy will be evaluated in VAMC patients with depressive/anxiety disorders that likely will improve access to these services in the VAMC system. Thus, the risk-benefit ratio is in favor of conducting this research.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Psychosocial treatments for the depressive/anxiety disorders are greatly limited in the DVA. The limitation may be a result of number of factors, including both VAMC provider and VAMC patient factors. Given the high prevalence of depressive/anxiety disorders in the DVA, the development and evaluation of a new treatment designed to treat VAMC patients with transdiagnostic presentations of depressive/anxiety disorders will represent an opportunity to improvement services and increase access for this population and outweigh the potential risks discussed above.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

The proposed investigation includes a clinical trial that involves the comparison of a newer evidence-based psychotherapy, transdiagnostic CBT, with an established evidence-based psychotherapy, BAT. Both treatment conditions involve active treatments have been shown to be effective in addressing symptoms in the selected disorders/population. Several steps were included in the proposed clinical trial for subject safety and minimizing risks of the research.

1. Treatment progress will be assessed throughout the active treatment phase (baseline to final session of psychotherapy) through participant interactions with the project therapist, self-monitoring and other between session exercises, biweekly self-report measures of various psychiatric symptoms (e.g., DASS, IIRS, & STICSA), and immediate post-treatment assessment. Participants who demonstrate worsening of symptoms at any point in treatment (i.e., 25% increase in symptom severity for two consecutive assessment points) or do not demonstrated any symptoms improvement at the midway point in treatment (session 8) will be offered alternative mental health treatments with appropriate VAMC providers. Similarly, alternative mental health treatments with appropriate VAMC providers will be offered at the 6-month follow-up assessment point to all participants, regardless of symptomatology.

2. During the active treatment phase, participants will be monitoring weekly during their psychotherapy appointments. Monitoring will involve interactions with the project therapist, self-monitoring and other between session exercises, and biweekly self-report measures of various psychiatric symptoms (e.g., DASS, IIRS, & STICSA).

3. Monitoring will be completed by the project therapist and reviewed by the Principal Investigator during weekly supervision meetings.

4. The study will be end at the completion of the 6-month follow-up assessment. Alternative mental health treatments with appropriate VAMC providers will be offered at the completion of the 6-month follow-up assessment point to all participants, regardless of symptomatology.

F. REFERENCES/LITERATURE CITATIONS

Barlow, D. H., Allen, L. B., & Choate, M. L. (2004). Toward a unified treatment for emotional disorders. *Behavior Therapy, 35*, 205-230.

Farchione, T. J., Fairholme, C. P., Ellard, K. K., Bosseau, C. L., Thompson-Hollands, J., Carl, J.R., et al. (2012). Unified Protocol for Transdiagnostic Treatment of Emotional Disorders: A randomized controlled trial. *Behavior Therapy, 43*, 666-678.

Norton, P. J. (2009). Integrated psychological treatment of multiple anxiety disorders. In M. M. Antony & M. B. Stein (Eds.), *Oxford handbook of anxiety and related disorders* (pp. 441-450). New York: Oxford University Press.

Norton, P. J,. (2012). A randomized clinical trial of transdiagnostic cognitive-behavioral treatments for anxiety disorders by comparison to relaxation training. *Behavior Therapy, 43*, 506-517.

Schmidt, N. B., Buckner, J. D., Pusser, A.,Woolaway-Bickel, K., Preston, J. L., & Norr, A. (2011). Randomized controlled trial of False Safety Behavior Elimination Therapy (F-SET): A unified cognitive behavioral treatment for anxiety psychopathology. *Behavior Therapy, 43*, 518-532.

G. CONSULTANTS

No consultants are involved in the management of the research project.

H. FACILITES AVAILABLE

The RHJ VAMC is located in downtown Charleston, SC adjacent to the MUSC campus. The RHJ VAMC is a primary, secondary, and tertiary referral medical center providing acute medical, surgical, and psychiatry inpatient care as well as primary care and specialized outpatient services. The primary service area extends from north of Myrtle Beach, SC to Hinesville, GA. For the most recent fiscal year, there were 875,731 total outpatient visits, with 46,812 of unique patients, for the combined medical center and six outpatient clinics. The RHJ VAMC operates community-based outpatient clinics (CBOCs) for Veterans in Myrtle Beach, SC, North Charleston, SC, Beaufort, SC, Goose Creek, SC, Savannah, GA, and Hinesville, GA.

The Mental Health Service Line (MHS) is charged with all aspects of clinical care, education, and research within mental health. Dr. Gros is a Staff Psychologist within the MHS with dedicated office space, support staff, and infrastructure. Dr. Gros also will have available the full range of resources associated with the MHS and associated programs. The resources of the MHS will be available to the Dr. Gros throughout the duration of the project. The MHS also includes the CBT Clinic and Primary Care – Mental Health Integration program, both of which Dr. Gros coordinates, that provide psychosocial and psychopharmacological treatments to over 300 Veterans with depressive and anxiety disorders each year. The Research Service at the RHJ VAMC is broad-based and has approximately 250 active research protocols being conducted by over 90 investigators. The Research Service is well integrated with clinical services at RHJ VAMC and coordinates research activities closely with MUSC. Additionally, the Charleston VA Office of Research, under ACOS, Dr. Rita Young, provides administrative support, including financial administration of projects, assistance with project budgets, advertising for and hiring new personnel, coordinating IPAs for MUSC employees, and ordering supplies.

I. INVESTIGATOR BROCHURE

n/a

J. APPENDIX

Each of the proposed self-report measures of psychiatric symptomatology were included below. The clinician rated structured clinical interviews will be uploaded separated due to an alternative file format (pdf).

Demographic Intake Questionnaire

Participant#: _____

Current Age: _____

For each of the questions below, please circle the answer that applies to you.

1. What is your racial or ethnic background?

1 White/Caucasian
2 Black/African American
3 Asian American
4 Hispanic
5 Native American
6 Other (Please list): _____

2. What is your sex/gender?

1 Male
2 Female

3. What is your relationship status?

1 Single (never married)
2 Single (previously married - separated, divorced, or widowed)
3 Married

4. What is your work status?

1 Unemployed/looking for work
2 Unemployed/retired (not actively looking for work)
3 Unemployed/disability (not actively looking for work)
4 Employed (part-time)
5 Employed (full-time)

5. What is your education history (highest level achieved)?

1 Did not graduate high school
2 High school diploma
3 Some college or 2-year college degree
4 4-year college degree
5 Post-graduate work or graduate degree

6. What is your disability status?

1 Not disabled (skipped to Question #7)
2 Disabled (go to Question #6b)

6b. If disabled through the Department of Veteran Affairs, please list percent of service connection: ____%_

6c. If disabled through the Department of Veteran Affairs, what type of disability are you connected for?
1 Physical health (e.g., diabetes, back injury, knee injury)
2 Mental health (e.g., PTSD, major depression, adjustment disorder)
3 Both physical and mental health

7. Which of the categories best describes your total annual combined income from all sources?

1 0 – < $20,000
2 $20,000 – < $40,000
3 $40,000 – < $60,000
4 $60,000 – < $80,000
5 $80,000 – < $100,000
6 > $100,000

8. Please circle which branch of the Armed Services that you participated in?

1 Army
2 Navy
3 Air Force
4 Marine Corps
5 Coast Guard

9. Please circle all of the combat theaters that you were deployed?

1 World War II
2 Korea
3 Vietnam
4 Desert Storm/Shield (First Gulf War)
5 OEF/OIF (Afghanistan/Iraq Wars)
6 Other (Please list): _____
7 None

10. Have you ever participated in combat (e.g., fired your weapon or fired upon)?

1 Yes
2 No

APPQ

Please rate, on the following scale, the amount of fear that you think you would experience in each of the situations listed below if they were to occur in the next week. Try to imagine yourself actually doing each activity and how you would feel.

Fear Scale:

0---------1---------2---------3---------4---------5---------6---------7---------8
No fear Slight Fear Moderate Fear Marked Fear Extreme Fear

1.	Talking to people	0	1	2	3	4	5	6	7	8
2.	Going through a car wash	0	1	2	3	4	5	6	7	8
3.	Playing a vigorous sport on a hot day	0	1	2	3	4	5	6	7	8
4.	Blowing up an airbed quickly	0	1	2	3	4	5	6	7	8
5.	Eating in front of others	0	1	2	3	4	5	6	7	8
6.	Hiking on a hot day	0	1	2	3	4	5	6	7	8
7.	Getting gas at a dentist	0	1	2	3	4	5	6	7	8
8.	Interrupting a meeting	0	1	2	3	4	5	6	7	8
9.	Giving a speech	0	1	2	3	4	5	6	7	8
10.	Exercising vigorously alone	0	1	2	3	4	5	6	7	8
11.	Going long distances from home alone	0	1	2	3	4	5	6	7	8
12.	Introducing yourself to groups	0	1	2	3	4	5	6	7	8
13.	Walking alone in isolated areas	0	1	2	3	4	5	6	7	8
14.	Driving on highways	0	1	2	3	4	5	6	7	8
15.	Wearing striking clothes	0	1	2	3	4	5	6	7	8
16.	Possibility of getting lost	0	1	2	3	4	5	6	7	8
17.	Drinking a strong cup of coffee	0	1	2	3	4	5	6	7	8
18.	Sitting in the center of a cinema	0	1	2	3	4	5	6	7	8
19.	Running up stairs	0	1	2	3	4	5	6	7	8
20.	Riding on a subway	0	1	2	3	4	5	6	7	8
21.	Speaking on the telephone	0	1	2	3	4	5	6	7	8
22.	Meeting strangers	0	1	2	3	4	5	6	7	8
23.	Writing in front of others	0	1	2	3	4	5	6	7	8
24.	Entering a room full of people	0	1	2	3	4	5	6	7	8
25.	Staying overnight away from home	0	1	2	3	4	5	6	7	8
26.	Feeling the effects of alcohol	0	1	2	3	4	5	6	7	8
27.	Going over a long, low bridge	0	1	2	3	4	5	6	7	8

DASS

Please read each statement and indicate the number which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement. The rating scale is as follows:

0 = Did not apply to me at all
1 = Applied to me to some degree, or some of the time
2 = Applied to me to a considerable degree, or good part of the time
3 = Applied to me very much or most of the time

1.	I found it hard to wind down.	0	1	2	3
2.	I was aware of dryness of my mouth.	0	1	2	3
3.	I couldn't seem to experience any positive feelings at all.	0	1	2	3
4.	I experienced breathing difficulty (e.g. excessive rapid breathing, breathlessness in the absence of physical exertion).	0	1	2	3
5.	I found it difficult to work up the initiative to do things.	0	1	2	3
6.	I tended to over-react to situations.	0	1	2	3
7.	I experienced trembling (e.g., in the hands).	0	1	2	3
8.	I felt that I was using a lot of nervous energy.	0	1	2	3
9.	I was worried about situations in which I might panic and make a fool of myself.	0	1	2	3
10.	I felt that I had nothing to look forward to.	0	1	2	3
11.	I found myself getting agitated.	0	1	2	3
12.	I found it difficult to relax.	0	1	2	3
13.	I felt down-hearted and blue.	0	1	2	3
14.	I was intolerant of anything that kept me from getting on with what I was doing.	0	1	2	3
15.	I felt I was close to panic.	0	1	2	3
16.	I was unable to become enthusiastic about anything.	0	1	2	3
17.	I felt I wasn't worth much as a person.	0	1	2	3
18.	I felt that I was rather touchy.	0	1	2	3
19.	I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat).	0	1	2	3
20.	I felt scared without any good reason.	0	1	2	3
21.	I felt that life was meaningless.	0	1	2	3

IIRS

The following items ask about how much your anxiety and/or depression interfere with different aspects of your life.

Not very much → → Very Much
1 2 3 4 5 6 7

1.	Health	1	2	3	4	5	6	7
2.	Diet	1	2	3	4	5	6	7
3.	Work	1	2	3	4	5	6	7
4.	Active Recreation	1	2	3	4	5	6	7
5.	Passive Recreation	1	2	3	4	5	6	7
6.	Financial Situation	1	2	3	4	5	6	7
7.	Relationship with your Spouse (girlfriend or boyfriend if not married)	1	2	3	4	5	6	7
8.	Sex Life	1	2	3	4	5	6	7
9.	Family Relations	1	2	3	4	5	6	7
10.	Other Social Relations	1	2	3	4	5	6	7
11.	Self-Expression/Self-Improvement	1	2	3	4	5	6	7
12.	Religious Expression	1	2	3	4	5	6	7
13.	Community and Civic Involvement	1	2	3	4	5	6	7

Multidimensional Assessment of Social Anxiety

For each question, please indicate the degree to which you feel the statement is generally characteristic or true of you.

1 = Not at all characteristic or true of me
2 = Slightly characteristic or true of me
3 = Moderately characteristic or true of me
4 = Very characteristic or true of me
5 = Extremely characteristic or true of me

1.	I feel dizzy when I am in a crowd of people.	1	2	3	4	5
2.	I have used drugs and/or alcohol to forget about my worries.	1	2	3	4	5
3.	My social anxiety is out of control.	1	2	3	4	5
4.	There are very few things that I enjoy doing.	1	2	3	4	5
5.	I distract myself when I start to think about things that bother me.	1	2	3	4	5
6.	I avoid speaking with people that I do not know.	1	2	3	4	5
7.	I get tension headaches before social situations.	1	2	3	4	5
8.	My anxiety has gotten in the way of my relationships.	1	2	3	4	5
9.	I try to avoid working on tasks when other people are around.	1	2	3	4	5
10.	I avoid talking to people in authority.	1	2	3	4	5
11.	I try to push upsetting thoughts away.	1	2	3	4	5
12.	I have missed work or school opportunities due to my anxiety.	1	2	3	4	5
13.	I have difficulty talking with people to whom I am attracted.	1	2	3	4	5
14.	I am disinterested in what people have to say.	1	2	3	4	5
15.	I avoid calling attention to myself in social situations.	1	2	3	4	5
16.	I have trouble asking others for help.	1	2	3	4	5
17.	I regularly try to block certain thoughts.	1	2	3	4	5
18.	I avoid performing in public (e.g., singing or dancing).	1	2	3	4	5
19.	I am rarely in a good mood.	1	2	3	4	5
20.	When I start experiencing negative thoughts, I try to distract myself.	1	2	3	4	5
21.	There is very little that gets me excited.	1	2	3	4	5
22.	I need several drinks of alcohol in order to go to a bar or club.	1	2	3	4	5
23.	I have no interest in being with others.	1	2	3	4	5
24.	I avoid talking about things that I do not know much about.	1	2	3	4	5
25.	I avoid speaking in front of groups of people.	1	2	3	4	5
26.	I do not expect anything exciting or pleasurable will happen to me.	1	2	3	4	5
27.	I would describe myself as unmotivated.	1	2	3	4	5
28.	My physical health has suffered due to my anxiety.	1	2	3	4	5
29.	I try to stay active to prevent my mind from wandering.	1	2	3	4	5
30.	My social anxiety prevents me from doing the things I want to do in my life.	1	2	3	4	5
31.	I frequently have to use drugs and/or alcohol to cope with my anxiety.	1	2	3	4	5

32. I often keep my hands in my pockets so people will not notice that they are trembling.	1	2	3	4	5
33. When I feel anxious in social situations, I fear that I might have a heart attack.	1	2	3	4	5
34. I avoid making eye contact with people that I do not know very well.	1	2	3	4	5
35. I avoid situations in which I might embarrass myself.	1	2	3	4	5
36. I try to keep socially anxious thoughts out of my head.	1	2	3	4	5
37. If I am thinking about something that I do not like, I immediately try to think of something else.	1	2	3	4	5
38. I tend to drink alcohol in social situations to help me cope with my anxiety.	1	2	3	4	5

PCL-S

Instructions: Below is a list of problems and complaints that people sometimes have in response to stressful life experiences. Please read each one carefully, then circle one of the numbers to the right to indicate how much you have been bothered by that problem IN THE PAST MONTH.

	Not at all	*A little bit*	*Moderately*	*Quite a bit*	*Extremely*
1. Repeated, disturbing *memories, thoughts, or images* of the stressful experience?	1	2	3	4	5
2. Repeated, disturbing *dreams* of the stressful experience?	1	2	3	4	5
3. Suddenly *acting or feeling* as if the stressful experience *were happening again* (as if you were reliving it)?	1	2	3	4	5
4. Feeling *very upset* when *something reminded you* of the stressful experience?	1	2	3	4	5
5. Having *physical reactions* (e.g., heart pounding, trouble breathing, sweating) when *something reminded you* of the stressful experience?	1	2	3	4	5
6. Avoiding *thinking about or talking about* the stressful experience or avoiding *having feelings* related to it?	1	2	3	4	5
7. Avoiding *activities or situations* because *they reminded you* of the stressful experience?	1	2	3	4	5
8. Trouble *remembering important parts* of the stressful experience?	1	2	3	4	5
9. *Loss of interest* in activities that you used to enjoy?	1	2	3	4	5
10. Feeling *distant or cut off* from other people?	1	2	3	4	5
11. Feeling *emotionally numb* or being unable to have loving feelings for those close to you?	1	2	3	4	5
12. Feeling as if your *future* somehow will be *cut short*?	1	2	3	4	5
13. Trouble *falling or staying asleep*?	1	2	3	4	5
14. Feeling *irritable* or having *angry outbursts*?	1	2	3	4	5
15. Having *difficulty concentrating*?	1	2	3	4	5
16. Being "*superalert*" or watchful or on guard?	1	2	3	4	5
17. Feeling *jumpy* or easily startled?	1	2	3	4	5

STICSA: Your General Mood State

Instructions

Below is a list of statements which can be used to describe how people feel. Beside each statement are four numbers which indicate how often each statement is true of you (e.g., 1 = not at all, 4 = very much so). **Please read each statement carefully and circle the number which best indicates how often, in general, the statement is true of you.**

	Not at all	A little	Moderately	Very much so
1. My heart beats fast	1	2	3	4
2. My muscles are tense	1	2	3	4
3. I feel agonized over my problems	1	2	3	4
4. I think that others won't approve of me	1	2	3	4
5. I feel like I'm missing out on things because I can't make up my mind soon enough	1	2	3	4
6. I feel dizzy	1	2	3	4
7. My muscles feel weak	1	2	3	4
8. I feel trembly and shaky	1	2	3	4
9. I picture some future misfortune.	1	2	3	4
10. I can't get some thought out of my mind.	1	2	3	4
11. I have trouble remembering things	1	2	3	4
12. My face feels hot	1	2	3	4
13. I think that the worst will happen	1	2	3	4
14. My arms and legs feel stiff	1	2	3	4
15. My throat feels dry	1	2	3	4
16. I keep busy to avoid uncomfortable thoughts	1	2	3	4
17. I cannot concentrate without irrelevant thoughts intruding	1	2	3	4
18. My breathing is fast and shallow.	1	2	3	4
19. I worry that I cannot control my thoughts as well as I would like to	1	2	3	4
20. I have butterflies in the stomach.	1	2	3	4
21. My palms feel clammy	1	2	3	4

The Satisfaction With Therapy and Therapist Scale—Revised (STTS–R)

Please circle the number that best describes your opinion of your satisfaction with the therapy and therapists ( ) you attended/completed treatment with recently.

Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
1	**2**	**3**	**4**	**5**

1.	I am satisfied with the quality of the therapy I received.	1	2	3	4	5
2.	The therapist listened to what I was trying to get across.	1	2	3	4	5
3.	My needs were met by the program.	1	2	3	4	5
4.	The therapist provided an adequate explanation regarding my therapy.	1	2	3	4	5
5.	I would recommend the program to a friend.	1	2	3	4	5
6.	The therapist was not negative or critical towards me.	1	2	3	4	5
7.	I would return to the clinic if I needed help.	1	2	3	4	5
8.	The therapist was friendly and warm towards me.	1	2	3	4	5
9.	I am now able to deal more effectively with my problems.	1	2	3	4	5
10.	I felt free to express myself.	1	2	3	4	5
11.	I was able to focus on what was of real concern to me.	1	2	3	4	5
12.	The therapist seemed to understand what I was thinking and feeling.	1	2	3	4	5

How much did this treatment help with the specific problem that led you to therapy?

1	2	3	4	5
Made things a lot better	Made things somewhat better	Made no difference	Made things somewhat	Made things a lot