Study Protocol and Statistical Analysis Plan

1. Administrative Information

1.1 Title, Registration, versions, and revisions

Title: Reducing Anxiety and Improving Functioning in Older Veterans
IRB: 32239 (last approved date: 01/31/2021)
Clinicaltrials.gov number: NCT02400723
Funding: Department of Veterans Affairs

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3 Background

3.1 *Anxiety in Older Veterans.* Older Veterans represent the majority (45%) of VA patients (Karlin, Zeiss, & Burris, 2010) and often are afflicted with mental health problems (Hankin, Spiro, Miller, & Kazis, 1999). Of these mental health problems, anxiety disorders are one of the most common late-life disorders (Gum et al., 2009). The consequences of anxiety can be costly (Marciniak et al., 2005) and devastating, including greater risk of a second myocardial infarction (Kubzansky et al., 1997) and cognitive impairment (Beaudreau & O'Hara, 2008). Anxiety in older adults is associated with increased health care utilization (de Beurs et al., 1999), poor medication adherence (Gentil, Vasiliadis, Préville, Bossé, & Berbiche, 2012), and poor quality of life (de Beurs et al., 1999). Anxiety disorders are also comorbid with chronic medical conditions and depression in older patients (Byers et al., 2010; Qureshi et al., 2012). A critical but understudied issue relevant to anxiety and functioning is the role of these co-occurring disorders, or comorbidities. Because functional impairment and disability are already pervasive among patients with comorbidity, comorbid medical conditions in anxious individuals are very concerning (Marengoni et al., 2011). Anxiety is therefore a crucial issue for VA patients given the multitude of adverse consequences that accompany presence of anxiety and comorbid medical conditions, thus significantly limiting patients' ability to function independently.

3.2 *Non-Pharmacological Interventions.* Behavioral, non-pharmacological treatments for anxiety have been effective in treating late-life anxiety and avoidance. In a meta-analysis of late-life anxiety psychotherapies, Thorp and colleagues (2009) found that Progressive Muscle Relaxation (PMR) resulted in the largest reductions in anxiety compared with waitlist controls, supportive therapy, and other efficacious therapies such as cognitive behavioral therapy (CBT). PMR is a component of CBT for anxiety (e.g., Stanley et al., 2009), yet only one session of CBT is typically devoted to teaching PMR, which may be inadequate for older individuals to fully learn the skill. As such, older adults may not consolidate the techniques for utilizing PMR despite its potential to significantly reduce anxiety. Furthermore, dissemination of efficacious non-pharmacological treatments to older Veterans with anxiety disorders has yet to be achieved. Few VA outpatient mental health programs focus on the treatment of older Veterans with anxiety. Moreover, disparities in the receipt of mental health services exist among Veterans with different anxiety diagnoses (Barrera et al., 2014). Veterans with anxiety disorder not otherwise specified are both older less likely to receive mental health services compared with Veterans with other anxiety diagnoses (Barrera et al., 2014).

3.3 *BREATHE Overview.* To address the aforementioned barriers to accessing non-pharmacological interventions, the PI developed a self-directed program to treat late-life anxiety called Breathing, Relaxation, and Education for Anxiety Treatment in the Home Environment

(BREATHE). BREATHE is a four-week behavioral intervention that uses evidence-based behavioral techniques (diaphragmatic breathing and progressive muscle relaxation) to reduce anxiety symptoms and avoidance in older adults. BREATHE is designed to be aligned with the tenets of Social Learning Theory (Bandura, 1971). BREATHE incorporates experiential and observational learning to promote decreased avoidance of identified activities. In Social Learning Theory, Bandura posits that learning can take place through observation of a model's behavior in addition to the observer's direct experience. Thus, decreasing reliance on avoidance as a coping strategy among those with anxiety disorders can be accomplished through: (1) the reduction of anxiety symptoms through experiential learning of relaxation and breathing skills, (2) experiential learning through approaching situations that are uncomfortable and avoided after using PMR, and (3) observation of a model who engages in an anxiety-evoking situation avoided by the observer. eHealth interventions for young adults use vignettes and case examples to model how to apply newly learned skills to overcome common life obstacles, such as work stress. The BREATHE videos use this format and incorporate age-appropriate examples such as anxiety about engaging in exercise, health-promoting activities, financial worries, and worries about one's own health and health of family members rather than vignettes about work, school, and interpersonal concerns that are less relevant to older adults (e.g., Gould & Edelstein, 2010). The combination of experiential and observational learning will help participants apply the skills learned in treatment to situations encountered in daily life. Vignettes will be used to model these behaviors aligned with Social Learning Theory. Our preliminary studies refined the BREATHE program for older Veterans (Gould et al., 2017).

4. Study Summary and Aims

4.1 *Summary*. The present study is a pilot randomized controlled trial of BREATHE versus an active control (psychoeducation) in older Veterans with an anxiety disorder. The study will last 12 weeks. The study will consist of four weeks of treatment (weekly video lessons) and two months of home practice (in the case of BREATHE). Two primary outcomes will be evaluated: anxiety, measured with the Geriatric Anxiety Scale (GAS; Segal, June, Payne, Coolidge & Yochim, 2010), and functioning, measured with the Activity Card Sort (Baum & Edwards, 2008). The specific aims for the study are as follows:

(1) To determine whether BREATHE leads to a statistically greater reduction in anxiety symptoms compared with an active control (psychoeducation) in a randomized control trial (RCT) of 60 older Veterans (based on power analysis).

(2) To determine whether BREATHE resulted in better functioning compared with an active control (psychoeducation) in the RCT.

To address aims 1a and 1b, older Veterans with anxiety disorders (Generalized Anxiety, Panic, Social Phobia, and other specified anxiety disorder) will be recruited for a RCT in years 3 and 4. Two primary outcomes will be evaluated. The first primary outcome, anxiety, will be measured with the Geriatric Anxiety Scale (aim 1a). The second primary outcome, functioning, will be measured with a modified version of the Activity Card Sort (aim 1b). BREATHE is hypothesized to result in a statistical reduction of anxiety symptoms (1a) and statistical improvement in functioning (1b) at post treatment compared with the control condition. The Hamilton Anxiety Scale (Hamilton, 1959) and VR-12 will be included as secondary outcome measures.

5. Inclusion and Exclusion Criteria

5.1 *Inclusion Criteria.* Veterans of any gender aged 60 and older who meet DSM-5 criteria for an anxiety disorder(s) (Generalized Anxiety Disorder, Panic Disorder, Agoraphobia, Social Anxiety Disorder or Other Specified/Unspecified Anxiety Disorder or Anxiety Disorder Other Specified). Participants must understand English well enough to participate in treatment.

5.2 *Exclusion Criteria*. Comorbid psychiatric disorders are acceptable unless participant has a psychotic disorder or serious mental illness (bipolar disorder). Participants with dementia or cognitive impairment, defined as a score of 6 or greater on the Short Blessed Test (SBT; Katzman et al., 1983) will be excluded. Participants enrolled in other psychological or pharmacological treatment studies for psychiatric conditions will be excluded. If participants are taking psychotropic medications and are not on a stable dose for at least 30 days, they will be excluded.

6. Study Endpoints: Assessments will occur at baseline, 4 weeks, 8 weeks, and 12 weeks.

7. Study Procedures:

7.1 *Telephone Screen*. A telephone interview will be conducted with potential participants to determine study eligibility. During the interview, study staff will explain the study, its requirements and answer any questions that the potential participant has. Upon the potential participant's willingness to be screened, study staff will determine whether patients meet age criteria (60+) and cognition exclusion criteria based on performance on the Short Blessed Test (SBT). The SBT is a weighted 6-item brief cognitive assessment that can be administered in person or over the phone. On this measure, also called the Blessed Orientation-Memory-Concentration Test, scores of 0 to 5 indicate normal cognition and scores 6+ suggest the presence of cognitive impairment. The SBT is administered to assess for cognitive impairment, an exclusion criterion. The SBT evaluates the following cognitive domains: orientation, registration, attention, and memory recall. It has acceptable test-retest reliability, convergent validity with other cognitive measures, and high specificity and adequate sensitivity for the detection of dementia (Milne et al., 2008). Any participants who do not pass the SBT (>6) will be excluded from the study at that time. Participants excluded due to cognitive scores will be provided the feedback that their performance may suggest the presence of cognitive problems, but further assessment is needed. Referrals will be provided to them at that time. Participants must also not have a diagnosis of dementia or a serious psychiatric disorder (psychotic disorder, schizophrenia, schizoaffective disorder, or bipolar disorder) as determined by questions asked during the telephone screen. Additional screening questions about medication use (as needed benzodiazepine use) and participating in ongoing psychotherapy (individual or group) will be included. Participants who are deemed to meet initial inclusion/exclusion criteria for age, absence of serious mental illness, and cognition status will be invited to participate in a baseline assessment including obtaining informed consent to participate.

7.2 *Baseline Visit*. At the beginning of the face-to-face baseline assessment, written informed consent and consent for audiotaping of the Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2015), will be obtained. Audiotaping will be used for supervision purposes and to assess inter-rater reliability of diagnoses. During the COVID-19 pandemic, participants provided oral consent to participate per approved modifications of the IRB protocol. During this time, assessments took place by phone with no in-person contact.

The baseline visit is used to both assess for the presence of a current anxiety disorder (i.e., diagnosis of Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Anxiety Disorder, Agoraphobia, or Unspecified or Other Specified Anxiety Disorder) using the SCID-5 and to collect baseline data on the primary and secondary outcomes. Assessment of anxiety disorders will be completed by study staff trained to administer the SCID-5. All diagnoses will be reviewed with the PI or a Co-Investigator prior to participants being randomized. Individuals with a previously unreported psychotic disorder or bipolar disorder will be excluded from the study at this time (if not already excluded during telephone screen). Participants who are not eligible or not interested in treatment will be provided with referral information for treatment if they desire.

Following the SCID-5 and completion of the Hamilton Anxiety Scale, participants will complete the self-report measures described below (demographic questionnaire, Geriatric Anxiety Scale, PROMIS anxiety measure (Reeve et al., 2007), Anxiety Control Questionnaire (Rapee et al., 1996), Veterans Rand-12 item questionnaire (Kazis et al., 1999), and Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001). Finally, the Activity Card Sort (ACS) will be administered All participants who participate in the baseline assessment will receive $60 compensation for their time. Those participants that meet inclusion/exclusion criteria will be randomized to either BREATHE or the psychoeducation condition (Healthy Living for Reduced Anxiety).

Then, participants will receive materials for their condition. Materials include a DVD video and instructions to view the videos on the website. Each condition included a binder with materials specific to each condition. Portable personal DVD players will be lent to participants who do not have access to a DVD player.

After the baseline assessment is complete, participants assigned to BREATHE will be instructed on how to complete Subjective Units of Distress Scale (SUDS; Wolpe (1969) before and after each PMR practice throughout the study. SUDS ratings ranging from 0 to 100 (least to most distressed) have been used to document a patient's subjective experience during anxiety disorder treatments such as systematic desensitization and trauma- focused therapies. This measure was selected to track anxiety (0 = no anxiety, 100 = extreme anxiety) before and after practicing PMR. This is an important part of the clinical intervention in that it draws the patient's attention to the changes in anxiety following the PMR intervention. SUDS may help monitor homework compliance and identify problems, such as relaxation-induced anxiety.

7.3 *Measures*. In the baseline **demographic questionnaire**, basic participant characteristics including gender, marital status, race, and ethnicity will be collected. Additional questions about participants' previous experience with relaxation, breathing training, meditation, Tai chi, and any other similar techniques will be assessed. The information needed about medical conditions to complete the Deyo-adjusted Charlson Comorbidity Index (Charlson, Pompei, & MacKenzie, 1987) will come from the comorbidity questions (Katz et al., 1996) about medication conditions on the demographic questionnaire.

The **Structured Clinical Interview for DSM-5 Disorders (SCID-5;** First*,* Williams, Karg, & Spitzer, 2015**)** is a structured interview that assess diagnostic criteria each DSM-5 disorder. The interview can take 90 to 120 minutes. The SCID-5 is included to assess inclusion and exclusion criteria.

Geriatric Anxiety Scale (GAS; Segal et al., 2010**).** The GAS is a 30-item measure of somatic, cognitive, and affective symptoms of anxiety. The first 25 items of the measure are used to compute the total score; the last 5 items provide information about the content of worries or fears. Participants provide severity ratings for items using on a four-point Likert-type scale. The GAS is administered to assess severity of anxiety symptoms and is the primary outcome in this study.

The **Patient Health Questionnaire-9 (PHQ-9;** Kroenke, Spitzer, & Williams, 2001**)** is a 9-item depression assessment rated on a four-point Likert-type scale with scores ranging from 0 to 27. The PHQ-9 is administered to characterize participants' depression symptoms.

PROMIS Anxiety 7 item anxiety scale (Reeve et al., 2007) is included to assess anxiety symptoms. This measure will be used to quantify the severity of anxiety symptoms. The benefit of using this measure is that it is valid for older and younger adults and the findings can be used to compare and contrast our cohort to other studies in the literature.

Anxiety Control Questionnaire (**ACQ**; Rapee et al., 1996) is a 30- item self-report measure assessing one's perceived ability to control anxiety-evoking situations and emotional reactions to these situations. This measure assesses aspects of avoidance and was included to examine whether BREATHE has an effect on perceived anxiety control compared with the psychoeducation control condition.

Hamilton Anxiety Scale (**HAM-A**; Hamilton, 1959) is a clinician-administered rating scale, assesses the severity of anxiety using 14-items rated on a five-point scale. The Structured Interview Guide for Hamilton Anxiety Scale (Shear et al., 2001) provides descriptive anchors to guide clinician decision making ratings based on both frequency and severity.

Activity Card Sort (ACS; Baum & Edwards, 2008**).** The ACS contains 80 photographs that depict the performance of instrumental activities, low-physical-demand leisure activities, high-physical-demand leisure activities, and social activities. The ACS was selected as a measure of activity engagement for the present study because it assesses the presence and the loss of activity. We will administer the ACS using an interactive sorting task (Q-sort procedure; Albert et al., 2009). Participants will be asked to divide the stack of photographs into piles of activities that they currently do not perform and activities that they do perform. Then, participants will divide the stack of activities that are currently not performed into two additional piles: "never-performed" and "used-to-but-no-longer- perform" activities. For the stack of activities that are currently performed, these will be divided into "hard-to-do" and "easy-to-do" activities based on a time frame of "today or the past 30 days."

The four piles will be used to calculate lifestyle-adjusted function (Albert et al., 2009). By excluding activities that participants never performed, the lifestyle-adjusted function score will accurately reflect loss, gain, or changes in activity participation. We also have participants select their top five activities that they would like to do more frequently if not experiencing anxiety. Participants will make ratings of these measures before and after treatment.

Veterans RAND Health Survey (**VR-12**; Kazis et al., 1999) is a 12-item measure assessing mental and physical health and functioning.

Cumulative Illness Rating Scale for Geriatrics (CIRS-G; Miller & Towers, 1991). The CIRS-G was selected to measure comorbidity. The measure will be completed based on the demographic questionnaire responses and based on a medical record review. Research assistants have used retrospective scoring with the CIRS-G to obtain inter-rater ICC of .81 (Salvi et al., 2008).

7.4 *Study Design*. The objectives will be addressed with a 12-week randomized control trial (RCT) that compares a 4-week treatment, BREATHE (described below), and 8-week follow-up period, with a psychoeducation control (Healthy Living). All participants will be offered the option to enroll in the alternative treatment after the post-treatment assessment.

7.5 *Randomization*. Participants will be randomized to BREATHE or psychoeducation. A statistician will create a randomization scheme with varying sized blocks and a researcher/evaluator independent from the study team will take the randomization scheme and enclose the assignments in sealed envelopes that are sequentially numbered. At the baseline visit, the study coordinator, evaluator, or the PI will open the sealed envelope that contains the results of the randomization.

7.6 *BREATHE Intervention*. The BREATHE program consists of weekly video lessons that participants watch on DVD or on a password-protected website along with weekly telephone check-ins. The videos teach two behavioral interventions: diaphragmatic breathing and progressive muscle relaxation (PMR) as described earlier in the background section. Participants will receive a telephone call from study staff on a weekly basis to check in about problems with the videos or the intervention. Participants will be instructed to complete one module a week. Each module consists of a lesson video and a video to be used to guide daily practices. Participants will receive a telephone call from study staff (i.e., BREATHE coach) on a weekly basis to check in about problems with the videos or the intervention. Participants will be asked to report the number of times they practiced relaxation and their SUDS ratings before and after the PMR practice during weekly telephone check ins. Each weekly video lesson will consist of brief psychoeducation, teaching of new skills, and assigned home practice. The content of the weekly sessions is available from the PI or is described elsewhere (Gould et al., 2017; 2019). At the end of the BREATHE treatment (week 4), participants will be asked to complete the telephone assessment as described below.

7.7 *Psychoeducation Intervention*. Like the BREATHE group, the psychoeducation group (Healthy Living for Reduced Anxiety) will receive weekly telephone calls to provide technological assistance and other trouble shooting during weeks 1 through 4. The format of Healthy Living will be similar to BREATHE in that there are 20 to 35-minute video lessons viewed by participants once a week for four weeks. The videos will be primarily lecture based with no instructions to increase activities or engage in relaxation. Video content draws from information about stress, anxiety, and aging based on VA and NIA psychoeducational information and videos. Week 1 focuses on what anxiety is and what causes anxiety. Week 2 focuses on how to cope with anxiety and healthy sleep tips. Week 3 focuses on healthy living through physical activity (walking, gentle stretching). Week 4 focuses on healthy eating. Weekly telephone calls will address issues with the videos or answer specific questions about the materials. Participants in the Healthy Living group will also have additional readings that correspond to the videos.

7.8 *Week 4 and 8 Assessments*. At the end of the 4-week intervention (BREATHE or psychoeducation), participants will be asked to complete the GAS, PHQ-9, VR-12, and ACS [5 activities frequency only] over the telephone. Participants will also be instructed to continue with home practice of PMR for four weeks. Participants will be paid $10 for each assessment.

7.9 *Post-treatment Assessment/12 weeks*. At post-treatment, a participant completes the GAS, PHQ-9, VR-12, PROMIS Anxiety, ACQ, and ACS. Study personnel also conduct the HAM-A and a qualitative interview to seek feedback on the interventions. Participants are paid $60 for completing this assessment.

8 Statistical analyses

8.8 *Baseline analyses*. Baseline group means and distributions using χ^2 and independent samples t-tests are compared to determine whether randomization results in equivalent groups.

8.9 *Dropouts*. We will examine whether participants completing the study differed from those who do not complete the study (i.e., drop-outs). Efforts are made to obtain data from individuals who discontinue participation.

8.10 *BREATHE Intervention*. Engagement with the BREATHE intervention is examined by estimating the intervention dose via a calculation of relaxation practices completed during the four-week intervention phase. The activities that participants engage in using breathing or PMR skills are summarized.

8.11 *Outcome analyses*. Mixed effects models are used to examine the primary and secondary hypotheses using intent-to-treat principles. Maximum likelihood estimation for missing values will be used in the mixed effects models. In all models, the fixed factor is treatment type (BREATHE vs. Healthy Living), with four timepoints (GAS, VR-12) or two timepoints (ACS lifestyle adjusted functioning scores). Effect sizes are measured using Hedges' *g* to adjust for small sample size.

9 *Publication*

The outcomes of this trial are being written up in a publication to be submitted. The findings were presented at the 2021 Gerontological Society of America Conference.

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