Comparing Individual Therapies for Veterans with Depression, PTSD, and Panic Disorder

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A. SPECIFIC AIMS

Cognitive behavioral therapy (CBT) is robustly effective in treating Veterans with depressive/anxiety disorders (Butler et al., 2006; Hofmann et al., 2012). CBT also is brief and cost-effective, and promotes recovery by protecting against relapse (Hofmann et al., 2012). However, access to specialized CBT by Veterans is limited, in part, because the sheer number of different CBT protocols for specific disorders limits the extent to which providers can receive training in, and subsequently deliver each of these interventions with a high level of fidelity and competence (Barlow et al., 2004; Gros et al., 2016). Most CBT protocols also are limited as disorder-specific therapies (DSTs), focusing solely on a specific set or class of symptoms and therefore limited in their coverage of psychiatric comorbidity and cooccurring symptomatology and related impairments. Together, this state of affairs suggests that there are unique opportunities to enhance outcomes and recovery in Veterans within the VA through recent innovations in CBT.

In contrast to the multiple, expensive provider trainings necessary for the DSTs and the DSTs' limited coverage of comorbid symptoms and related symptom severity and impairments, a shift to transdiagnostic CBT practices for Veterans with depressive/anxiety disorders would eliminate much of the unnecessary procedures, time commitment, and financial burden from DVA providers, as well as provide superior coverage of comorbid presentations and related symptom severity and impairments in Veterans. Transdiagnostic Behavior Therapy (TBT) is a transdiagnostic psychotherapy that was designed in the VA to address psychiatric symptomatology and related impairments in Veterans, without limiting treatment to a single psychiatric diagnosis as is standard practice in the field (Gros, 2014; Gros et al., 2016). TBT was developed as a 12-session psychotherapeutic treatment, that can be delivered effectively to Veterans with depressive/anxiety disorders, including posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) (Gros, 2014). Initial studies of TBT evidence that the treatment is effective in reducing psychiatric symptomatology and related impairments across disorder presentations and comorbidities (Gros, 2014). These studies include a funded CSR&D Career Development Award (CDA) that involved a small randomized controlled trial (RCT) comparing TBT and behavioral activation. In addition to contributing to the mounting evidence for the efficacy of TBT, the CSR&D CDA project also demonstrated significantly improved treatment effects for symptoms of depression and anxiety in Veterans with depressive/anxiety disorders receiving TBT as compared to behavioral activation. Together, these findings demonstrate the promise of TBT as an efficacious treatment in terms of clinical outcomes, feasibility, and acceptability, as well as ease of dissemination and implementation (Gros et al., 2017a).

The primary goal of the proposed study is to compare TBT and matching DSTs in a large, randomized investigation in a Veteran sample via a non-inferiority design. The study will use a repeated measures RCT design to compare TBT to DSTs in 306 Veterans with PTSD, MDD, panic disorder and/or agoraphobia (PD/AG) and related symptoms of depression/anxiety and impairments. DSTs will be matched to participants' targeted diagnosis (e.g., Cognitive Processing Therapy for PTSD, CBT for MDD, and CBT for PD/AG). Assessments of disorder-specific symptomatology, as well general symptoms of the depressive/anxiety disorders and related impairments, will be used due to the transdiagnostic approach and related research aims of the proposed study. Assessments will be completed at baseline, mid-treatment, immediate post-treatment, and 6-month post-treatment follow-up. Process variables (satisfaction, attendance, discontinuation rates) also will be recorded.

Primary Aim: To examine efficacy of TBT on improving psychiatric symptomatology and related impairments in Veterans with depressive/anxiety disorders compared to DSTs.

Hypothesis: TBT will result in non-inferior improvements in psychiatric symptomatology, as assessed by the PTSD Checklist for PTSD, PHQ-9, Panic Disorder Severity Scale for PD/AG, and transdiagnostic anxiety on the State Trait Inventory for Cognitive and Somatic Anxiety and transdiagnostic impairment on the Illness Intrusiveness Rating Scale, compared to the DST control conditions.

Secondary Aim: To examine feasibility and acceptability of TBT

Hypothesis: TBT will be well tolerated by Veterans as demonstrated by improved attendance (number of weeks to complete treatment), treatment discontinuation rates (yes/no), and patient satisfaction questionnaires, as assessed by the Satisfaction with Therapy and Therapist Scale – Revised, as compared to the DSTs.

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 returned home with psychiatric disorders and related symptomatology post-deployment, resulting in functional and social impairments as well as reduced quality of life (Hoge et a., 2004; Thomas et al., 2010). As a result, the Department of Veterans Affairs (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. Although coverage is improving (FY 2004, 21%; FY 2007, 22%; and FY 2010, 27%), this volume of new patients is making it difficult for the DVA to provide high quality psychosocial treatments for mental health concerns (Cully et al., 2008; Mott et al., 2014).

One priority area is the treatment of depressive/anxiety disorders and their related impairments, representing the most common psychiatric disorders in the United States (prevalence: 28% past year; 49% lifetime) (Kessler et al., 2005a; 2005b; Magruder et al., 2005). The category of depressive/anxiety disorders includes PTSD, MDD, and PD/AG, as well as several others. These disorders are associated with severe occupational, educational, and social impairment, as well as elevated risk for cardiovascular disease, suicide, substance use, and increased difficulties with pain management in Veteran and civilian populations (Barlow, 2002). 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 (Marshall et al., 2000). There are high rates of comorbidity within the depressive/anxiety disorders, and the diagnostic (and hence treatment) distinction between disorders is not routinely reliable (Kessler et al., 2005b; Magruder et al., 2005).

Cognitive behavioral therapy (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 (Butler et al., 2006; Hofmann et al., 2012). Although CBT is a short-term intervention, the benefits of CBT typically persist following the termination of treatment (Hofmann et al., 2012), with long term studies demonstrating maintenance of treatment effects at least two years after treatment ends (Bruce et al., 1999). Another benefit of CBT is its impact on the financial burden associated with the depressive/anxiety disorders. Psychosocial interventions, including CBT, significantly reduce the treatment utilization and long-term medical costs in patients with depressive/anxiety disorders (Tuerk et al., 2013).

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 DSTs, representing a major obstacle to providers through separate manuals and workbooks for each disorder, each with significant direct costs and time and training requirements (Gros et al., 2016). In addition, indirect costs also can be a significant hurdle for both providers and facilities (e.g., loss of revenue during training activities). Only a few 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; $3000 direct cost estimate per workshop). Similar concerns have been expressed by the DVA leadership involved in CBT dissemination efforts, despite direct costs being covered by the DVA (Ruzek et al., 2012). Added to these limitations is that most DSTs are focused solely on the most common symptoms for the specific disorder targeted (e.g., worry in GAD, situational avoidance in PD/AG, compulsive symptoms in OCD) (Butler et al., 2006). However, comorbidity is a more common presentation than single diagnoses lacking comorbidity and is associated with significantly greater

symptom severity and related impairment (Gros et al., 2012). Together, these findings suggest that DSTs may not be best-suited to treat the wide range of symptoms, comorbid presentations, and related impairments in Veterans with depressive/anxiety disorders.

In contrast to the multiple lengthy and expensive provider trainings necessary for the DSTs and the DSTs' limited coverage of comorbid symptoms and related impairments, a shift to transdiagnostic CBT practices for Veterans with depressive/anxiety disorders would eliminate much of the unnecessary procedures, time commitment, and financial burden from therapists and the DVA, as well as provide superior coverage of comorbid presentations and related symptom severity and impairments. Transdiagnostic treatments are based on the notion that various DSTs contain *important but overlapping* treatment components that can be distilled into a single treatment, thereby addressing 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 many overlapping symptoms and related components of CBT exist. These techniques are based on the same theories, guided by the same principles, and thus, are nearly identical across each of the DSTs.

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 DSTs. 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 to address the cross-cutting/overarching symptoms most related to increased symptoms severity and functional impairment. Transdiagnostic treatments also 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 and related symptom severity and impairments without requiring providers to successfully identify and implement multiple treatment protocols.

A small number of transdiagnostic treatment approaches have been developed and studied for patients with the depressive/anxiety disorders (Andersen et al., 2016; Norton & Paulus, 2016), with preliminary outcomes demonstrating moderate-to-high treatment effect sizes (Barlow et al., 2017; Farchione et al., 2012; Gros, 2014; Norton, 2012; Norton & Barrera, 2012; Schmidt et al., 2012). As reviewed by Andersen et al. (2016), transdiagnostic CBT protocols evidenced similar outcomes to the active comparison treatments across three studies, while providing potential benefits in terms of provider training (Barlow et al., 2017; Norton, 2012; Norton & Barrera, 2012). However, one particularly relevant difference between the most studied transdiagnostic protocols is their coverage of the various depressive/anxiety disorders. In terms of their potential benefits for reduced provider trainings and improved coverage of comorbid symptoms compared to disorder-specific protocols (Barlow et al., 2004; Gros et al., 2016), a transdiagnostic protocol covering a wider range of diagnoses would provide superior benefits over protocols covering fewer diagnoses.

One transdiagnostic CBT protocol, Transdiagnostic Behavior Therapy (TBT), was developed for and evaluated in Veterans within a VA setting as well as in Veterans with DSM-5 anxiety disorders, PTSD, and MDD (Gros, 2014). TBT was designed to address overall psychiatric symptomatology and comorbidity in Veterans, without limiting treatment to a single psychiatric diagnosis or set of symptoms (Gros, 2014; Gros et al., 2016). Initial pilot studies of TBT have shown the treatment to be effective in reducing symptoms of depression, anxiety, stress, and PTSD, as well as improving impairment across multiple domains of functioning, in Veterans with various depressive/anxiety disorders and related comorbidities (Gros, 2014). Of note, these preliminary findings for TBT contributed to the funding of a CSR&D Career Development Award (CDA) award for Dr. Gros to further the study of TBT via a small randomized controlled trial (RCT) comparing TBT to one specific DST across disorders. An additional study recently demonstrated the ease of dissemination to VA providers and implementation to VA patients of TBT (Gros et al., 2017). The findings from these and other newer studies are described in detail in Preliminary Studies section.

The proposed investigation seeks to study TBT in Veterans with MDD, PTSD, and PD/AG. The primary goal of the proposed study is to compare TBT to DSTs in an RCT to investigate the potential benefits of TBT in addressing psychiatric symptomatology and severity, comorbidity, and impairment in Veterans with depressive/anxiety disorders and related conditions/symptoms. In contrast to the CDA RCT of TBT that included a single control DST and a smaller sample size, the proposed study will match DSTs for each of the recruited diagnoses to provide a fuller and more accurate comparison between TBT and DSTs. If efficacious, TBT will have the potential to improve psychiatric symptomatology, comorbidity, and related severity and impairment, and

reduce VAMC provider-training burden and associated costs and therefore improve the quality of care and access provided to Veterans with depressive/anxiety disorders by further improving access to CBT.

C. PRELIMINARY STUDIES

Table 1: How to Interpret the Scores on the Measures

Scale	Items (Score Range)	Mild	Moderate	Severe	Diagnostic
IIRS-Impairment	13 (13-91)	-	-	-	52.2 – 59.0
PTSD Checklist	17 (17-85)	-	-	-	50
PTSD Checklist – 5	20 (0-80)	-	-	-	33
DASS-Depression	7 (0-21)	5-6	8-10	10-14	-
DASS-Anxiety	7 (0-21)	4-5	5-7	9-13	-
DASS-Stress	7 (0-21)	7-9	9-13	13-16	-

Note. Interpretation scores based upon available review papers on each of the measures. Diagnostic refers to the "cut score" recommended for the diagnosis (e.g., PTSD diagnosis for PTSD Checklist) or range of scores expected for an individual with a diagnosis (e.g., diagnosis of an anxiety disorder for IIRS).

Initial Pilot of TBT Protocol

A VAMC Research and Development (R&D) and Medical University of South Carolina (MUSC) Institutional Review Board (IRB) approved pilot project was completed in Veterans with depressive/anxiety disorders and related comorbidities to assess feasibility and efficacy of TBT (Gros, 2014). The trial involved an initial evaluation, revision/refinement of the protocol, and then a second evaluation of the revised version. In the first trial, 15 Veterans were recruited to complete the treatment. All participants were diagnosed with multiple comorbid depressive/anxiety disorders, and reported severe, pre-treatment symptoms of anxiety and depression. Twelve of the fifteen participants finished TBT (80.0%). Treatment completers attended an average of twelve 50-minute sessions. As presented in Table 2, participants demonstrated significant improvements in symptoms across all disorders and comorbidities.

Table 2: Efficacy of Initial TBT Protocol in Veterans with Depressive/Anxiety Disorders

Scale	Pre *M (SD)*	Post *M (SD)*	*t* (*p*)	*d*
IIRS-Impairment	**66.0 (14.9)**	**41.2 (19.8)**	**6.4 (< .001)**	**1.42**
PTSD Checklist	56.1 (13.1)	37.0 (14.0)	5.6 (< .01)	1.41
DASS-Depression	13.1 (5.4)	5.2 (5.2)	5.3 (< .001)	1.51
DASS-Anxiety	12.6 (5.4)	5.9 (4.6)	5.5 (< .001)	1.35
DASS-Stress	13.2 (5.4)	7.9 (4.8)	3.6 (< .01)	1.04

Results from the initial pilot project were used to inform minor revisions of the TBT protocol. The revisions involved further focusing the TBT protocol on a transdiagnostic behavioral approach (i.e., exposure therapy), and relegating other CBT techniques to secondary/optional modules that could be provided later in treatment, if needed to improve exposure success (Gros, 2014). In the second trial, 29 Veterans were recruited and all participants were diagnosed with multiple comorbid depressive/anxiety disorders and reported severe pre-treatment symptoms and impairment. The 21 participants completed treatment (72.4%). As presented in Table 3, participants demonstrated significant improvements in symptoms across all disorders and comorbidities.

Table 3: Efficacy of Revised TBT Protocol in Veterans with Depressive/Anxiety Disorders

Scale	Pre *M (SD)*	Post *M (SD)*	*F* (*p*)	*d*
IIRS-Impairment	64.2 (13.7)	39.4 (17.0)	45.8 (<.001)	1.61
PTSD Checklist	57.8 (14.8)	33.7 (10.9)	47.1 (< .001)	1.42
DASS-Depression	12.4 (6.1)	5.1 (4.4)	45.9 (< .001)	1.37
DASS-Anxiety	11.1 (5.3)	5.2 (3.5)	42.1 (< .001)	1.31
DASS-Stress	13.8 (5.0)	7.3 (3.8)	38.0 (< .001)	1.46

Naturalistic Comparison of Group TBT and Group DSTs

An IRB-approved pilot trial was completed on group psychotherapy version of TBT compared to group DSTs in Canadian civilians with depressive/anxiety disorders (Gros et al., 2019). The study investigated 100 participants with various diagnoses of depressive/anxiety disorders that attended either Group TBT (*n* = 34) or Group DSTs for SOC, PD/AG, or OCD (*n* = 66). Participants in both treatments demonstrated significant improvements across all measures. Although no statistical differences were observed between groups, participants that received Group TBT demonstrated roughly twice the treatment effect size compared to participants in the DST groups, as presented in Table 4.

Table 4: Comparison of Group TBT and Group DSTs Across Depressive/Anxiety Disorders

	TBT (*n* = 34) Within Group Outcome				Disorder-Specific (*n* = 66) Within Group Outcome				Between Groups	
Scale	Pre *M(SD)*	Post *M(SD)*	*t*	*d*	Pre *M (SD)*	Post *M (SD)*	*t*	*d*	*F*	η_p^2
IIRS	63.5 (14.4)	48.5 (19.5)	4.0***	**0.88**	56.7 (17.7)	48.1 (19.4)	4.9**	**0.46**	1.2	.013

Note. ***p < .001; **p < .01; *p < .05.

CSR&D CDA involving RCT of Individual TBT Compared to Behavioral Activation
In addition to the unfunded pilot trials, Dr. Gros's CSR&D CDA funded a small RCT to compare TBT with one specific individual DST, behavioral activation (BA), in Veterans with depressive/anxiety disorders. The study originally targeted a sample of 36 per group; however, the management of the grant and referral process allowed for a larger than expected sample to better test the hypotheses within the original timelines (TBT n = 44; BA n = 46). In contrast to the proposed study, this small RCT was designed to provide initial findings for TBT via an RCT with a single comparison group to inform future investigations. Results demonstrated reductions in outcome variables from pre-treatment to post-treatment for those in TBT. Large effects were found across all outcome variables. To examine the effects of treatment on several outcome variables (Table 5), linear mixed regression models were conducted using an intent-to-treat approach and handling missing data via robust maximum likelihood. Results revealed significant treatment effects from pre-treatment through 6-month follow-up, that were qualified by marginal to significant group by session effects for depression, anxiety, and somatic anxiety such that participants receiving TBT showed greater treatment gains on these outcome variables than did participants receiving BA. Although not significant, all other outcome variables favored TBT as well.

Table 5: Comparison of TBT and Behavioral Activation in Veterans with Depressive/Anxiety Disorders

	DASS-Stress	DASS-Depression	DASS-Anxiety	STICSA-Cognitive	STICSA-Somatic	PCL-PTSD	IIRS-Impairment
	B (*SE*)	*B* (*SE*)	*B* (*SE*)	*B* (*SE*)	*B* (*SE*)	*B* (*SE*)	*B* (*SE*)
Intercept	10.73* (0.76)	9.65* (0.87)	7.73* (0.82)	24.82* (1.04)	20.49* (1.02)	38.29* (2.56)	50.01* (2.44)
Group	-0.71 (1.06)	0.49 (1.10)	-1.39 (1.06)	-1.82 (1.34)	-1.64 (1.28)	-3.27 (3.45)	1.72 (3.53)
Session	-3.19* (0.67)	-3.54* (0.71)	-2.69* (0.61)	-5.08* (1.10)	-3.18* (0.62)	-10.27* (2.32)	-11.76* (2.19
GrpXsess	0.62 (0.88)	1.49^{t} (0.90)	1.59* (0.73)	1.89 (1.35)	1.66^{t} (0.90)	3.43 (2.70)	1.69 (2.82)

Note. Intercept is centered on baseline session. GrpXsess = Group by session (baseline, post-intervention, 6-month follow-up [0, 1, 2]) interaction. *p < .05, ^{t}p < .10.

D. RESEARCH DESIGN AND METHODS

Table 6: Project Timeline

Proposed Component	Year	Timeframe
Preparing for RCT	Y01	month 01 – 06
Hiring staff	Y01	month 01 – 03
Training on procedures/protocols	Y01	month 03 – 06
Randomized controlled trial	Y01-Y05	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
Dissemination of findings	Y05	month 54 – 60

RCT of TBT
Objective
To examine efficacy of TBT on improving psychiatric symptomatology and related impairments in Veterans with PTSD, MDD, and/or PD/AG compared to DSTs via a non-inferiority design. Patient satisfaction and predictors of feasibility (attendance and discontinuation) also will be assessed.

Recruitment Strategy
Veterans will be recruited through the Primary Care Mental Health Integration, General Outpatient Mental Health, and CBT Clinic programs at the Ralph H. Johnson VAMC and all affiliated VA community-based outpatient clinics. IRB-approved study flyers will be distributed through each clinic/setting. Within these programs, all Veterans reporting symptoms of depression and anxiety meet with a mental health staff member to complete a clinical interview and self-report measures. If Veterans endorse symptoms consistent with a depressive/anxiety disorder, interest in participating in research will be assessed and, if agreeable, the Veteran will be referred to project staff.

Intake Procedures

A study-specific intake appointment will be completed with the project staff to complete consent documentation as well as assess inclusion and exclusion criteria (with a targeted sample of 306 VAHCS patients), including a semi-structured clinical interview and self-report questionnaires focused on quality of life, social integration, and psychiatric symptoms (described later). Screening and consent will take place at the participant's residence via telehealth by research staff or in person at the VAHCS, based upon the preference of the participant.

Docusign

Participants will have the option of signing the informed consent via Docusign. The informed consent and HIPAA documents will be uploaded via the VA's Docusign Research Use Request Sharepoint portal. Study staff will explain, in detail, each aspect of the informed consent form and HIPAA authorization before instructing the participant to electronically sign the documents. Copies of the completed forms will be stored electronically on the VA secured research drive behind the VA's firewall. Printed copies will be kept in locked cabinets inside locked offices in preparation for VA audits. Access to both electronic and printed copies will be restricted to authorized study personnel on the IRB personnel list and Delegation of Authority log.

Eligibility Criteria

Inclusion criteria: 1) participants must be clearly competent to provide informed consent for research participation, 2) participants must meet DSM-5 criteria for either MDD, PTSD, or PD/AG, and 3) participants must be 18 - 80 years of age. **Exclusion criteria involve:** 1) recent history ($\leq$ 2 months) of psychiatric hospitalization or a suicide attempt and/or suicidal ideation with acute intent as documented in their medical record or reported during clinical interview, 2) 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), 3) recent start of new psychiatric medication ($\leq$ 4 weeks), or 4) diagnosis of traumatic brain injury (TBI) in their medical record and/or endorsement of screener questionnaire (McAllister et al., 2016). Additional comorbid psychiatric diagnoses that were not listed as exclusion criteria are permitted as long as they are considered secondary to the principal diagnosis of MDD, PTSD, or PD/AG as determined by the diagnostic interview. Of note, if participants request changes to their psychiatric medications at any time during the treatment, a medication consult will be completed with a prescriber in VA Mental Health. Any changes in medications and/or initiation of non-study psychotherapy will be recorded for inclusion in the analyses as a possible covariate. Ineligible Veterans will be referred for non-study-related treatments within mental health at the RHJ VAMC.

Procedures

Participants who meet inclusion/exclusion criteria 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 (Brown et al., 2001), principal diagnosis, or the most impairing of the diagnosable disorders, will be used to inform randomization. Principal diagnosis will be determined via diagnostic severity scores in the Anxiety Disorders Interview Schedule-5 (ADIS-5) (Brown, 2014). To balance diagnoses across the two conditions, a stratified random assignment based on principal diagnosis will be used (MDD, PTSD, and PD/AG) (Gros, 2015). Based on referrals to the PI's CDA, it is expected that at least 45% of the recruited Veterans will have served in OEF/OIF and $\geq$50% will be representative of minority groups.

Eligible VAMC patients will be randomized into one of two treatment conditions: TBT or DSTs. Both treatment conditions will include 12 weekly 45- to 60-minute treatment sessions. Both treatment conditions will be delivered either in-person and via VA-approved telehealth technologies, based upon the preference of the participant. 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.

Randomization Procedures

Participants will be randomly assigned (1:1) to one of the two study arms (n = 108 per arm) using a permuted block randomization procedure. Randomization will be stratified by diagnostic group (PTSD, PD/AG, MDD) 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 their treatment condition by the Research Project Therapist/Coordinator using a computer-generated randomization scheme. Once a participant is randomized, they will be included in the modified intent-to-treat (MITT) analysis. The Research Project Therapy/Coordinator and the statistical analyst in charge of randomization (Dr. Allan) will be the only

research team members aware of the randomization assignment. 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 VA providers will be informed of their patients' participation in the study, but will be blinded to the treatment condition. Although some variability is expected due to the varying prevalence rates of PTSD, PD/AG, and MDD in Veterans, recruitment strategies will be adjusted accordingly if any of the three disorder groups is under-represented (e.g., recruit more heavily in PTSD clinic if PTSD is under-represented).

DSTs Control Condition Matching and Assignment

To provide an evidence-based comparison for the TBT condition, DSTs will be used that are matched to the participant's most severe diagnosis, based upon the average of the ADIS interference and distress scores. If the scores are equivalent for two or more diagnoses, participants will be asked to list which diagnosis/symptoms that they find most impairing. DSTs will be included for each of the three targeted diagnoses, including PTSD (CPT for PTSD), PD/AG (CBT for PD/AG), and MDD (CBT for MDD). Each of these DSTs have published manuals for administration and have received extensive support in the literature (Barlow, 2014). Although several DSTs are available for each disorder (e.g., PE for PTSD, applied relaxation for PD/AG, and behavioral activation for MDD), these three DSTs were selected based on their similarities in cognitive-behavioral techniques as well as their robust evidence in the literature. In addition, all three DSTs have been shown to improve comorbid symptomatology and therefore may be a more accurate comparison to TBT as compared to other available DSTs that may have less effect on comorbidity (e.g., applied relaxation for PD/AG) (Nishith et al., 2005; Tsao et al., 2002).

Treatment Training and Fidelity

Training workshops (3 days each) will be provided for each of the four treatment protocols, consistent with the standard VA rollout for DSTs. Although less time may be needed for the TBT training (Gros et al., 2017), all four workshops will be standardized in duration to control for potential training differences. Established trainers/experts will be recruited to provide each of the trainings. Trainings will be supported by weekly supervision on the four protocols co-led by VA staff psychologists well-versed in the study therapies for the duration of the study, with additional supervision sessions provided as needed. Backup clinical supervision will be provided by Drs. Gros (PI).

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, treatment-specific rating forms will be used to determine if the therapist appropriately covered the content of each session. External experts will be recruited to rate the recordings independently, with feedback provided to the therapists throughout the duration of the study to maintain/improve treatment delivery.

Safety Measures for Suicidal Ideation or Intent

All assessment 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 suicidal ideation and acute intent will be excluded from the study and immediately offered emergency psychiatric care at the VAMC. All participants will be completing the PHQ-9 biweekly during the active treatment, in addition to completing those measures and several others at the mid-treatment, post-treatment, and 6-month follow-up time points. During each assessment, the PHQ-9 item 9 will be inspected by the treating therapist/assessor for the presence of suicide ideation ($\geq$1 on item 9). If identified, the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed in CPRS. If the C-SSRS is positive, the staff will initiate a warm handoff to a provider in PCMHI or Mental Health with support of the project team (Dr. Gros is a supervisor in Mental Health) to complete a comprehensive suicide risk assessment. If hospitalization is needed, the PCMHI/MHC staff will initiate that process. Upon completion of the warm handoff and comprehensive suicide risk assessment, the provider, research staff, and clinical supervisor (Dr. Gros) will discuss ongoing plan. 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. The safety procedures in the study will be comparable to the current clinical procedures in the VA.

Assessment of Quality of Life, Psychological Well-Being, Social Reintegration, Psychiatric Symptomatology, and Treatment Satisfaction

Follow-up assessments will be conducted for all participants during VA visits or via home based telehealth by trained interviewers blind to treatment conditions. The battery of self-report questionnaires and a diagnostic interview will be completed pre-, mid-, and post-treatment and at the 6-month follow-up to track participant progress through the treatment and maintenance phases. Of note, the diagnostic interview will not be completed at mid-treatment to limit within-treatment time and scheduling obligations. These time points for the assessments are consistent with CBT research with Veterans with emotional disorders, as well as with other TBT studies by the research team (Gros & Allan, 2019).

Participant assessments may be completed either in person, via USPS mailed questionnaire packets and accompanying self-addressed, stamped envelope to be mailed back to the project team, or in Qualtrics or VA Redcap. Redcap and Qualtrics are VA-approved programs for survey data collection. The VA provides a national license to use these programs which will be obtained by the researchers. These programs will be used to implement the surveys and are optimized for computer, smartphone, and tablet. HIPAA compliant data will be utilized and accessed by authorized users on the study who will download this data on the secure research network drive.

Participants will be compensated $40 for pre-treatment, $60 for mid-treatment, $80 for post-treatment, and $120 for 6-month follow-up for completion of assessment procedures for a total of $300 for the entire study. Payments will be made via VA direct deposit. To reduce the likelihood of missing data, all assessments will be scheduled separately from normal treatment sessions. Assessments of disorder-specific symptomatology, as well general symptoms of the depressive/anxiety disorders and related impairments, were chosen due to the transdiagnostic focus of the proposed study (Gros, 2015). All assessments will be completed by the Project Research Recruiter and Assessor. Additional training will be required prior to administration of the diagnostic interview (ADIS-5). The assessor will be required to observe the PI administer the ADIS-5 twice and then administer the ADIS-5 twice themselves under the direct observation of the PI. The assessor will be blinded to treatment condition and supervised by the PI. ADIS-5 assessments will be recorded to investigate inter-rater reliability of diagnoses, with 20% of recordings being re-assessed by an external ADIS-trained assessor after the participant has completed all study procedures, with feedback provided to the assessor throughout the duration of the study to improve reliability. In addition to the four assessment points, select measures (PHQ-9, PDSS, and PCL-5) will be administered every other treatment session to monitor safety and treatment progress.

Albany Panic and Phobia Questionnaire (APPQ). The APPQ is a 27-item self-report measure that assesses agoraphobia, social anxiety, and interoceptive avoidance (Rapee et al., 1994/1995). Each subscale has been shown to have good internal consistency (αs > .85) and temporal stability (rs > .87) (Brown et al., 2005).

Anxiety Disorder Interview Schedule-5 (ADIS-5). The ADIS-5 is a semi-structured interview designed to assess a wide range of Axis I disorders (Brown, 2014). 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-5 has demonstrated excellent inter-rater reliability and validity of depressive/anxiety disorder diagnoses.

Anxiety Sensitivity Index 3 (ASI-3). The ASI-3 is an 18-item self-report measure of AS. This scale was developed to provide a more stable measure of the three most widely recognized AS subfactors (cognitive, social and physical concerns) than the previous ASIs provided (Taylor et al., 2007). The measure has shown good psychometric properties (Taylor et al., 2007). The ASI-3 will be utilized to assess level of overall AS.

Attentional Control Scale - Straightforward (ACS-S). The ACS-S is a 20-item scale that measures the voluntary attentional focusing and attentional shifting related to anterior system functioning. The scale measures a general capacity for attentional control with subfactors related to the abilities: to focus attention, to shift attention between tasks, and to flexibly control thought. The ACS is internally consistent (Derryberry & Reed, 2002).

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 (Lovibond & Lovibond, 1995). The reliability and validity of the subscales have been supported in the literature (Antony et al., 1998). The DASS scales also have demonstrated excellent convergence with similar measures of depression and anxiety and high internal consistency (Antony et al., 1998).

Illness Intrusiveness Rating 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 (Devin et al.,

1983). The IIRS has been shown to have strong psychometric properties in the previous literature in participants with physical and/or emotional health concerns (Devins, 2010), and has been used in previous TBT studies (Gros, 2014; Gros et al., 2017; 2018).

Intolerance of Uncertainty Scale Short Form (IUS-12). The IUS-12 is a 12-items scale for measuring trait intolerance of uncertainty (Carleton, Norton, & Asmundson, 2007). In other words, it is used for assessing the degree to which individuals are able to tolerate the uncertainty of ambiguous situations, the cognitive and behavioral responses to uncertainty, perceived implications of uncertainty, and attempts to control the future.

Medical Outcomes Study Social Support Survey Form (MOSSS). The MOSSS is a widely used 19-item self-report measure designed to assess social support. Responses are given on a 6-point scale ranging from 1-6 with greater scores indicating greater support. The MOSSS has been shown to be an accurate measure of social support in veteran samples with mental health issues (Jakupcak et al, 2011).

Panic Disorder Severity Scale (PDSS). The PDSS is a 7-item scale for the frequency and distress of panic attacks and related symptoms (Shear et al., 1997). The scale has demonstrated good internal consistency, test-retest reliability, and sensitivity to change during the course of treatment (Houck et at., 2002). *The PDSS will be used to assess symptoms of PD/AG.*

Perseverative Thinking Questionnaire (PTQ). The PTQ is a 15-item measure of repetitive negative thinking (Ehring et al. 2011). Perseverative thinking is repetitive, negative thoughts that persist intrusive to the point of being seen as unproductive to the individual. The thought process and the individual seeing the thoughts as dysfunctional can also characterize this thinking. Items are measured on a 5-point Likert-type scale of Never (0) to Almost Always (4). These 15 questions address repetitiveness, intrusiveness, difficulty to disengage, unproductiveness, and capturing mental capacity. Studies have shown that the PTQ hold convergent validity, predictive validity, internal consistency, and test-retest reliability.

PHQ-9. The PHQ-9 is a 9-item depression scale derived from the *Patient Health Questionnaire* to assess the symptoms and diagnosis of depression (Kroenke et al., 2001). The PHQ-9 has been shown to have good reliability as well as validity in clinical samples (Kroenke et al., 2001). In addition, the PHQ-9 has been incorporated into standard screenings at the VA. *The PHQ-9 will be used to assess symptoms of MDD.*

PTSD Checklist 5 (PCL-5). The PCL-5 is a 20-item self-report measure that assesses DSM-5 criteria PTSD symptoms (Weathers et al., 2013). Previous versions of the PCL have been shown to have excellent internal consistency and excellent test-retest reliability in veterans (Orsillo et al., 2001). In addition, the PCL-5 has been incorporated into standard assessment for PTSD at the VA.

Satisfaction with Therapy and Therapist Scale – Revised (STTS-R). The STTS-R assesses patients' level of satisfaction with their therapeutic experiences (Oei & Green, 2008). 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 and high positive correlations with indicators of successful group CBT outcomes (Oei & Green, 2008).

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 (Gros et al., 2007; Ree et al., 2008). The cognitive and somatic subscales have been supported in the literature and both subscales have high internal consistency (Gros et al., 2007). In addition, the STICSA-Trait scale was found to remain stable over repeated administrations during several stress manipulations.

Structured Assessment for Evaluation of TBI (SAFE-TBT). The SAFE-TBI was designed to identify the level of evidence for exposure to mild TBI (McAllister et al., 2016). The SAFE-TBI includes a definition of mild TBI as well as three multi-part screening questions, regarding: 1) exposed to, screened for, or put on restricted duty due to any head or brain injury from six examples (e.g., blast or explosion); 2) associated symptoms that occurred immediately after the head or brain injury (e.g., duration of loss of consciousness, feeling dazed or confused, amnesia); and 3) memory loss of events just before or after the injury. The SAFE-TBI has demonstrated moderate

levels of agreement for inter-rater and test-retest reliabilities (McAllister et al., 2016). In addition, the SAFE-TBI demonstrated reasonable convergent validity with more extensive measures of TBI.

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 (Kazis, 2000). The V/SF-36 was adapted from the original SF-36, which has received extensive support in the literature (Ware & Sherbourne, 1992).

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 VA network shared drive 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 VA computers that require secure login, 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. Participant information always will be treated as confidential.

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 VA maintains firewall protection. The backup schedule at the RHJ VAMC consists of fully-verified daily backups.

All data will be entered into an SPSS database. The SPSS database will be created by the PI, statistical analyst (Dr. Allan), and project staff 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 with consistency.

Sample Size Determination for Proposed Analyses

For all study outcomes (ADIS-5, IIRS, PCL-5, PDSS, PHQ-9, and STICSA), Veterans will be randomly assigned (1:1) to the TBT and specific DST conditions. The power analysis was calculated to be powered at 80% with a Bonferroni-corrected 1-tailed $\alpha = .006$ (.025/4 primary outcomes) to detect non-inferiority for TBT in comparison to the aggregated DST effect. Meta-analyses for CBT for MDD, CPT for PTSD, and CBT for PD/AG reveal large treatment effects (CBT for MDD bias-adjusted $g = .53$; Cuijpers et al., 2013; CPT for PTSD in military personnel $g = 1.33$; CBT for PD $g = 0.35$; Hofmann & Smits, 2008). Thus, the average effect size for DSTs was expected to range from small-to-medium to large. A power analysis was conducted using procedures recommended by Chow, Shao, and Wang (2017), Flight and Julious (2014), and Julious (2004) as well as recommendations by the United States Food and Drug Administration and the European Medical Association (Food and Drug Administration, 2017). An important topic in non-inferiority designs is selection of the “appropriate” prespecified non-inferiority limit. Current best practice involves selecting a non-inferiority margin that is not greater than the smallest effect size expected for the DSTs in comparison to a control condition. As a tradeoff between sample size needs and feasibility of recruitment, we conducted power analysis setting the non-inferiority margin to 0.5, indicating that we would consider TBT non-inferior to the DSTs if TBT were to perform less than half a standard deviation worse than the DSTs. We set the expected group different to 0.3 given our pilot data demonstrating that TBT outperforms DSTs by this margin across primary outcome variables. Using procedures recommended by Chow, Shao, and Wang (2017) for non-inferiority designs, which utilize the pre-specified non-inferiority margin (here prespecified as $\Delta d = 0.5$) and the estimated effect in the active comparison treatment ($d = 0.3$), we determined that 144 participants (72 per cell) would be needed. However, this does not account for potential attrition or for potential design effect issues involving therapist effects or for potential missing data related to telehealth delivery of services. To account for possible attrition and missing data as well as the potential influence of design effects, we increased the sample size to 306 participants based on the data available to date. Based on pilot data, we expect to find large within-person effects ($d \geq .80$) for TBT, indicating 4/5ths of a SD reduction in each of the primary outcome measures. This sample size would leave us powered to detect small-to-medium within-person effect sizes

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, symptom variables, and related impairments 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 MITT analysis set will comprise all randomized participants. Missing data in the full analysis set will occur if participants discontinue treatment prior to the end of the study or do not complete an outcome measure. In general, participants will remain in the study unless consent is withdrawn or if there are concerns regarding participant safety. However, participants will be required to complete the full course of treatment (12 sessions) within a maximum of 18 weeks, in order to maintain the integrity of the treatments (Barlow et al., 2017). If participants fail to do so within 18 weeks, treatment will be discontinued and follow-up assessments will be completed. Missing data for the MITT analysis set will be accounted for using full information maximum likelihood (ML), which is superior to most alternative missing data approaches even when data is missing completely at random (MCAR) or missing at random (MAR; Schafer & Graham, 2002; Enders, 2010). Although the use of ML will result in the least biased parameters, regardless of data missingness, several approaches will be undertaken to better understand the exact mechanisms for missing data. Little's (1988) MCAR test will be applied to all final models to determine whether data can be considered MCAR. Further, the results of analyses using study completers and protocol adherers (completer and per-protocol analyses) will be compared with results using the MITT analysis set to test sensitivity of study conclusions to study discontinuations and protocol non-adherence. Baseline differences also will be explored between treatment completers and those that discontinue. If baseline differences are detected, these covariates will then be included in the final model as auxiliary variables to improve the plausibility of assuming data is MAR (Collins et al., 2001; Enders, 2010; Graham, 2003;). Finally, discontinuation proportion will be used as one of the outcome measures of intervention feasibility.

Efficacy Measures Analyses (Primary Aim)

The continuous measures included measures of disorder severity scales (ADIS-5), disorder-specific symptomatology (PCL-5, PDSS, PHQ-9, and STICSA), general related symptomatology (STISCA), and quality of life and impairment (IIRS). Of these variables, the PCL-5, PDSS, PHQ-9, and STICSA are the primary outcomes of interest. All other analyses will be conducted in an exploratory fashion to inform future studies and compare findings to previous studies (Gros, 2014; Gros et al., 2017; 2019). Parameter estimates to calculate the effect size difference will be arrived at using three-level (measurement occasions nested within participants nested within assigned treatment condition) generalized mixed-effects regression models (MRM). MRM is a method of repeated measures analyses that allows for modeling of continuous and categorical independent and dependent variables and for appropriate modeling of covariance structures when observations are correlated across time and/or across condition. This analytic approach fully captures variability in outcomes across multiple follow-up assessments and accounts for any potential effect of the group to which a participant is assigned and is thus preferred over methods that collapse data over time. We will calculate between-group treatment differences as Cohen's d, based on the effect of treatment condition on the intercept parameter when the model is centered on post-intervention and on the effect of treatment condition on the intercept parameter when the model is centered on month 6. We prespecified the non-inferiority margin (d) to be 0 (indicating we expected TBT to be at least equivalent to the aggregate DST effect) and the one-sided CI for our four primary analyses at $\alpha = .006$. In the primary analyses of outcome variables, we will covary for the baseline value of the variable of interest. We also will include the linear effect of time as well as a time by condition interaction effect to determine whether treatment differences (or lack thereof) were stable from post-intervention through the follow-up. Additional covariates (e.g. age, number of psychiatric comorbidities, race, sex, combat theatre, number of treatment sessions, specific DST received) will be added to the model to adjust for putative confounding variables. Effect size CIs that do not contain 0 provide evidence in support of noninferiority for TBT. The primary outcome time point is at the end of the active treatment phase and the secondary time point is at the end of the naturalistic 6-month follow-up period. Further, within-subject effect sizes from baseline to post-intervention and to 6-month follow-up also will be calculated within the TBT condition to quantify TBT-specific reductions in symptoms. These analyses will be probed to examine potential therapist effects. First, design effects will be calculated for the primary outcome variables. Design effects > 2 are often used as a heuristic to judge when these effects can be problematic.

Following testing of design effects, sensitivity analyses will be conducted using the complex estimator in Mplus which can adjust the model for potential therapist effects.

Feasibility and Acceptability Analyses (*Secondary Aim*)
Measures of feasibility and acceptability are discontinuation proportions (discontinuation y/n), proportion of sessions attended, proportion of homework assignments completed, and patient satisfaction scores on the STTS-R. Frequency distributions describing the participants' reasons for noncompliance and discontinuation of participation will be developed. Because feasibility and acceptability analyses involve changes from baseline to post-intervention only and several of the outcomes are categorical, the generalized linear mixed model (GLMM) framework will be used to compare TBT to DST on treatment satisfaction, retention (discontinuation), and treatment adherence (% missed sessions, % homework completion). Discontinuation proportions (dichotomous outcome), % 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 treatment (e.g. whether the probability of missing visits is less/greater at earlier or later time points).

E. PROTECTION OF HUMAN SUBJECTS

RISKS TO THE SUBJECTS

Risks to the Subjects

Participants will include 306 VAMC patients in the mental health service. The inclusion criteria are that participants must: 1) be an adult (18 – 80 years in age), 2) be competent to provide informed consent for research participation, and 3) be diagnosed with MDD, PTSD, and/or PD/AG as determined by a semi-structured diagnostic assessment (ADIS-5). Based on referrals to the Principal Investigator's ongoing CDA study, it is expected that at least 45% of the recruited Veterans will have served in OEF/OIF and ≥50% will be representative of minority groups.

Several exclusion criteria exist for the proposed investigation, including 1) recent history (≤ 2 months) of psychiatric hospitalization or a suicide attempt and/or suicidal ideation with acute intent as documented in their medical record or reported during clinical interview, 2) 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), 3) recent start of new psychiatric medication (≤ 4 weeks), and 4) diagnosis of traumatic brain injury (TBI) in their medical record and/or endorsement of screener questionnaire regarding the symptoms of TBI (McAllister et al., 2016). Additional comorbid psychiatric diagnoses that were not listed as exclusion criteria (e.g., eating disorder, adjustment disorder, or insomnia) are permitted as long as they are considered secondary to the principal diagnosis of MDD, PTSD, and/or PD/AG as determined by the diagnostic interview. Of note, if participants request changes to their psychiatric medications at any time during the treatment, a medication consult will be completed with their existing prescriber in VA Mental Health, or a provider will be assigned. Any changes in medications and/or initiation of non-study psychotherapy will be recorded for inclusion in the analyses as a possible covariate.

Targeted/Planned Enrollment Table

Total Planned Enrollment 306

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	13	15

Not Hispanic or Latino	69	222	291
Ethnic Category: Total of All Subjects *	71	235	306
Racial Categories			
American Indian/Alaska Native	2	5	7
Asian	1	3	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	36	105	141
White	32	122	154
Racial Categories: Total of All Subjects *	71	235	306

Sources of Materials

All participants will be randomized into either Transdiagnostic Behavior Therapy (TBT) or a disorder-specific therapy (DST). DSTs will be provided for the targeted diagnoses, including CPT for PTSD, CBT for MDD, and CBT for PD/AG. Throughout the course of treatment, a multi-method assessment of psychiatric symptomatology and related impairments and treatment satisfaction will be completed/monitored. Participants will be compensated $40 for pre-treatment, $60 for mid-treatment (session 6), $80 for post-treatment, and $120 for 6-month follow-up for completion of assessment procedures for an estimated total of $300 for the entire study.

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 (APPQ).* The APPQ is a 27-item self-report measure that assesses agoraphobia, social anxiety, and interoceptive avoidance (Rapee et al., 1994/1995). Each subscale has been shown to have good internal consistency and temporal stability (Brown et al., 2005).
3. *Anxiety Disorder Interview Schedule-Revised (ADIS-5).* The ADIS-R is a well-established, semi-structured interview designed to assess a wide range of Axis I disorders (Brown, 2014). The ADIS-R assesses current and past diagnoses with DSM diagnostic criteria, severity scores, and lists of feared and avoided situations for the anxiety disorders. The ADIS-R has demonstrated excellent inter-rater reliability and validity of depressive/anxiety disorder diagnoses.
4. *Anxiety Sensitivity Index 3 (ASI-3).* The ASI-3 is an 18-item self-report measure of AS. This scale was developed to provide a measure of cognitive, social and physical concerns (Taylor et al., 2007). The measure has shown good psychometric properties (Taylor et al., 2007). The ASI-3 will be utilized to assess level of overall anxiety sensitivity.
5. *Attentional Control Scale - Straightforward (ACS-S).* The ACS-S is a 20-item scale that measures the voluntary attentional focusing and attentional shifting related to anterior system functioning. The scale measures a general capacity for attentional control with subfactors related to the abilities: to focus attention, to shift attention between tasks, and to flexibly control thought. The ACS is internally consistent (Derryberry & Reed, 2002).
7. *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 (Lovibond & Lovibond, 1995). The factor structure, reliability, and validity of the subscales have been supported in the literature (Antony et al., 1998). The DASS scales also have demonstrated excellent convergence with similar measures of depression and anxiety and high internal consistency.
8. *Illness Intrusiveness Rating 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 (Devin et al., 1983). The IIRS has been shown to have strong psychometric properties in the previous literature in participants with physical and/or emotional health concerns (Devins, 2010), and has been used in previous TBT studies (Gros, 2014).

9. *Intolerance of Uncertainty Scale Short Form (IUS-12).* The IUS-12 is a 12-items scale for measuring trait intolerance of uncertainty (Carleton, Norton, & Asmundson, 2007). It is used for assessing the degree to which individuals are able to tolerate the uncertainty of ambiguous situations, the cognitive and behavioral responses to uncertainty, perceived implications of uncertainty, and attempts to control the future.
10. *Medical Outcomes Study Social Support Survey Form (MOSSS).* The MOSSS is a widely used 19-item self-report measure designed to assess social support. Responses are given on a 6-point scale ranging from 1-6 with greater scores indicating greater support. The MOSSS has been shown to be an accurate measure of social support in veteran samples with mental health issues (Jakupcak et al, 2011).
11. *Panic Disorder Severity Scale (PDSS).* The PDSS is a 7-item scale for the frequency and distress of panic attacks and related symptoms (Shear et al., 1997). The scale has demonstrated good internal consistency, test-retest reliability, and sensitivity to change during the course of treatment (Houck et at., 2002).
12. *Perseverative Thinking Questionnaire (PTQ).* The PTQ is a 15-item measure of repetitive negative thinking (Ehring et al. 2011). Perseverative thinking is repetitive, negative thoughts that persist intrusive to the point of being seen as unproductive to the individual. The thought process and the individual seeing the thoughts as dysfunctional can also characterize this thinking. Studies have shown that the PTQ hold convergent validity, predictive validity, internal consistency, and test-retest reliability.
13. *PHQ-9.* The PHQ-9 is a 9-item depression scale derived from the patient health questionnaire to assess the symptoms and diagnosis of depression (Kroenke et al., 2001). The PHQ-9 has been shown to have good reliability as well as validity in clinical samples (Kroenke et al., 2001). In addition, the PHQ-9 has been incorporated into standard screenings at the VA.
14. *PTSD Checklist 5 (PCL-5).* The PCL-5 is a 20-item self-report measure that assesses DSM-5 criteria PTSD symptoms (Weathers et al., 2013). Previous versions of the PCL have been shown to have excellent internal consistency and excellent test-retest reliability in veterans (Orsillo et al., 2001). In addition, the PCL-5 has been incorporated into standard assessment for PTSD at the VA.
15. *Satisfaction with Therapy and Therapist Scale – Revised (STTS-R).* The STTS-R assesses patients' level of satisfaction with their therapeutic experiences (Oei & Green, 2008). 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 and high positive correlations with indicators of successful treatment outcome.
16. *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 (Gros et al., 2007; Ree et al., 2008). The cognitive and somatic subscales have been supported in the literature and both subscales have high internal consistency. In addition, the STICSA-Trait scale was found to remain stable over repeated administrations during several stress manipulations.
17. *SAFE-TBT.* The SAFE-TBI was designed to identify the level of evidence for exposure to mild TBI (McAllister et al., 2016). The SAFE-TBI includes a definition of mild TBI as well as three multi-part screening questions, regarding: 1) exposed to, screened for, or put on restricted duty due to any head or brain injury from six examples (e.g., blast or explosion); 2) associated symptoms that occurred immediately after the head or brain injury (e.g., duration of loss of consciousness, feeling dazed or confused, amnesia); and 3) memory loss of events just before or after the injury. The SAFE-TBI has demonstrated moderate levels of agreement for inter-rater and test-retest reliabilities (McAllister et al., 2016). In addition, the SAFE-TBI demonstrated reasonable convergent validity with more extensive measures of TBI in a VA sample.
18. *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 (Kazis, 2000). The V/SF-36 was adapted from the original SF-36, which has received extensive support in the literature (Ware & Sherbourne, 1992).

Participants will be asked to complete the assessment materials four times throughout the duration of treatment: pre-treatment, mid-treatment (session 6), post-treatment and six-month follow-up. Participants also will complete select measures bi-weekly to monitor treatment progress.

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 treatments are 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.

There is a risk of a loss of confidentiality of personal information as a result of participation in this study. There is a risk of being randomly assigned to a treatment condition that is less effective than the other.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent

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 before any study procedures are initiated.

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 members of the mental health service at the VAMC, the Principal Investigator and Co-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 assessment and treatment providers will be trained and supervised by the Principal Investigator, Co-Investigator, or one of the staff psychologists involved in the study, each of which is a licensed psychologist. At intake, participants identified by clinical interview with suicidal ideation and acute intent will be excluded from the study and immediately offered emergency psychiatric care at the VAMC. All participants will be completing the PHQ-9 biweekly during the active treatment, in addition to completing those measures and several others at the mid-treatment, post-treatment, and 6-month follow-up time points. During each assessment, the PHQ-9 item 9 will be inspected by the treating therapist/assessor for the presence of suicide ideation ($\geq$1 on item 9). If identified, the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed in CPRS. If the C-SSRS is positive, the staff will initiate a warm handoff to a provider in PCMHI or Mental Health with support of the project team (Dr. Gros is a supervisor in Mental Health) to complete a comprehensive suicide risk assessment. If hospitalization is needed, the PCMHI/MHC staff will initiate that process. Upon completion of the warm handoff and comprehensive suicide risk assessment, the provider, research staff, and clinical supervisor (Dr. Gros) will discuss ongoing plan. 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 therapist as well as completion of self-report measures. Participants who do not respond to treatment or do not complete 12 sessions within a maximum of 18 weeks 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 and data monitoring boards.
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 Annual Ethics, Privacy and HIPAA Training, and Privacy and Information Security Awareness and Rules of Behavior courses as well as the Miami University CITI course.

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 Veterans 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, TBT will be evaluated in Veterans 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.

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.

E. 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, TBT, with established evidence-based psychotherapies, CPT, CBT for Depression, and CBT for PD/AG. 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 mid-treatment and immediate post-treatment assessments. 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.

Gros, D. F. (2014). Development and initial evaluation of Transdiagnostic Behavior Therapy (TBT) for veterans with affective disorders. *Psychiatry Research, 220*, 275-282.

Gros, D. F., Allan, N. P., & Szafranski, D. D. (2016). The movement towards transdiagnostic psychotherapeutic practices for the affective disorders. *Evidence Based Mental Health, 19,* e10-e12.

Gros, D. F., Merrifield, C., Rowa, K., Szafranski, D. D., Young, L., & McCabe, R. M. (2019). A naturalistic comparison of group Transdiagnostic Behavior Therapy (TBT) and disorder-specific cognitive behavioral therapy groups for the affective disorder. *Behavioural and Cognitive Psychotherapy, 47,* 39-51.

Norton, P. J., & Paulus, D. J. (2016). Toward a unified treatment for emotional disorders: update on the science and practice. *Behavior Therapy*, *47*, 854-868.

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, across six community-based outpatient clinics (CBOCs) for Veterans in Myrtle Beach, SC, North Charleston, SC, Goose Creek, SC, Beaufort, SC, Savannah, GA, and Hinesville, GA. The Mental Health Service Line is charged with all aspects of clinical care, education, and research within mental health. In the most recent fiscal year with available data (FY17), the MHSL provided services to over 25,000 unique patients with over 175,000 visits, representing an 11.1% increase in uniques from the previous year (FY16). Mental health includes general outpatient mental health and inpatient mental health as well as numerous specialty clinics, including PCMHI and CBT programs, PTSD Clinical Team, Substance Treatment and Recovery program, Psychosocial Rehabilitation and Recovery Center, Homeless Patient Aligned Care Teams, Couples Therapy and Neuropsychology programs, and several housing and employment programs for Veterans in need. Drs. Gros is a Supervisory Psychologist/Program Manager within the mental health service line with dedicated office space, support staff, and infrastructure.

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, R. Amanda LaRue, Ph.D., 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. Project investigators also have available the full range of resources of the Mental Health Research Building. The Mental Health Research Building has ~14,929 sq. ft of space and has 36 patient care examination and staff rooms, 2 group rooms (on a separate hallway from study allocated research offices), a patient waiting room, general wet laboratories, and record storage space.

I. INVESTIGATOR BROCHURE

n/a

J. APPENDIX

Each of the proposed measures of psychiatric symptomatology were included in the attached appendices: 1) clinician rated structured clinical interview, and 2) self-reported measures.