1. TITLE
Dose Timing of D-Cycloserine to Augment CBT for Social Anxiety Disorder

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3. PURPOSE

D-cycloserine (DCS) is a partial N-methyl-D-aspartate glutamate agonist that has been shown to enhance exposure therapies for anxiety disorders. This approach is grounded in recent research advances in understanding the neural circuitry underlying fear extinction and is based upon one of the striking successes of translational research. Most human clinical studies to date have administered DCS at least 1 hour prior to the exposure sessions. This dose-timing strategy limits the clinical utility of this highly promising augmentation strategy, especially since accumulating research suggest that the efficacy of DCS for enhancing exposure therapy outcomes may depend on the success of exposure sessions. Specifically, post-hoc analyses of our previous studies (Smits et al., 2013a,b) evaluating DCS enhancement of exposure therapy indicate that, compared to placebo, DCS enhances exposure outcomes when patients end their therapy sessions with low fear levels, but does not enhance exposure therapy outcomes when patients end their sessions with higher fear levels. Of note, there is no evidence to suggest that DCS causes an absolute worsening of symptoms, even when session end fear levels are high.

Importantly, pre-clinical and initial clinical data suggest that the DCS exposure-augmentation effect can also be obtained when DCS is administered immediately after an extinction trial when it follows successful exposure sessions. The proposed study builds upon this extant research by testing the efficacy of tailored post-session DCS administration (i.e., only following successful exposure sessions) for augmenting exposure therapy. In order to maintain high internal validity in this R34 study, we will enroll patients with social anxiety disorder (SAD) in a previously validated 5-session CBT protocol and randomize them to: (1) tailored post-session DCS administration; (2) pre-session DCS administration; (3) placebo administration; or (4) non-tailed post-session DCS administration. The primary outcomes will be short- and long-term improvements in social anxiety severity: We expect that the tailored post-session DCS administration condition will outperform the pre-session DCS administration, placebo administration, and non-tailed post-session DCS administration conditions, respectively, at posttreatment, 1-month and 3-month follow-up. In addition, we will explore potential moderators of the efficacy of tailored post-session DCS administration for augmenting exposure therapy. This application is the logical next step in the study of DCS. It provides an important innovative move toward
the realization of personalized medicine by providing the first step in the eventual development of an algorithm for administering DCS in CBT with the goal of maximizing the efficacy and cost-effectiveness of therapy for anxiety disorders, which are some of the most prevalent mental conditions, making this a project of potentially high public health significance.

A secondary aim of this study is to determine whether DCS can enhance fear extinction retention – the hypothesized mechanism of action of CBT for the anxiety disorders. To this end, we will subject eligible study participants to a validated protocol for testing fear extinction retention in humans (Zeidan et al., 2012; see below) and randomly assign them to either precede this procedure with the administration of 50 mg of DCS or pill placebo. This experiment will be conducted following eligibility screening and prior to baseline testing for the clinical trial as outlined above. We expect that participants assigned to the DCS condition will evidence greater fear extinction retention relative to participants assigned to pill placebo. By obtaining data on the efficacy of DCS for enhancing fear extinction retention in humans, this secondary experiment will allow us to (1) make inferences with the respect to the mechanisms of action of DCS for enhancing CBT outcomes and (2) interpret possible null findings in the clinical trial - i.e., primary aim of this study.

A third aim of this study is to examine the impact of sleep quality on in-session extinction and treatment outcome of CBT for social phobia. Research shows that poorer baseline sleep quality and higher levels of nonrestorative sleep the night after a treatment session predict poorer treatment outcome in CBT for social phobia (Zalta et al., 2013). However, the mechanisms driving the relationship between sleep and treatment outcome remain unclear. One possibility is that poor quality sleep before a treatment session negatively impacts in-session learning. Another possibility is that sleep the night after a session impacts the relationship between in-session learning and treatment outcome (i.e., good in-session learning is not consolidated if sleep is poor the night after the session). To explore this issue, we will have subjects in the study complete a baseline sleep assessment (PSQI). Subjects will then complete a sleep diary for the night before and the night after each treatment session. We expect that poor sleep quality the night before a session will reduce in-session learning. We also expect that poor sleep quality the night after the session will moderate the relationship between in-session learning and treatment outcome as measured by the The Liebowitz Social Anxiety Scale (LSAS) and the Social Phobic Disorders Severity and Change Form (SPD-SC Form).

### 4. PROCEDURES

We will recruit 156 adults (18-70) with social anxiety disorder (52 per site; Rush University Medical Center, Boston University, University of Texas at Austin). After eligibility screening, all participants will be invited to take part in two experiments. In the first experiment, which takes place during the seven days following eligibility screening, participants will be enrolled in a validated protocol for testing fear extinction retention in humans (Zeidan et al., 2012; see below) and randomly assigned to either precede this procedure with the administration of 50 mg of DCS or pill placebo. During day 1 of experiment, participants will take the study pill and then undergo fear conditioning procedures which are followed by fear extinction training procedures. During day 2 of the experiment, which occurs 7 (+/- 3 days) later, participants will return for extinction retention testing. The primary outcome is extinction retention which is indexed by the skin conductance response (SCR) to testing on day 2 relative to SCR during the conditioning procedures on day 1. Following this experiment, participants will be invited for baseline testing and enrolled in a 5-session CBT protocol.
session 2, they will be randomly assigned to: (1) Tailored post-session DCS: pre-session PBO and selective post-session DCS administration during sessions 2-5; (2) Pre-session DCS: pre-session administration of 50 mg of DCS and post-session administration of pill placebo (PBO) (during sessions 2-5); (3) Placebo; pre- and post-session session administration of PBO (during sessions 2-5) or (4) Non-tailored post-session DCS: pre-session PBO and post-session DCS administration (during sessions 2-5; see Table 1). Eligible participants will be randomly assigned to either condition (blocked by condition assignment in the first experiment) by the project biostatistician (David Rosenfield, Ph.D. – Consultant at Southern Methodist University). Primary outcome measures will be short- and long-term improvements in social anxiety severity. Proposed moderators include demographics, clinical characteristics, and personality traits. These variables will be assessed at baseline, weekly during the treatment phase, and at posttreatment, 1-month, and 3-month follow-up.

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<thead>
<tr>
<th>Table 1. Conditions</th>
<th>Pre-session Pill</th>
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<td>1. Tailored Post-session DCS</td>
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<td>DCS After Successful Sessions</td>
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<td>PBO After Non-successful Sessions</td>
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<td>PBO</td>
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<tr>
<td>4. Non-tailored Post-session DCS</td>
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Eligibility Screening

**Internet and Telephone Prescreen.** A telephone prescreen will be conducted for all potential participants. Persons who appear eligible will be asked to come to the study site for diagnostic screening. The prescreen procedure is the first point of contact for participants, and it will allow us to ask critical information about the potential participant’s willingness and ability to commit to the frequency of clinic visits as well as the assessment of inclusion criteria. Participants will also be asked during the phone screen whether they have sufficient command of the English language, as visits will be conducted in English and all self-report measures are in English. Persons who appear eligible based on the telephone prescreens will be asked to come to the study site facility for diagnostic and medical screening.

**Screening Visit 1: Diagnostic Screening.** Upon arrival, participants will receive an informed consent form explaining the details of the study, potential benefits and risks of participation, and the procedures they will undergo if they choose to participate. If the individual chooses to sign the informed consent, he or she will begin the psychiatric evaluation process, which will include the Structured Clinical Interview for DSM-IV (SCID) and the Liebowitz Social Anxiety Scale (LSAS) to evaluate the presence of psychiatric inclusion and exclusion criteria. The interview will also allow for assessment of primary and secondary diagnoses if applicable (see 6C1.a for integrity of diagnostic assessment).
Screening Visit 2: Medical Screening. A study physician will review the patient’s medical history and conduct a complete physical examination, ensuring that there are no medical conditions that preclude study participation. Safety evaluations will also include laboratory tests (CBC, chemistry profile, thyroid function test, and urinalysis). A urine pregnancy test will be performed on all female participants of childbearing potential at intake and monthly following randomization. The physician will also discuss the potential side effects of DCS with potential participants. Any positive pregnancy tests resulting in exclusion from the study will be handled by having the PI or physician meet with the participant to provide a feedback session.

Fear Extinction Retention Experiment. Prior to the baseline visit, eligible participants will take part in a previously validated 2-day fear conditioning and extinction paradigm (Zeidan et al., 2012. In this paradigm, participants will undergo Habituation, Conditioning, and Extinction Learning on Day 1 (total duration is 60 minutes), and Extinction Recall, and Fear Renewal on Day 2 (total duration is 60 minutes) (see Figure 1). Prior to initiation of experimental procedures, recording electrodes will be attached to the palm of the participant’s left hand to measure SCR, and stimulating electrodes will be connected to two fingers of the participant’s right hand through which the electric shock will be delivered. SCR will be measured through a 9-mm (sensor diameter) Sensor Medics Ag/AgCl electrodes. During the experiment, participants will be seated upright in a chair and view images on a computer monitor 3 feet away. Digital photographs of two different rooms constitute the visual context. Within each room, an unlit lamp will be shown before being “switched on” to one of three colors (blue, red, or yellow), which constitute the conditioned stimuli (CSs). Only two colors will be shown in any given visit. The CS+ color (followed by shock), the CS− color (no shock), and the contexts will be pseudorandomly selected and counterbalanced across participants and across visits. The US is a 500 ms electric shock previously selected by the participant to be “highly annoying but not painful” and delivered to electrodes attached to the second and third finger of the right hand. The shock electrodes will remain attached to the fingertips throughout both days of the experiment, but the US will be administered only during the Conditioning session on Day 1. On Day 1, the to-be CS+ and the to-be CS− (four trials of each will be presented within each virtual context in a counterbalanced manner with no US presentation (Habituation phase). The Conditioning phase will follow with five CS+ trials that will be immediately followed by the US (100% reinforcement), and five CS− trials (i.e., not followed by shock). All conditioning trials will use the same context. The Extinction phase will be divided into two identical subphases separated by a 1-min rest period. For each Extinction phase, five CS+ trials and five CS− trials will be presented within the extinction context. On Day 2, which will be scheduled 7 days (+/- 3 days) from Day 1, the Extinction Recall phase will be presented and is identical to an Extinction subphase on Day 1. The Renewal phase will be similar to the Conditioning phase, but without US presentation. Upon conclusion of participation, each subject will be debriefed and arrangement made to be sent the $50 participation fee.
Randomization

The project biostatistician, Dr. David Rosenfield, will oversee the randomization for both experiments. We will block-randomize patients by site, using variable-sized permuted block-randomization (block sizes will vary from 4 to 12). Randomization for each site will be calculated before the first subject is run, and the condition assignment be put in numbered envelopes. Envelopes will be opened and randomization will occur at the inception of the second session. Prior to data analyses, Dr. Rosenfield will check the balance of randomization and control for any factors that are imbalanced.

Intervention Modules

**CBT Protocol.** Consistent with our previous study (Hofmann et al., 2006) and an independent replication trial (Guastella et al., 2008), we will use a 5-session version of a group CBT protocol with 4-6 patients and 2 therapists per group emphasizing repeated exposure practices. Session 1 involves an introduction and orientation to the CBT model. Sessions 2-5 emphasize repeated exposure tasks, which consist of role-play activities to confront fearful situations in a group setting while disputing cognitive distortions (coupled with the fading of safety behaviors). Therapists are PhDs or advanced, trained doctoral students supervised by Drs. Hofmann and Smits. In the first session (60 minutes), patients are provided with a model of social anxiety disorder and its treatment with exposure therapy. In sessions 2-5 (90 minutes each), patients will be introduced to the social exposure procedures. The exposure practices of increasing difficulty consist of giving speeches about topics chosen by the therapists in front of the other group members, confederates, and a video camera. Patients’ videotaped performance will then be reviewed. At the conclusion of each exposure session, patients will be encouraged to continue to apply home-practice strategies (such as giving speeches in
front of a mirror). Continued practice of the interventions will be considered part of treatment, and patients will be asked to refrain from alternative treatment for four weeks following completion of the last treatment session.

**Pill (D-cycloserine or Placebo) Administration Protocol.** The study medication will be implemented in two separate portions of the protocol: 1) Fear extinction retention experiment 2) CBT Sessions 2-5. All study capsules will be compounded by Abrams Royal Pharmacy in Dallas, TX containing: (a) 50 mg DCS (derived from Seromycin 250 mg capsules) and polyethylene glycol 3350 powder or (b) polyethylene glycol 3350 powder (Placebo). In order to maintain the blind, we will implement the following procedures for both study components: (1) All capsules will be identical in appearance; (2) All capsules will be administered by research staff blind to study condition and not involved in the treatment or assessment of study participants.

**Fear Extinction Retention Experiment:** The participant will receive one 50-mg study pill (i.e. dcs vs. placebo) immediately before Day 1 of the experiment. Individual doses of study medications, prescribed by Dr. Tirado, will to be dispensed to patients by study personnel. Because all pill taking is observed, no pill counts are necessary to help ensure adherence to the randomized drug condition. All medications will be stored in a refrigerator.

**CBT Session Pill Administration:** The pharmacist will fill three bottles (one pill each) for each patient for each session according to the schedule in Table 2. Research staff will administer a pill from Bottle 1 to each participant one-hour before the session and administer a pill from either Bottle 2 or 3 immediately after the session. The selection of Bottle 2 vs. Bottle 3 will be guided by the end fear level. Specifically, a pill from Bottle 2 will be administered when end fear is ≤40, whereas a pill from Bottle 3 will be selected when end fear is >40; (4) Both therapist and staff member will be blind to the contents of the bottles and additionally, the therapist will be blind to which post-session bottle is employed.

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<tr>
<th>Conditions</th>
<th>Pre-Session</th>
<th>Post-Session</th>
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<tbody>
<tr>
<td>Bottle 1</td>
<td>Bottle 2</td>
<td>Bottle 3</td>
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<tr>
<td>1. Tailored Post-session DCS</td>
<td>DCS</td>
<td>PBO</td>
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<tr>
<td>2. Pre-session DCS</td>
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<tr>
<td>3. Placebo</td>
<td>PBO</td>
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<tr>
<td>4. Non-tailored Post-session DCS</td>
<td>PBO</td>
<td>DCS</td>
</tr>
</tbody>
</table>

**A. LOCATION**

Data will be collected at the University of Texas at Austin, Rush University Medical Center (Rush), and Boston University (BU). Upon completion of data collection, data from the three sites will be merged and analysis will take place at UT, Rush University (PI: Mark Pollack), Boston University (PI: Stefan Hofmann), and Southern Methodist University (David Rosenfield; project statistician). All data will be encrypted with numeric codes so that no identifying information will be
included in analyses. Drs. Pollack, Hofmann, and Rosenfield will obtain IRB approval from their respective instructions prior to accessing the data.

Dr. Pollack can be reached at mark_pollack@rush.edu or 312-942-5372. Dr. Hofmann (BU) can be reached at shofmann@bu.edu or (617) 353-9233. Dr. Rosenfield (SMU) can be reached at or 214-768-1135. The IRB contact number for Rush University is (312) 942-5498, 617-358-6115 for Boston University, and 214-768-2030 for Southern Methodist University.

B. RESOURCES

The project is funded through the National Institute of Mental Health (NIMH) grant number R34MH099318.

C. STUDY TIMELINE

Data collection will begin upon IRB approval (tentatively, July of 2014) and has an anticipated end date of March 2017. Data will be analyzed until the end date of the NIMH grant period; 3/31/2017.

5. MEASURES

Assessment Instruments

Screening Variables

Eligibility Screen. This telephone-screening questionnaire will assess inclusion and exclusion criteria.

Psychiatric History. Baseline psychiatric functioning will be assessed by clinician-rated measures. Diagnostic exclusions and lifetime prevalence of Axis I diagnoses will be determined by the Structured Clinical Interview for DSM-5 (SCID; First et al., 2007) during the screening visit. The diagnostic interview will be administered by trained graduate student-level therapists and will be supervised by the PIs. This interview will serve to contextualize participants’ psychiatric history at baseline.

Laboratory Testing. A study physician will review the patient’s medical history and conduct a complete physical examination. Safety evaluations will also include laboratory tests (CBC, chemistry profile, and thyroid function test). A urine pregnancy test will be performed as part of the general physical medical evaluation of patients during screening and to assess for study exclusion criteria. In addition, a urine pregnancy test will be performed at intake as well as each month following randomization. Blood draws will be performed in our laboratory at the University of Texas by a certified phlebotomist and Clinical Pathology Laboratories in Austin will analyze the samples.

Suicide. The Columbia Suicide Severity Rating Scale (C-SSRS; Posner, Oquendo, Gould, et al. 2007) is a standardized measure of current and past self-injurious behavior, suicidal intent, and suicidal behaviors. The C-SSRS has demonstrated good reliability and validity (Hammad et al., 2006; Posner et al., 2007). The C-SSRS will be administered as part of the diagnostic interview in order to assess for a history of suicide attempts or current suicidal thoughts or plans.
Primary Outcome Measures

Fear Extinction Retention Measure. Consistent with Ziedan et al. (2012), the context will be displayed for 6 seconds with the lamp “turned off,” immediately followed by the light “turning on” for 12 seconds, with different colors representing the CS+ and CS− trials. The total stimulus presentation time will be 18 seconds (6 + 12 seconds). The intertrial interval will range from 12 to 21 seconds with an average of 16 seconds. SCR will be calculated for each trial by subtracting the mean SC level (SCL) for the 2 seconds immediately preceding context onset from the highest SCL recorded during the 12-second CS+/CS− presentation. Each SCR will be square root transformed to reduce heteroskedasticity (for negative SCR values, the square root of the absolute value was taken and then the negative sign replaced). A differential SCR will be calculated by subtracting the SCR to the CS− from the SCR to the CS+. A baseline SCL will be calculated for the Habituation phase by averaging the SCL over the 5 seconds prior to the onset of each context presentation and then averaging these values across all eight trials. An unconditioned response (UCR) will be calculated by subtracting the average SCL during the 1 second immediately following the shock (before onset of an SCR) from the maximum SCL during the 5 seconds after the shock. A measure of extinction memory (“extinction retention index”) during the Recall phase on Day 2 will be calculated as the average SCR during the first two trials of the Extinction Recall phase divided by the largest SCR during the Day 1 Conditioning phase and then multiplying this ratio by 100, thereby yielding a percentage of the maximum conditioned response. This value will then be subtracted from 100% to yield the extinction retention index. We will use the maximum SCR during the Conditioning phase as a reference to assess the extinction performance on Day 2. Animal studies typically use the last few conditioning trials for this calculation; however, SCR magnitude generally declines toward the end of conditioning in humans so this will not be used.

An independent evaluator (IE), blind to study condition, will administer the diagnostic assessments and clinician-rated symptom scales to be used during the clinical trial. All IEs will be experienced clinicians who will have undergone specific assessment training. We will adopt the specific guidelines for completing the scales based on experiences in previous trials of social anxiety disorder and other related disorders conducted by our group 3. Specifically, the scales used in this study have specific, carefully defined, anchors. Furthermore, Dr. Powers, who will lead the quality assurance/quality control effort for this trial, will periodically review assessment recordings and meet with clinical assessors to address potential drift.

The Liebowitz Social Anxiety Scale (LSAS). The Liebowitz Social Anxiety Scale (Liebowitz, 1987) is a 24-item scale that provides separate scores for fear and avoidance in social and performance situations; it is widely used in treatment studies of SAD. The instrument shows very good psychometric properties (Heimberg et al., 1999; Safren et al., 1999). The LSAS will be administered by the IE at intake, baseline, at each treatment session, post-treatment, and the 1- and 3-month follow-up assessment.

Social Phobic Disorders Severity and Change Form (SPD-SC Form). The Social Phobic Disorders Severity and Change Form (Liebowitz et al., 1992) is an expansion and adaptation of the Clinical Global Impression Scale (CGI) by Guy (1970) to
social anxiety disorder. Similar to the original CGI scale, the SPD-SC Form is rated on a 7-point scale to indicate severity and improvement. We chose this scale over the original CGI scale because it provides a more detailed analysis of psychological functioning for individuals with SAD. Furthermore, other studies (e.g., Heimberg et al., 1998) used the SPD-SC Form, but not the CGI. The SPD-SC Form will be administered by the IE at intake, baseline, each treatment session, at post-treatment, and the 1- and 3-month follow-up assessment.

**Secondary Outcome Measures**

Montgomery Asberg Depression Rating Scale (MADRS). The Montgomery Asberg Depression Rating Scale (Montgomery et al., 1979) is designed to measure the overall severity of depressive symptoms and has demonstrated good reliability, specificity for depressive compared to anxiety symptomatology, and sensitivity to change with treatment. The MADRS will be used to assess depression as a potential treatment moderator. The MADRS will be administered by IEs at intake, baseline, weekly during treatment, at post-treatment, and the 1- and 3-month follow-up assessment.

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). The Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott et al., 1993) is questionnaire rates 16 aspects of quality of life, including physical health, mood, activities of daily living, and overall life satisfaction.). The Q-LES-Q will be used to examine changes in quality of life with treatment. It will be self-administered at baseline, post-treatment, and the 1- and 3-month follow-up assessment.

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a well validated self-report instrument that assesses sleep quality in the past month. The measure consists of seven component items (range 0–3): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. These component items are summed to create a global PSQI score with higher scores reflecting poorer sleep quality (range 0–21).

Consensus Sleep Diary (CSD). The Consensus Sleep Diary was developed in collaboration with insomnia experts in order to adopt a standard form to facilitate comparisons across the field. The core CSD contains 9 consensus determined critical parameters of sleep. The core CSD was formatted so that one week of nightly sleep data is recorded on a single diary page.

**Potential Predictor Variables**

Dot-probe Paradigm The dot-probe paradigm is a computer-based reaction-time task, which is used to assess visual attentional biases. Subjects will sit in a small room, approximately 60 cm from the computer screen on which the words will be displayed. Each trial will begin with a fixation cross displayed at the center of the screen for 500ms. Following the disappearance of the cross, two words will appear 2cm above and 2cm below center. Two types of word pairs will be presented: threat-neutral pairs and neutral-neutral pairs. 48 threat-neutral word pairs from MacLeod et al. (2002) and 48 neutral-neutral pairs from Lueken and Appelhans (2005) will be used for this study; each pair will be presented twice (please see Word List). 500ms after the words appear on the screen, the words will disappear and a probe will appear (the letter “E” or “F”) in one of the locations previously occupied by the words. Congruent threatening trials are
trials in which the probe replaces the threat word, and incongruent trials are those in which the neutral word is replaced. The participant’s task will be to identify the letter as quickly and as accurately as possibly by pushing a key. The probe will remain on the screen until a response is detected. The time between trials will be 500ms.

An attentional bias for a word type will be defined by a participant’s increased speed of detection (faster reaction time) when the probe appears in the location held by a certain word type relative to the other word types.

**Moderator Variables**

**Demographic Variables.** Participants will be asked to provide standard demographic information (age, sex, race/ethnicity, level of education, cohabitation status) using forms employed in previous studies.

**Clinical Characteristics.** Baseline psychiatric functioning will be assessed by clinician-rated measures. This domain comprises clinical severity as assessed by the Social Phobic Disorders Severity Form; (SPD-SC; Liebowitz et al., 1992), depressive symptom severity as assessed by the MADRS (Montgomery et al., 1979), Axis I comorbidity (i.e., number of comorbid Axis I disorders as assessed by the SCID) as well as history of antidepressant and other psychotropic use.

**Personality Traits.** At the baseline session, participants will complete the 60-item NEO-Five-Factor Inventory (NEO-FFI; Costa et al., 1992), which is a psychometrically-sound measure of the five traits from the Five-Factor model of personality: agreeableness, conscientiousness, extraversion, neuroticism, and openness.

**In-Session Fear Ratings**

**Subjective Units of Distress Scale (SUDs).** Participants will provide fear ratings at the beginning of an exposure exercise (i.e., Beginning Fear) and just prior to the conclusion of an exposure exercise (i.e., End Fear). In addition, they will indicate their highest level of fear experienced during exposure after the exercise (i.e., Peak Fear). Fear ratings will be assessed using the subjective units of distress scale (SUDs; Wolpe, 1958), which ranges from 0 to 100 (0=no fear, relaxed; 25=mild fear, able to cope; 50=moderate fear, trouble concentrating; 75=severe fear, thoughts of leaving; 100=very severe fear, worst ever experienced). The procedures for collecting fear ratings were similar to that in previous social anxiety disorder treatment studies from our group and other groups (Hayes et al., 2008; Smits et al., in press; Smits et al., 2013; Smits et al., 2006a; Smits et al., 2006b). Specifically, during the first session, therapists will introduce patients to the SUDs scale as they work together to develop a fear and avoidance hierarchy. Attention will be given to the anchors such that patients can distinguish the different levels along the scale. Accordingly, by the time patients initiate exposure practice (i.e., session 2), they will have had ample practice using the scale. We will use a fear rating at the end of exposure of ≤ 40 as an index of exposure success (see Table 2).

**Measures of treatment integrity, safety, and acceptance**

**Credibility and Expectancy.** The Credibility/Expectancy Questionnaire (CEQ) is a widely used 6-item measure assesses treatment credibility and expectancy. It will be self-administered after the first treatment session.
Patient Adherence. Patient adherence to each intervention will be assessed as the number of total sessions attended.

Safety Monitoring and Concerns. Patients will be queried at each visit regarding the presence of adverse effects associated with the study medication. Review of medical history, physical examination, and laboratory tests will be performed at admission, and vital signs measured at the baseline visit. Patients with clinically significant abnormalities in vital signs (e.g., systolic blood pressure >150 mm Hg or diastolic blood pressure<50 mm Hg) at baseline will be excluded from further study participation and referred for appropriate clinical management.

AlcoBreath Screening. At each of the four study visits during which participants are asked to take medication, participants will be asked to breathe into an AlcoBreath tube in order to assess for the presence of alcohol before they are administered the study medication.

Assessment Schedule

Participants will receive thorough assessments prior to and over the course of this study. A tabular synopsis of the intervention and assessment data collected throughout the study is provided in the table below.

Table 3. Assessment Schedule for the Clinical Trial

<table>
<thead>
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<th>SV1</th>
<th>SV2</th>
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<th>Each Session</th>
<th>Posttreatment</th>
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### Exposure Success

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**NOTE:**  
1. Alcohol screening will be completed prior to sessions 2-5, which include DCS/PBO administration.  
2. Pregnancy tests will be conducted at intake (SV2) and monthly following randomization (week 2).  
3. Subjects will complete the CSD the night before and the night after each session.

### 6. PARTICIPANTS

#### A. TARGET POPULATION

We will recruit 52 participants ages 18 years and older. We have chosen to study adults with a primary psychiatric diagnosis of generalized social anxiety disorder as defined by DSM-5 criteria.

**Inclusion of Women and Minorities**
Fifty percent of participants will be female. We will make a concerted effort to promote awareness of our research project among women to ensure adequate representation in our sample. These efforts will include a) involving female research staff in patient recruitment; and b) advertisements in local media outlets popular with women. Recruitment materials will be tailored to low-literacy populations. Those who do not have adequate command of the English language will not be included in the study. All materials for the study including the measures are written in English and developing psychometrics for non-English speaking populations is beyond the scope of this project. Given the ethnic and racial compositions of the greater Austin area (approximately 35.1% Hispanic/Latino, 48.7% non-Hispanic; 68% White, 8.1% Black, .1% Asian/Pacific Islander, .9% American Indian; 2007 estimates), an ethnically and racially diverse sample is expected. If eligible, participants will be enrolled without regard to ethnic background. To increase minority participation, we will utilize a multimedia campaign with the following strategies: public service announcements on local radio stations, announcements in church bulletins, information booths at community functions, community presentations, promotional mailings, and placement of informational materials in retail outlets and organizations known to serve minorities. In addition, we will work with health clinics to target minorities. We expect that the ethnic/minority composition of the sample obtained by our recruitment efforts will mirror that of the communities in Austin.

Inclusion of Children

The study population will include adults and children of 18 years of age or older with social anxiety disorder. Though the treatment of SAD in younger children is a growing area of clinical focus and research study, assessment of social anxiety in these children is best accomplished with specific instruments that differ from those used with adults. Inclusion of different sets of instruments for youths would markedly complicate data analysis and interpretation. Further, the administration of CBT in younger children and adolescents requires modification of that which is administered to adults, often, for instance, including ongoing family involvement, which is beyond the scope of the present project. There is also a lack of empirical data regarding the safety of DCS in youths. Thus, we will not include children under age 18 in the study. Children between the ages of 18 and 21 will be included.

B. INCLUSION/EXCLUSION

Inclusion Criteria:

• Male or female outpatients ≥ 18 years of age with a primary psychiatric diagnosis (designated by the patient as the most important source of current distress) of social anxiety disorder as defined by DSM-5 criteria.
• A total score ≥ 60 on the LSAS.
• Physical examination and laboratory findings without clinically significant abnormalities.
• Willingness and ability to participate in the informed consent process and comply with the requirements of the study protocol.

Exclusion Criteria:
• A lifetime history of bipolar disorder, schizophrenia, psychosis, delusional disorders or obsessive-compulsive disorder; an eating disorder in the past 6 months; organic brain syndrome, mental retardation or other cognitive dysfunction that could interfere with capacity to engage in therapy; a history of substance or alcohol abuse or dependence (other than nicotine) in the last 6 months or otherwise unable to commit to refraining from alcohol use during the acute period of study participation.
• PTSD within the past 6 months. Entry of patients with other mood or anxiety disorders will be permitted if the SAD is judged to be the predominant disorder, in order to increase accrual of a clinically relevant sample. Patients with significant suicidal ideation (MADRS item 10 score > 3) or who have enacted suicidal behaviors within 6 months prior to intake will be excluded from study participation and referred for appropriate clinical intervention.
• Patients must be off concurrent psychotropic medication (e.g., antidepressants, anxiolytics, beta blockers) for at least 2 weeks prior to initiation of randomized treatment.
• Significant personality dysfunction likely to interfere with study participation.
• Serious medical illness or instability for which hospitalization may be likely within the next year.
• Patients with a current or past history of seizures.
• Pregnant women, lactating women, and women of childbearing potential who are not using medically accepted forms of contraception (e.g., IUD, oral contraceptives, barrier devices, condoms and foam, or implanted progesterone rods stabilized for at least 3 months).
• Any concurrent psychotherapy initiated within 3 months of baseline, or ongoing psychotherapy of any duration directed specifically toward treatment of the SAD is excluded. Prohibited psychotherapy includes CBT or psychodynamic therapy focusing on exploring specific, dynamic causes of the phobic symptomatology and providing management skills. General supportive therapy initiated > 3 months prior is acceptable.
• Prior non-response to adequately-delivered exposure (i.e., as defined by the patient’s report of receiving specific and regular exposure assignments as part of a previous treatment).
• Patients with a history of head trauma causing loss of consciousness, seizure or ongoing cognitive impairment. Current use of isoniazid or ethionamide compounds
• Insufficient command of the English language

C. BENEFITS

No direct benefits to the subjects are anticipated from this study. However, it is hoped that the information obtained from this study will advance our insight into the mechanisms of exposure therapy efficacy and DCS efficacy for augmenting exposure therapy for the anxiety disorders. It is also possible that subjects who participate in this study may benefit from the close monitoring and interventions provided to them. These potential benefits are provided without charge. Information provided as part of the treatment program may also help participants better understand the relationship between behaviors, thoughts and anxiety, and through understanding their disorder, maintain improvement over the long term. The primary risks to the patient are medication-related side effects, which based on review of the literature and experience to date appear to be
minimal, and discomfort associated with the assessments. Study personnel will be monitoring the patients’ clinical condition carefully and will withdraw patients from the study if their clinical condition warrants withdrawal. This study promises to provide important information about the relative efficacy and safety of a novel treatment strategy to improve outcome for patients with social anxiety disorder. The potential benefits of this study to patients suffering from social anxiety disorder justify the risks involved.

D. RISKS

With regards to the fear extinction retention paradigm, a subject can request that a study be stopped at any time. The electrical shock that will be applied to the fingers is uncomfortable but not painful.

This study is designed to provide dose-timing information on the relative efficacy of the addition of DCS to exposure based CBT for SAD compared to the addition of placebo. In addition to providing well-monitored clinical interventions with an effective psychosocial treatment for SAD, and the possibility that augmentation with DCS may offer additional benefit to participants in this study, information derived from the study may improve the treatment of future patients with SAD. The possible side effects for d-cycloserine include: headache, confusion, tremor, vertigo, memory difficulties, paresthesias (itching or tingling of the skin), seizure, drowsiness, confusion, dizziness, drowsiness, irritability, restlessness, depression, muscle twitching, trembling, nervousness, and speech problems. However, these side effects are most commonly related with doses greater than 500mg/day (i.e., chronic dosing), which is ten times the amount that participants will receive in this study. DCS is a safe medication in the dosage provided; indeed 10-fold doses are safely administered in chronic doses in other applications. Participants will be asked not to use any alcohol prior to the sessions and prior to the assessments. They will also be asked to breathe into a tube so that members of the study team can perform a test for the presence of alcohol. It should be noted that patients have been given acute 250mg doses in a previous study of obsessive-compulsive disorder and 1000mg doses in a previous study of depression, with no significant adverse side effects associated with the administration in either study (Heresco-Levy et al., 2013; Storch et al., 2007).

Some participants may feel uncomfortable about having treatment sessions audiotaped and reviewed by others (necessary for therapist supervision and treatment adherence). Additionally, clients may experience some disruption of daily activities due to scheduling of treatment sessions. Some treatment procedures, particularly the in vivo exposures are likely to provoke some discomfort. Participants will be informed about these risks and told that they may withdraw from the study at any time and may refuse to complete any treatment procedures they find too uncomfortable.
We developed and followed strict safety guidelines during previous and pilot studies that will be applicable to the proposed study:

1. Careful screening to identify patients whose risk for potential adverse outcomes is elevated were they to participate in the proposed research. Such patients including actively suicidal patients would be excluded from study participation and provided with appropriate clinical treatment.

2. All patients will meet regularly with a physician to monitor the emergence of adverse effects, as well as with clinicians experienced in the assessment and treatment of patients with social anxiety disorder. The treatment program formalizes assessment and monitoring of symptoms and adverse effects.

3. The study exclusion criteria include comorbid psychiatric disorders that may complicate the treatment process.

4. Patients are tested for alcohol prior to the administration of study medication in order to reduce the possibility of an adverse interaction.

5. In all phases of the research, participants will be instructed to contact study personnel at any time in the event of worsening of symptoms or relapse. Participants whose clinical condition has deteriorated will be removed from the study and given appropriate clinical care. This will be operationalized as all patients who have an increase in the Social Phobic Disorders Change Form (SPD-C) of greater than 5 (more than minimally worse) for two consecutive visits and any patient who becomes suicidal will be removed from the study protocol and treated clinically. All sites have trained clinical staff available by pager at all times to handle emergencies.

6. Participants failing to benefit from the study interventions will be provided with appropriate clinical care. Participants who begin the intervention and experience adverse outcomes sufficient to require removal from the study will receive open clinical care. The exact nature of "appropriate clinical care" will be determined by the judgment of clinicians familiar with the specific participant in collaboration with the subject and may include CBT, other psychotherapy, or referral for psychiatric treatment. Following completion of the study protocol, we assist participants in finding appropriate follow up care if needed.

7. The DSMB will oversee safety and other related issues pertinent to the ongoing study. Twenty-four hours/day emergency coverage with a study clinician will be available at each of the 3 sites. Patients are provided with cards with the emergency contact number. In the event of an emergency, the clinician will determine the necessary clinical intervention and provide and coordinate appropriate care.

8. As in any type of treatment or clinical research program, participants' confidentiality must be carefully guarded and respected. All data with identifying information will be stored in locked files or password-protected computer files. Data being analyzed will be identified by subject codes, and identifying information will be removed. The identity of participants will not be revealed in the presentation or publication of any results from the project. All assistants and others working on the project will be educated about the importance of strictly respecting participants' rights to confidentiality and will have completed training concerning proper practice in accordance with the Healthcare Information Portability and Accountability Act (HIPAA) regulations.

9. Recording of IE clinical interviews will be a required procedure. The purpose of the recording will be explained, confidentiality will be respected, and both informed consent and authorization for recording will be obtained as per requirements put forth by HIPAA. Digital recordings will be stored and moved between sites using a secure, password-protected and HIPAA-compliant website. Recordings will be stored under lock and key for use in further ratings and maintained until three years after the publication of study results.
10. If the person is in imminent danger of harming him/herself, the interview will be stopped and 911 will be called. If the person is not in imminent danger, but seems to be in need of psychological services for suicidality, they will be encouraged to call the counseling center if he/she is a student or a local community agency if he/she is a community participant, to set up an appointment. The interviewer will make one follow-up call to the participant in the week following the assessment to ascertain whether he/she made the appointment and to get the name of the counselor he/she has been assigned to in order to inform the counselor of the participant’s suicidality. If the participant decides not to make an appointment, no further action will be taken by Dr. Smits. If the participant makes the appointment and gives the name of the counselor, Dr. Smits will call the counselor within 24 hours to inform the counselor of the participant’s suicidality (accompanied by the release of information form). If the participant is currently in therapy, Dr. Smits will call his/her therapist within 24 hours of the assessment if possible (accompanied by a release of information form) in order to inform the therapist of the participant’s suicidality.

11. Regarding the administration of DCS, the prescribing psychiatrist will be Carlos Tirado, M.D., M.P.H., F.A.S.A.M. Dr. Tirado will meet with the study participants for a single visit at the start of the study, will review the medical history of patients (for exclusion factors), and will prescribe the four doses of study medication (DCS vs. PBO) to be taken during assessment weeks (weeks 2-5). Patients will be encouraged to call the study physician should they experience any side effects or have any questions regarding the medication.

12. To deal with the potential risk of loss of privacy (judged to be minimal), we will maintain confidentiality by numerically coding all data, by disguising identifying information, and by keeping all data in locked file drawers. Audio recordings will be coded by participant ID and will be deleted after therapist adherence ratings. Participant information will be accessible only to research staff. Identifying information will not be reported.

**Functions of the Data and Safety Monitoring Board (DSMB)**

A Data and Safety Monitoring Board (DSMB) will be created to ensure that the safety of study subjects is protected and that the scientific goals of the study are being met. To support those purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality.

**Membership of the DSMB.** To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for psychiatric disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues (Drs. Murray Stein, Gail Steketee, and Sabine Wilhelm).
As in any clinical trial, it is not possible to anticipate all possible adverse events. We do extensive training with our staff on ascertaining, monitoring, and documenting adverse events. The study investigators have extensive experience in clinical trials organization and management, including data safety monitoring for single site and multi-site trials. We have established procedures for rendering first aid and life threatening emergencies. Dr. Smits will oversee these procedures.

**Reporting Mechanisms of AEs/SAEs to the IRB and NIMH**

*Unblinded Reporting.* Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

*Range of Safety Reporting to the DSMB.* It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between groups. This includes treatment retention rates and reasons for dropout.

**Serious Adverse Events.** Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs; i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, study condition, concomitant medications, the subject’s medical history and current conditions, and all relevant laboratory data. Notification by e-mail and FAX transmittal of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study interventions. Additional reporting to local IRBs will be done within 24 hours of the SAE; reporting to NIH will be made according to their respective regulations governing SAE reporting.

**Non-Serious Adverse Events.** At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

**Other Safety-Related Reports.** At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
Study Stopping Rules. If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Collection and Reporting of AEs and SAEs

Information regarding AEs is to be obtained by questioning or examining the subject. At each visit all new complaints and symptoms (i.e., those not existing prior to signing of informed consent) must be recorded on the AE Form. Pre-existing complaints or symptoms that increased in intensity or frequency after having signed the Informed Consent Form must be entered on the AE Form also. All AEs must be characterized in terms of their start and stop dates, start and stop times, intensity, action taken on Intervention, relationship to Intervention, subject outcome and whether or not the AE led to a Serious Adverse Event (SAE). Any clinically relevant increase or decrease to the intensity or frequency of a reported AE requires a separate entry on the AE Form. If the event meets the definition of an SAE, the procedure for reporting SAEs must be followed; the event should not be reported on the AE Form also incase the start and stop dates are equal to the start and stop dates of the SAE.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious too.

All serious events occurring between signing of the Informed Consent Form by the subject and signing of the End of Trial Form by the investigator, except those pre-specified in the protocol, must be reported as soon as practical (within 24 hours of awareness) to the IRB and the DSMB. This includes serious events, which could be associated with the trial procedures, even if occurring outside the treatment period.

Follow-up of SAEs, which occurred during the trial, should in principle take place until resolution of the SAE. Under this protocol, the following event(s) will not be considered as (an) SAE(s) and should not be entered on the SAE form:
E. RECRUITMENT

Participants will be obtained through: (a) referral from area medical and mental health professionals, (b) community outreach, and (c) advertisements placed in local media. Recruitment sources include: 1) posting newspaper and Craigslist advertisements; 2) utilizing fliers in community-based organizations and bulletin boards; and 3) utilizing social media sites (e.g., Facebook, Twitter, LinkedIn). Any subjects meeting the entrance inclusion criteria will be provided the opportunity to participate in this study. Specific procedures are in place to maximize our aggregation of a racially and ethnically diverse sample. Community mental health centers and medical clinics will be informed of the project and referrals will be encouraged from primary care physicians and clinics. If necessary, special attention will be given to churches and other social groups with high minority representation to ensure adequate accrual of racially/ethnically diverse subjects.

F. OBTAINING INFORMED CONSENT

Any subjects meeting the entrance inclusion criteria will be provided the opportunity to participate in this study. In accordance with HIPAA regulations, written informed consent will be obtained from each participant after a thorough explanation of procedures by a project staff person and the participant will be given the opportunity to ask and receive answers to questions. Participants will be informed of the nature of the investigation, the types of assessments and interventions involved, alternative interventions, and the potential risks involved in participation. In addition, an explanation of how information related to their case will be handled, including data management and plans to publish data in group format without identifying information, will be presented. Informed consent will be obtained from all participants prior to undergoing any screening procedures. The Institutional Review Board will have approved the protocol, consent, and HIPAA authorization forms prior to the initiation of the study. The Institutional Review Board at the University of Texas (UT) consists of independent bodies of reviewers. Research associates and physicians will receive training regarding procedures required to obtain informed consent, and training is completed yearly in order to continually reinforce such procedures.

7. PRIVACY AND CONFIDENTIALITY

Data and Safety Monitoring Plan
Data Entry Methods

Our general policy for data management is that research assistants copy all data files and these files are brought to the PIs on a bi-weekly basis. Data forms and accompanying narrative summaries will undergo a systematic and rigorous editing process prior being keyed into the database. The research assistants routinely evaluate the data and discuss any problems and questions with the study staff at the weekly team meetings. Accuracy of data entry will be ensured by a standard double-entry procedure. Data management formal reports on record status across the three following domains will be employed: entered, verified, and edited. These reports of data records will be evaluated 1 time a month during the final team meeting of the month. To help ensure data protection, backup copies, automatically generated by our computer systems, will be available. Additionally, our hard copy record systems, as described previously, will be maintained in fire-resistant locked cabinets.

This study will utilize a web page-internet data collection and management system used in previous work. All data for the current study including demographic information, laboratory values, and participant and clinician rated measures will be directly entered into an electronic case report form (eCRF). The eCRF will be entered into web pages using a dedicated personal computer at each respective site. The web pages will be accessed at a central site using a standard Internet browser.

The eCRF will consist of a series of separate web pages for study personnel and participants. A series of passwords will be programmed to ensure that participants are unable to access pages reserved for study personnel. The eCRF will be constructed so that all requested information must be entered into each page in the fields provided, or the system will not permit access to the next page. The system is designed so that only completed eCRFs can be transmitted. If information for a field is either not available or not applicable, the system will require that it be documented as such in the eCRF. Field parameters will be specified such that suspect values are either disallowed or flagged for the immediate attention of the study coordinators and Principal investigators.

The completed eCRF will be transmitted to the central site using encryption code, at the completion of the study visit. In addition to transmitting the completed eCRF to the central site, at each visit a hard copy of the eCRF will be printed and promptly reviewed, signed, and dated by the investigator for clinician rated measures and by the participant for participant rated measures. Data will not be transmitted until reviewed by the participant, investigator and research assistant for completeness and accuracy. A print out of the data will then be made, authenticated (with signature and date) by the investigator and participant and kept in the participant’s study file.

Confidentiality is assured by a number of factors. Most importantly, participants will be identified on the eCRF only by participant number, visit number, and date of visit, assuring confidentiality of the anonymized data on the web. By recording the study data in this manner, the information can be considered ‘de-identified,’ and therefore, compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 ("HIPAA"). Additional measures to ensure the confidentiality of study data include the following: A dedicated personal computer at each investigational site will permit the electronic authentication/signature of all
information and data collected during the study. When data are submitted, the user id, password, date, time, and IP address of the computer are logged. As a result, the number of locations from which the database can be accessed will be limited, effectively restricting access to individual computers. Access to the dedicated personal computer at the study site will be restricted to participants, investigators and staff involved in the study. Each user of the system will be assigned a unique user-id. Each user-id will be associated with a subset of participants. Thus, project staff will only be able to access the records of participants for whom they are responsible and for those individuals registered in the study at that site (to allow for cross coverage of participants when necessary). Data will be accessed by participant number, visit number, and specified form of interest. Participants will have access only to the current visit, and only to the subset of forms that they will be filling out. As a result, participants will require the assistance of project staff member to access other aspects of their record.

The security of the database is maintained and any changes or modifications to the eCRF record rigorously documented. The current record is modified using the web page-internet technology each time an eCRF data file is accessed. Every access of an eCRF will be logged in a separate archival file, which will permit PIs to track who made the data changes, the dates and times of the data changes, and which data fields were changed. In addition, the technology permits the recovery of the data entered previous to any given change. It is important to note that this recording is invisible (and inaccessible) to users at the study site (the end user), and will be available only to the Data Manager and the PIs. The physical security of the data will be maintained in a number of ways. All data will be maintained on the mainframe computers the respective sites. As a result, the data will be fully backed up and fire protected. Backups are performed in real time, and the back up tapes are stored in a fire protected setting in an off-site location. All forms will be printable, if necessary. At the conclusion of the study, the database will be permanently archived at each respective site.

Some study data (eCRF) will be collected and managed using Qualtrics. Qualtrics is a high-end web survey tool that has been used in experimental research and is designed in a way that ensures the security of data transmission and protection. Qualtrics offers Transport Layer Security (TLS) encryption (HTTPS) and survey security options like password protection and HTTP referrer checking. Qualtrics is a HIPAA compliant company, and servers are stored in a tier one data storage facility that includes adequate security measures.

8. COMPENSATION

Subjects who participate in the fear extinction experiment will receive $25 for the session on Day 1 and an additional $25 for the session on Day 2.

In addition, subjects who participate in this study may benefit from the close monitoring and intervention provided to them. These potential benefits are provided without charge. Thus, participants will not be compensated for study CBT-sessions or follow-up assessments.