# Study Protocol and Statistical Analysis Plan

1. Administrative Information
   1.1 Title, Registration, versions, and revisions
   Title: Reducing Late-Life Anxiety and Improving Function with Self-Directed Relaxation
   IRB: 32239 (last approved date: 03/17/2017)
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3 Background
   3.1 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, 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. Despite evidence in support of PMR for late-life anxiety (Thorp et al., 2009) and reduction of somatic symptom (e.g., Gift, Moore & Soeken, 1992), this intervention is not widely available to older adults. Dr. Gould began to address this issue by developing a self-directed version of PMR: Breathing, Relaxation, and Education for Anxiety Treatment in the Home Environment (BREATHE).

4 Study Summary and Aims
   4.1 Purpose: 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). This program consists of weekly video lessons that participants watch on DVD along with weekly telephone check-ins. In BREATHE participants will learn two behavioral interventions: diaphragmatic breathing and progressive muscle relaxation (PMR). The purpose of the study is to examine whether the self-directed BREATHE program is superior to a wait list control in reducing anxiety in older adults with anxiety disorders.

5 Inclusion and Exclusion Criteria
   5.1 Inclusion Criteria: Men or women aged 60 and older who meet DSM-5 criteria for an anxiety disorder(s) (Generalized Anxiety Disorder, Panic Disorder, Agoraphobia, Social Anxiety Disorder or Anxiety 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 Obsessive Compulsive Disorder, psychotic disorders or serious mental illness (bipolar disorder). Participants must not be taking benzodiazepines more than once a week. Participants with dementia or cognitive impairment, defined as a score of 6 or greater on the Short Blessed Test

will be excluded. Participants enrolled in other psychological or pharmacological treatment studies for psychiatric conditions will be excluded.

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

7 Study Procedures

7.1 Screening Procedures: A telephone interview will be conducted with potential participants to determine study eligibility. Potential participants will be offered the opportunity to complete this interview as a face-to-face interview if the participant would prefer to do so. 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 (Katzman et al., 1983) is a weighted 6-item brief cognitive assessment that can be administered in person or over the phone. This measure, also called the Blessed Orientation-Memory-Concentration Test, and 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.

An additional screening question about whether individuals take any benzodiazepines will be included in the telephone screen to assess this exclusion criteria. Participants will be excluded if they use short-acting benzodiazepines (lorazepam, alprazolam) twice a day or more frequently. Participants will be excluded if they use long-acting benzodiazepines (flurazepam, librium, clonazepam, diazepam, temazepam) once a day or more frequently.

7.2 Baseline Visit: Participants who are deemed to meet inclusion/exclusion criteria for age, cognition, and benzodiazepine use will be invited to an approximately two to three hour face-to-face baseline assessment and paid $30. During the initial face-to- face assessment informed consent will be obtained and the baseline assessment visit will be completed. Those who are deemed not eligible for the treatment will be provided with appropriate referrals. The remaining assessment of inclusion/exclusion criteria will take place during the baseline assessment. Participants must meet DSM-5 criteria for an anxiety disorder(s) Generalized Anxiety Disorder, Panic Disorder, Agoraphobia, Social Anxiety Disorder or unspecified anxiety disorder. Those patients with Obsessive Compulsive Disorder (OCD) will be excluded as efficacious treatments for OCD are well established (e.g., exposure and response prevention). Assessment of anxiety disorders will be completed by trained study staff who use the Structured Clinical Interview for DSM-5 Disorders (SCID-5). At the beginning of the face-to-face baseline assessment, written informed consent and consent for audiotaping of the SCID-5 will be obtained. Audiotaping will

be used for supervision purposes and to assess inter-rater reliability of diagnoses. Participants will be allowed to continue with the study if they do not consent to audiotaping of the SCID-5 interview.

Participants with comorbid psychiatric disorders, such as depression or post-traumatic stress disorder, will be included. However, participants with documented diagnosis of dementia or a serious psychiatric disorder (psychotic disorder, schizophrenia, schizoaffective disorder, or bipolar disorder) of identification of serious psychiatric disorders by SCID-5 screening questions will be excluded. Additional baseline assessments include completion of a demographic questionnaire, administration of the Geriatric Anxiety Scale (GAS) to assess anxiety symptom severity, Activity Card Sort (ACS) to assess activity engagement, Somatic Symptom Scale – (SSS-8), Older Adult Social Evaluative Situations Scale (OASES), and depression symptoms measured with the Patient's Health Questionnaire (PHQ-9). Comorbidity will be measured with the Deyo-adjusted Charlson Comorbidity Index (CCI). This is calculated from the self-report comorbidity questionnaire in the demographic questionnaire.

Participants who do not meet SCID-5 criteria will be paid $30 and excluded from the study after completing the self-report measures and the ACS. Additional participants will be recruited to meet the goal of 40 participants randomized.

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 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 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). 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.

Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a 9-item depression assessment rated on a four-point Likert-type scale with scores ranging from 0 to 27. It includes one item that inquires about suicide ideation. The PHQ-9 is administered to characterize participants' depression symptoms.

Somatic Symptom Scale (SSS-8). The SSS-8 is an 8-item somatic symptom assessment rated on a

five-point Likert-type scale with scores ranging from 0 to 32. The SSS-8 is administered to characterize participants' somatic symptoms.

Older Adult Social Evaluative Situations Scale (OASES). This measure is a 37-item measure that assess anxiety about and avoidance of social situations. This is included as a secondary outcome measure.

Activity Card Sort (ACS). 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 a pile 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.

Physiological measures are systolic and diastolic blood pressure, pulse rate, and oxygen saturation measured with a Welch Allyn Spot Vital Signs monitor. Five-minute resting baseline assessments will be obtained at baseline and post-treatment. A five-minute post-relaxation practice will also be obtained at post-treatment.

7.4 Randomization: Participants will be randomized to BREATHE or wait list. A statistician will advise on completing randomization in order to obtain two equal groups. Randomization scheme will be created by individuals not related to the study. At the baseline visit, Dr. Gould or her research assistant will open a sealed envelope that contains the results of the randomization. Participants will not be told which group they are randomized to, but based on the differences in the active intervention compared with wait list; they will likely be able to ascertain what their randomization group is. Because of the nature of psychological interventions, it is difficult to achieve blindness in RCTs with psychological interventions.

7.5 Study Design

The objectives will be addressed with an 8-week randomized control trial (RCT) that compares a 4 week treatment, BREATHE (described below), and 4 weeks of practice of the intervention, progressive muscle relaxation, with a wait list control. Wait-list

participants will be offered the option to enroll in the active treatment after the 8 week post-treatment assessment.

7.5.1 Protocol for BREATHE Intervention Group:

Baseline Assessment/Pre-treatment Assessment Protocol: After the baseline assessment is complete, participants will be instructed on how to complete Subjective Units of Distress Scale (SUDS) 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.

Instructions on how to use and play the DVD will be provided. Portable personal DVD players will be lent to participants who either do not have access to a DVD player or would prefer to use a portable player. The surface of the DVD player will be cleaned with rubbing alcohol wipes to disinfect the players between participants. Participants will be provided their own copy of the BREATHE DVD to use throughout treatment and keep for future use.

BREATHE Intervention Overview: 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 will incorporate 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. BREATHE videos will use this format and will 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.

The innovative aspect of this treatment is that BREATHE will be delivered via video lessons recorded on DVDs. The script for the DVD treatment is included as an attachment. Participants can view the DVD on a personal DVD player. The treatment also involves telephone check-ins during weeks one through four. The treatment will be delivered via DVD. The following four chapters detail the skills that make up the program. Each session will be turned into video lesson approximately 20-40 minutes in duration. During weeks 1-4 participants will view a new video module each week. Practice exercises are assigned each week and separate videos will be filmed to guide participants during practice. Homework forms are included for patients to use to record their practices. Participants will be asked to practice PMR twice daily as part of the behavioral treatment.

Participants will receive a telephone call from study staff on a weekly basis to check in about problems with the videos or the intervention. Study staff will contact participants each week to troubleshoot and answer questions. Homework compliance will be reported by phone to study staff. Participants will be asked to report the number of times they practiced PMR and their SUDS ratings before and after the PMR practice during weekly telephone check ins. Each weekly session 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 in the published outcome paper.

7.6 Week 4 Assessment: At the end of the BREATHE treatment (week 4), participants will be asked to complete the GAS over the telephone. Participants will also be instructed to continue with home practice of PMR for four weeks. One additional reminder post card and telephone call at week 6 will occur to help patients with any issues that arise. After a month of home practice, which is 8 weeks from baseline assessment, participants will come to the VA for a face-to-face post-treatment assessment with study staff and will be paid $30.

7.7 Post-treatment Assessment/8 weeks: At post-treatment, a 5 minute baseline measurement of heart rate, blood pressure, and pulse will be obtained. Then, the 16-muscle group PMR will be practiced by the BREATHE and the control group by briefly viewing the initial PMR instructions video (control only) and then following along. BREATHE participants will be shown the 16 muscle group practice video to follow along with. Following this practice, a 5-min physiological measurement period will be obtained to examine physiological variables as a function of participant's experience with PMR. The Anxiety disorder sections of the SCID-5 will be administered at post treatment to determine if participants meet criteria for any anxiety disorders. Then, the participants will complete the GAS to assess anxiety symptom severity, SSS-8 to assess somatic symptoms, PHQ-9 to measure depressive symptoms, OASES to assess anxiety about and avoidance of social situations, and ACS to assess activity engagement. We will attempt to obtain partial follow-up data from lost to follow- up participants, through mailed questionnaires (GAS and PHQ-9) in participants do not complete the final face-to-face assessment. We will solicit feedback from participants on their experience with BREATHE to determine what participants liked, what issues arose, and

what participants did not like about the treatment or DVDs (see attached post-treatment questionnaire).

8 Statistical analyses

8.1 Baseline analyses: We compared baseline group means and distributions using $\chi^2$ and independent samples t-tests to determine whether randomization resulted in equivalent groups.

8.2 Dropouts: We examined whether participants completing the study differed from those who did not complete the study (i.e., drop-outs). Efforts were made to obtain data from individuals who discontinued participation.

8.3 BREATHE Intervention: Engagement with the BREATHE intervention was examined by estimating the intervention dose via a calculation of relaxation practices completed during the four-week intervention phase. The activities that participants engaged in using breathing or PMR skills were summarized.

8.4 Outcome analyses: Mixed effects models were used to examine the primary and secondary hypotheses using intent-to-treat principles. Maximum likelihood estimation for missing values was used in the mixed effects models. In all models, the fixed factor was treatment type (BREATHE vs. wait list), with three timepoints (anxiety) or two timepoints (activities; depression; somatic symptoms). Effect sizes were measured using Hedges' *g* to adjust for small sample size.

8.5 Responder Analyses: We conducted responder analyses using intent-to-treat principles with participants who dropped out classified as non-responders. Responder status was defined by SCID-5 anxiety diagnoses. To be classified as a responder, an individual would either no longer meet criteria for an anxiety diagnosis or would not meet full criteria for an anxiety disorder at post-treatment (i.e., *GAD* at baseline to *Anxiety Unspecified due to insufficient symptoms* at post-treatment).

9 Publication: The outcome of this trial have been published in the *American Journal of Geriatric Psychiatry.* https://doi.org/10.1016/j.jagp.2018.12.018