Procedural Manual
Efficacy Evaluation of Transdiagnostic CBT for Comorbid Alcohol Use and Anxiety Disorders (StAR2)

NIAAA Grant Number: 1R01 AA023676

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Contents

Study Overview

Data Analysis Aims:

1. Demonstrate that Unified Protocol (UP) treatment reduces alcohol consumption relative to Take Control (TC), as measured by our primary outcome measure, mean number of drinks consumed per week.

Comparisons will be made for data obtained for the treatment period for the two conditions. Specifically, the hypothesis that participants in the UP condition will evidence greater reductions in our primary efficacy measure (mean weekly number of standard drinks) than participants receiving TC will be examined using conditional latent growth models (LGM), modeled using MPlus 7.0 (Muthén & Muthén, 1998-2012). Research personnel will examine changes in the weekly mean number of drinks consumed per day over the course of treatment (i.e., study sessions 1 to 16). They will also examine whether the proportion of subjects achieving safe levels of drinking (males = 2 drinks per day; females = 1 drink per day) is significantly greater in the UP condition than in the TC group (guidelines from USDA, 2010). This will be done by calculating odds ratio effect sizes (with 95% confidence interval) contrasting safe levels of drinking in the UP vs. TC groups.

2. Demonstrate that the UP, relative to TC, reduces alcohol intake on other measures of alcohol consumption and evaluate the extent to which this also leads to a comparative decrease in measures of craving.

Conditional LGM will be used to test the hypothesis that UP will both demonstrate greater reductions in the secondary efficacy measures of percent days heavy drinking per week (defined as more than 3 drinks per drinking day for biological women and more than 4 drinks per drinking day for biological men [NIAAA guidelines]), percent days of drinking per week, and in alcohol craving (as assessed by the Alcohol Urge Questionnaire and the Obsessive Compulsive drinking scale) than the TC condition.

3. Demonstrate that the UP results in greater reductions in anxiety and depression as measured by the SIGH-A, SIGH-D, ODSIS, and OASIS than TC, and that there will be a correlation between these reductions and the decreases seen in mean weekly number of standard drinks consumed per day, percent days heavy drinking per week, percent days drinking per week, and alcohol craving.

This will be examined using conditional and parallel-process LGC. Research personnel will first conduct separate LGM for anxiety and depression. Then they will conduct a series of parallel process LGM to examine how changes in anxiety and depression relate to changes in the primary and three secondary alcohol outcomes. Separate parallel process LGM will be conducted for

each alcohol outcome, and both anxiety and depression will be included in each parallel process LGM.

4. Demonstrate that the UP results in greater changes in temperament (e.g., reductions in neuroticism) and emotion regulation (e.g., experiential avoidance) variables associated with anxiety and depression than TC, and that these changes are associated with changes in anxiety and depression.

This will be examined using LGM models similar to those described above. These parallel process LGM will not provide formal tests of mechanisms of change as these models will examine concurrent changes. If the results from these models are promising, they will be followed by models that permit more fine-grained examinations of temporal dependencies of change.

5. Demonstrate that the UP will reduce impulsive and risk-taking behaviors. Our working hypothesis is that the UP will decrease risk taking behavior as assessed using the Cambridge Gambling Task and the Balloon Analog Risk Task, and impulsivity as measured by the Go/NoGo and the Continuous Performance Test (CPT).

Repeated measures mixed models analysis will be used to analyze data obtained for pre-randomization and week 16 data for the Cambridge Gambling Task, the Balloon Analog Risk Task, the Go/NoGoTask, the CPT, and Go/No Go. Model generated group least square means values for week 16 will be compared using student t-tests.

fMRI Aims:

1. Demonstrate that the UP will attenuate changes resulting from performance on alcohol-word and negative-word Stroop tasks in the activity of frontal-parietal and midbrain regions and the connectivity to networks associated with these regions in AUD subjects. Our working hypothesis is that midbrain activity will be lower in UP participants than those in the TC condition following performance on alcohol and negative emotion Stroop task, which will occur in association with enhanced mid-brain-frontal connectivity and increased synchrony.

2. Demonstrate that the UP attenuates the enhanced regional brain activity and craving- induced by exposure to alcohol related cues in AUD subjects. Our hypothesis is that exposure to alcohol-related cues will increase brain activity in select limbic and prefrontal areas to a lesser degree in UP completers as compared to UP participants at baseline.

3. Demonstrate that the UP induced changes in brain activity are predictive of reduced ethanol consumption.

StAR2 Grant Information
Title: Efficacy Evaluation of Transdiagnostic CBT for Comorbid Alcohol Use and Anxiety Disorders
Granting Agency: National Institute on Alcohol Abuse and Alcoholism
Date of Submission: 09/01/2017
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Study Personnel: Research Team

Todd Farchione, Ph.D., Principal Investigator (PI)
Dr. Farchione is a research associate professor of psychology at Boston University, and has worked full time at CARD for the past 13 years. Dr. Farchione oversees several research and clinical treatment programs provided at CARD and most recently served as the project director of the previous open trial aimed at evaluating the efficacy of the unified treatment protocol relative to existing evidence-based single diagnosis treatment protocols. Dr. Farchione will be responsible for day-to-day scientific and clinical management of the study. Dr. Farchione will assist Dr. Barlow in the certification and training of UP therapists. He will also work with Dr. Barlow to oversee recruitment, subject retention in the study, data collection, data management, and protocol adherence.

Shannon Zavala, Ph.D., Co-Investigator
Dr. Sauer-Zavala is a research associate professor of psychology at Boston University and director of the Unified Protocol Institute. She will provide consultation on assessment measures and advise the team on other study design elements and procedures. She received her Ph.D. in clinical psychology from the University of Kentucky. She completed her predoctoral internship at Duke University and her postdoctoral fellowship at Boston University. Dr. Sauer-Zavala's research is focused on identifying emotional factors that are important in the development and maintenance of a range of mental disorders. She is also interested in using information gleaned from her basic psychopathology research to develop streamlined, easily disseminated interventions that directly target the factors that maintain disorder symptoms. In particular, Dr. Sauer-Zavala is interested in treatment development for borderline personality disorder.

Marc J. Kaufman, Ph.D., Co-Investigator
Dr. Kaufman is director of McLean's Translational Imaging Laboratory, associate professor of psychiatry at Harvard Medical School, co-director of the NIDA T32 post-doctoral training program at McLean, and a Partners Human Research Committee member. He conducts translational research in addiction, psychiatric, and neurodegenerative disorders. He will be overseeing all study procedures conducted at BU CILSE.

Amy C. Janes, Ph.D., Co-Investigator

Dr. Janes is an assistant professor of psychiatry at Harvard Medical School, and the director of McLean's Functional Integration of Addiction Research Laboratory. Dr. Janes uses multi-modal neuroimaging techniques in clinical populations to study addiction, with a specific focus on nicotine dependence. Dr. Janes' research interests include: identifying individual vulnerabilities for developing and maintaining addictive disorders, evaluating brain changes following treatment, and determining how other cognitive, affective, and psychiatric disorders contribute to addiction. She will work with Dr. Kaufman in supervising the study procedures conducted at BU CILSE.

Matthew W. Gallagher, Ph.D., Co-Investigator
Dr. Gallagher is an assistant professor of clinical psychology at the University of Houston. He has extensive experience with the data analytic techniques that will be used in this trial. Dr. Gallagher will oversee data analyses related to alcohol consumption and behavioral outcomes. He will also advise on any statistical or other methodological issues that arise during the trial, will assist in the coordination, management, and verification of the dataset, and will assist in the preparation of reports to the DSMB.

Kateri McRae, Ph.D., MRI Consultant
Dr. Kateri McRae is a consultant on our study, who is specialized in the event-based reappraisal fMRI task. She will oversee our task design, provide us with standard procedures and materials, and give us guideline on data analysis from the event-based reappraisal task.

Margaret Ross, M.D., Study MD, (0.30 calendar months in each year).
Dr. Ross is the Medical Director at CARD, where subjects will be seen and treated in the proposed study. She will oversee any abnormal lab results.

Pearl Hu, M.D., Study MD
Dr. Hu is a psychiatrist at CARD. She will oversee any abnormal lab results, determine if participants are healthy enough to participate in the trial, and communicate with participants' primary care physicians when medically necessary.

Bonnie Brown, RN, Study Nurse, (0.60 calendar months in years one through four and 0.30 calendar months in year five).
Bonnie Brown will maintain medical records, monitor vital signs and general medical status. She will conduct the initial medical evaluations and will review all lab results. Ms. Brown's effort reduces slightly in year 5 in view of projected reduced participants flow.

Postdoctoral Research Associates

Elizabeth Eustis, Ph.D., Independent Evaluator (IE) and Study Therapist
Dr. Eustis will serve as an IE and will assist in the training of doctoral student IEs. She will also

administer the ADIS-5 to participants to assess diagnostic criteria for eligibility into the project, and is trained to "gold standard" criterion for reliability. Dr. Eustis will also act as a study therapist for both the UP and Take Control conditions once trained and certified by Dr. Farchione. She will also oversee the RAs in all study related responsibilities, and meet weekly with graduate student IEs to lead a diagnostic consensus meeting to review recently completed baseline assessments.

Graduate Research Assistants

[redacted]

Graduate research assistants (GRA) are doctoral students in the Clinical Psychology Program at Boston University. These students will serve a number of important functions, including assessing diagnostic criteria for eligibility into the project (both are trained to "gold standard" criterion for reliability).

Research Assistants

[redacted]

Research assistants will be responsible for scheduling participants, conducting phone screens, running study sessions, data management, IRB related tasks, and MRI sessions.

General Contact Information

[redacted]

Staff Personnel Contacts and Locations

Name	Title	Office	Work Phone	E-mail	Cell Phone
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	eeustis@bu.edu	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Research Design

In this clinical trial, research personnel will further assess the UP's effectiveness in reducing alcohol consumption in participants with comorbid AUD/AXD. Participants will be randomized to one of two conditions: 1) treatment with the UP or 2) treatment with therapist-guided *Take Control* (TC; a psychoeducation-based, alcohol reduction program developed by NIAAA). In addition, a subset of twenty-five participants (UP condition only) will complete functional magnetic resonance scanning (fMRI) to examine the effects of the UP on changes in

brain activity in areas important to regulation of emotional and reward processes implicated in excessive alcohol consumption.

The primary hypotheses are that the UP compared to TC will: 1) be superior in acute symptom reduction from pre- to post-treatment, and 2) evidence greater reductions in percent days heavy drinking, percent days of drinking per week, and alcohol craving.

Study Timeline

The entire study is estimated to be completed in five years. The first six months of the project were dedicated to hiring staff, therapist training, and certification. Recruitment began in the 7th month of Year 1. Approximately 3-4 new participants will be recruited per month. Recruitment began in August 2017. We anticipate recruiting a total of 5 participants in Year 1, 15 participants in Years 2 through 4, and 10 participants in the beginning of Year 5. The majority of Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Subject Flow

Table 1 summarizes participant flow and projected visits for each grant year. The study will be conducted over the course of 5 years. Based on prior study experience, we project the number of participants who consent and are randomized to treatment will be one-tenth the number of phone screens and one-half the number of diagnostic evaluations completed.

Table 1. Visit Projection Table

Visit Type/ Study Year	01	02	03	04	05	Total
Phone screens	50	150	150	200	50	60
Diagnostic evaluations	10	30	30	40	10	120
Consented & randomized to treatment	5	15	15	20	5	60
Study treatment visits	48	182	182	243	72	727
IE initial assessments	15	25	25	25	15	20
IE brief assessments	15	68	71	91	39	284
IE follow-up assessments	7	28	30	39	16	120

Subjects

A total of 60 participants will be enrolled, with a target male to female ratio of 33:27. This ratio reflects the higher prevalence rates of AUDs in biological men compared to biological women. Forty participants will be randomized to the UP condition and 20 to the Take Control condition. In addition, 25 participants from the UP group will receive two fMRI scans (pre- and post-treatment).

Participants will be recruited via flyers, brochures, lab website and StAR Facebook page, MBTA advertisements, etc. Telephone screenings will determine initial eligibility, and potential research participants will be invited to CARD, located at Boston University, for a more extensive assessment of alcohol use and emotional disorders.

Setting

All study procedures, except for MRI procedures, will be conducted at CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial research participant flow. CARD consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents. The MRI procedures will be conducted at Boston University's Center for Integrated Life Sciences & Engineering (CILSE).

Inclusion/ Exclusion Criteria

Inclusion Criteria:

1) DSM-5 diagnosis of an alcohol use disorder (AUD)
2) DSM-5 diagnosis of Social Anxiety Disorder (SAD), Panic Disorder/Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), and/or Obsessive Compulsive Disorder (OCD) as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for DSM-5 (ADIS-5). Clinically significant diagnoses will be determined by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis
3) Adults 21 years or older
4) Expressed desire to stop drinking alcohol completely or to reduce alcohol consumption
5) Reported drinking an average of at least 15 standard drinks per week for males, or 8 for females occurring over a 28-consecutive day period during the 90 day-long time window that preceded the screening session
6) Must be willing to discontinue any form of psychotherapy, except AA, for either anxiety or depression prior to screening

Exclusion Criteria:

(Exclusion criteria are the specific criteria, which would disqualify an individual from participating in the study, not simply the opposite of the inclusion criteria):

1) DSM-5 diagnosis of current major depressive disorder (with the exception of substance-induced depressive disorder) that requires immediate treatment with pharmacologic agents, bipolar disorder, schizophrenia, current bulimia/anorexia, dementia, or other substance dependence, with the exception of nicotine, marijuana, and caffeine dependence
2) Presence of suicidal ideation or history of suicide attempts (i.e. two or more hospitalizations related to significant suicidal ideation or following suicide attempts within the last five years or one such hospitalization within the last six months)
3) Non-English speakers
4) Previously received an adequate trial of cognitive-behavioral therapy (CBT; 8 sessions within the past 5 years)
5) Contraindications to MRI scans
6) History of head injury with >5-minute loss of consciousness
7) Pregnancy. Note: Women of childbearing potential (not postmenopausal for at least one year) will be required to provide a negative urine pregnancy test prior to each scan
8) Implantation of anything containing magnetically sensitive material including metal plates, aneurysm clips, cardiac pacemakers, and stents; history of sheet metal work; claustrophobia
9) Cognitive impairment (MoCA$\leq$21)
10) Serious medical illness or instability for which hospitalization may be likely within the next year

Exclusion from Participating in Active Treatment:

1) Reduction in the mean number of drinks consumed per week by 50% or more between the phone screen and the in-person screening
2) Report of average drinks per day falling within safe levels of alcohol consumption (i.e., 2 drinks/day for males and 1 drink/day for females by the HHS standard) two weeks prior to screening

Recruitment

The majority of participants are expected to be self-referred and treatment seeking. Referrals may be recruited through a variety of methods such as: word-of-mouth referrals from former participants, referral from area medical and mental health professionals, advertisements in local newspapers, radio advertisements, MBTA advertisements, brochures/flyers, web advertisements (Facebook page, study website, craigslist ad, BU Quickie Jobs page), digital billboard advertisements, movie theatre advertisements, and through the CARD intake process.

The StAR2 recruitment team consists of [redacted] This team is responsible for recruiting participants for this study, through the following methods:

1) Web Ads: Online advertisements:

- Facebook page: https://www.facebook.com/bostonstarstudy/
- Study website: https://studyforalcoholreduction.com/
- NIH website: https://www.nih.gov/

2) Radio Ads: Advertisements will be submitted to local radio stations.
3) Newspaper Ads: Advertisements will be put in local area newspapers.
4) Brochures/Flyers: Flyers will be posted on local bus stops, telephone poles and passed around the community.
5) MBTA Ads: Advertisements will be placed on MBTA trains, buses, and stations.
6) Digital Billboard Ads: Digital advertisements (e.g., the study flyer) will be used for recruitment.
7) Movie Theater Ads: Advertisements will be played on screens in movie theaters.
8) CARD referrals: CARD intakes that meet criteria for AUD and an anxiety disorder and have been assigned to the StAR waitlist.

CARD Referrals

Participants referred through the CARD intake process that have both an alcohol use disorder and a DSM-5 diagnosis of Social Anxiety Disorder (SAD), Panic Disorder/Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), and/or Obsessive Compulsive Disorder (OCD) as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for DSM-5 (ADIS-5), will be placed on the StAR waitlist. CARD Clinical Director, Lisa Smith, will email the Research Assistants (RAs) to let them know a case has been added to the waitlist. The RAs should check the waitlist on a weekly basis.
The RAs will call the eligible cases on the waitlist to conduct a 15-20 minute phone screen. The RA can call the participant candidate 3 times within a 2-week window to attempt to make contact. If the participant meets the phone screen criteria, the RAs will schedule the participant candidate for an in-person screening session.

All contacts for research participants must be logged into the Titanium waitlist Referral Comment box along with dates. The final disposition should be clear in the notes.
If a participant drops, or the RA is not able to contact the participant after calling 3 times in 2 weeks, it is the study's responsibility to send a letter confirming our closure of their case. A template can be found here: [redacted] Upon completion, all waitlists should be sent back to Dr. Smith by putting her name in the Assigned Clinician spot. The RA should also email Dr. Smith to let her know.

Initial Evaluation Period

Potential participants will be given information about the nature of the study over the telephone and will undergo an initial phone screening (see phone screening procedures for more information) to determine initial eligibility. Eligible participants will then be invited to the

Center for Anxiety and Related Disorders at Boston University for an in-clinic screening to further assess their eligibility for the study. At the screening, participants will be provided an informed consent form which will be verbally reviewed before signing. Participants who are eligible following the screening session will be randomized to one of two study conditions (UP or TC). A description of measures and procedures associated with the screening session can be found in the Assessment Measures Administration section of this manual and in the Participant Binder.

As of March 18th, 2020, screening procedures were changed from in-person to remotely, through Zoom. Individual breathalyzers are sent via mail to the participant prior to the consenting appointment, as well as a Qualtrics link via email containing the digital version of the consent form. Using a Qualtrics survey, participants are able to digitally sign consent which researchers are then able to sign the same form and email the completed form to the participant.

Treatment Conditions and Specifications

Participants will be assigned to one of two groups: UP or TC. Participants in the UP group may also be asked to undergo two brain MRI scans of less than two hours of duration. The first MRI scan will occur after the participant has been randomized but before the first treatment session, and the second brain MRI scan will occur within a two week window after the last treatment session.

Phone Screening

In order to conduct a phone screen with someone that has been referred to StAR2, the RA will attempt to contact the participant up to 3 times within a two week period. Should more contact attempts be necessary, the PD should be consulted. In the event that a participant is never successfully contacted, the RA will document this as "Unable to contact" in the StAR2 Recruitment Tracking Contact Log, and highlight their initials in red.

Once the RA reaches a participant, he/she will attempt to complete the phone screen (15-20 minutes), which includes reading the IRB approved phone screen script, and filling out the phone screen form to record study-specific questions and assess eligibility. The most up to date phone screen is saved on the Shared Drive file path: [redacted]
The phone screens should be saved with [redacted]

Upon completion of the phone screen, the RA determines whether the participant is eligible based on established inclusion/exclusion criteria and interest to participate. Potential participants who pass the telephone screening will be identified by their initials until they are enrolled after the in-person screening session and assigned an ID number. If they are scheduled for an in-person screening session this should be recorded in the StAR2 Recruitment Tracking Google sheet, on the Recruitment Tracking Tab.

If a phone screen has already been conducted and the RA is unable to make contact for scheduling the intake appointment (after 3 call attempts in 2 weeks), the RA should document the no contact in the log.

All cases that are not eligible for an in-person screening session will be provided a referral for the type of treatment they are seeking, if requested. The list of referral options is saved in: [redacted]

Informed Consent/Screening Session

The day before the in-person screening appointment, the RA will call the participant to confirm the appointment and remind him/her about the approximate length of the appointment. The screening session is expected to take approximately 4 hours to complete (Informed consent = 15 mins; Health assessment = 45 min; Self-report questionnaires = 1 hour; IE assessment = 1-2 hours).

On the day of the screening appointment, the RA greets the participant. Next, the participant's blood alcohol concentration (BAC) will be measured using a breathalyzer to ensure that the participant provides written informed consent while sober (BAC=0.00%). If the BAC is 0.00%, the RA will administer the Informed Consent Form. Discussion during the informed consent will include information about the treatment options, randomization procedures, and a brief rationale for these approaches. Participants will be invited to ask questions about the study procedures and expectations. Participants will also be provided information on the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will then be asked to sign an informed consent statement prior to participating in the research project. [redacted] A photocopy of the consent form will be given to the participant to keep. Participants will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

After the consent form is signed and all the participant's questions about the study have been answered, the RA will accompany the participant to the medication room where the study nurse will complete the health screen. The health screen involves a medical history questionnaire, a blood and urine sample, vitals and weight, and the Montreal Cognitive Assessment (MoCA). If the nurse is unable to complete the MoCA at this time, the RA can conduct this assessment (if they have been trained to do so). The nurse will also have the participant complete a Release of Information Form for their primary care physician.

Next, the RA will take the participant to a UP treatment room. The RA will then conduct the Alcohol Timeline Follow-Back assessment with the participant. The RA will need to collect drinking data for the past 90 days. Then, the RA will download the RealLife Exp application on the participants' phone to activate the EMA component of the study. The survey should be activated on the screening session. Seven days after the screening session the RA should email the participant to deactivate the survey (see EMA procedures for more information). We cannot

deactivate the survey pack remotely, which is why the participant needs to be instructed on when and how to do so. Deactivating the survey pack will only stop notifications from being sent to the participant during non-EMA weeks, it will not delete the account.

The RA will give the participant the EMA instructions handout and the "What is AUD" handout to take home, both of which can be found in the Screening tab of the participant binder. The RA then loads the Screening Self-report Qualtrics survey on the study computer in room 233D for the participant. All surveys are set up to ensure that participants answer every question, eliminating the possibility of blank responses. However, the RA must ensure the participant has reached the last page of the survey before moving on to the next portion of the session. Upon completion of the questionnaires, the participant notifies the RA and may take a break. The RA notifies the IE that the participant is ready for the assessment and emails the link to the IE assessment survey, which includes the ADIS, SIGH-A, and SIGH-D. Alternatively, the IE can access all assessment surveys through Qualtrics. When the IE finishes the assessment, he/she will alert the RA that the assessment is complete. The RA will thank the participant for his/her time, and inform the participant that he/she will receive a phone call about eligibility in the next 1-2 weeks after the team has established consensus for study enrollment.

Note: As of March 18th, 2020, screening procedures were changed from in-person to remotely, through Zoom. Individual breathalyzers are sent via mail to the participant prior to the consenting appointment, as well as a Qualtrics link via email containing the digital version of the consent form. Using a Qualtrics survey, participants are able to digitally sign consent which researchers are then able to sign the same form and email the completed form to the participant.

Consensus Meeting

Each week, the research and medical team will meet for approximately one hour to discuss all new participants that were evaluated for the study to come to consensus on study enrollment. The RA should bring the screening participant(s) binder(s) to the meeting, as well as the CSR sheet. The IE that conducted the ADIS will fill out the participant's diagnoses and CSRs pre and post consensus meeting on the CSR sheet. The CSR sheet can be found in the screening tab of the Participant Binder. This meeting will allow the IEs and medical staff an opportunity to discuss eligibility concerns and review inclusion/exclusion criteria. Once the team has come to consensus, the RA will contact the participant. If the pre and post consensus meeting CSRs do not match, the RA will be responsible for going into the Qualtrics Data and changing the CSRs to match what was decided in the meeting. The old Qualtrics ADIS data for the screening participant should be archived so as not to be confused with the correct, updated version.

Eligibility

If the participant is not eligible, the RA will contact the participant, and will provide the participant with an appropriate referral if relevant, which can be found in: [redacted] If the participant is not satisfied with

the explanation for why they are not eligible, the RA will inform them the PD will contact them to explain further.

If the participant is eligible, they will be randomized into either the UP or TC condition. They will be contacted for scheduling schedule for either session 1 or the baseline MRI (only a subset of UP participants will be contacted about the MRI).

Treatment/Intervention

Following the initial screening session (see description of assessment procedures for more information regarding the screening session), participants are randomized to one of two treatment conditions: 1) Unified Protocol, or 2) Take Control.

Unified Protocol (UP)

The UP is a 16 session, transdiagnostic, cognitive-behavioral therapy that has shown efficacy in treating emotional disorders. The efficacy of the UP to facilitate abstinence from alcohol consumption in individuals with comorbid AUD/AXD has also been examined, with results from this study indicating a reduction from baseline in drinks consumed per day (Ciraulo et al, 2013).

Take Control (TC)

TC is a 12 session, psychotherapy platform derived from the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) self-help approach, *Rethinking Drinking.* In this study*,* TC, originally designed as a computerized treatment, has been modified by our team to be administered by a therapist to control for effects that may be related to patient-therapist interaction (as opposed to elements of the treatment itself). Specifically, on a weekly basis, therapists will review material from TC and offer general advice on implementation of the alcohol reduction skills in daily life.

Randomization

Prior to the start of the trial, a random number generator was used to establish a randomization schedule that assigns participants to either the active treatment (UP) or comparison condition (TC). Once a new participant is enrolled in the trial, the RA will refer to the next assignment in the randomization schedule [redacted] The current trial aims to recruit 40 participants in the UP condition and 20 participants in the TC condition.

Once the participant is randomized, the RA will contact the participant to discuss scheduling and provide further information about length of the trial. TC participants will complete 12 sessions of therapy (in a maximum of 16 weeks), while UP participants will complete 16 weeks of therapy (in a maximum of 21 weeks). Additionally, follow-up assessments will be completed at one month and six months posttreatment.

If the participant is randomized to TC, the next session is session 1, and the RA will schedule the session based on the participant's and assigned therapist's availability. If the participant is randomized to the UP condition, the RA will potentially schedule the participant

for the fMRI session prior to scheduling session 1 with the therapist. The first study session will be scheduled within 4-weeks after the in-clinic baseline assessment. If the one-month window expires before the participant can complete the first session, then the assessment must be repeated to assess the participant's continued eligibility for the study (a "refresher").

To schedule an fMRI session, the RAs will need to refer to the CILSE scheduling calendar [redacted] to confirm that the scanner and the MRI technicians are available and to book the appointment. [redacted] The RA will need to book 30 minutes in the Med Lab at CARD for the urine, drug, and/or pregnancy test, and 1.5 hours at CILSE for the scan. Once appointments are scheduled, the RA will document the time and date for all involved study staff in Titanium (see How to Log a Treatment Session in Titanium).

Study Sessions

All participants are required to have a BAC of 0.02% or less to complete all study sessions. Each weekly study session will be approximately 60 to 90 minutes in duration, with the exception of session 1 and post treatment, which are expected to last for approximately 3 to 4 hours.

Follow-up Period

One month following completion of study treatment, participants will be asked to complete the 1-month in-person follow-up assessment. Six months after the completion of the study termination, participants will complete the 6-month in-person follow-up assessment. During the follow-up interview, the subject will provide data for the Alcohol Timeline Follow-Back (TLFB), ADIS, SIGH-A and SIGH-D, the self-report battery, and Treatment Involvement Form (TIF). The RA will administer the breathalyzer, TLFB and the TIF. The IE will conduct the ADIS, SIGH-A and SIGH-D, and the CGI-I and CGI-S on Qualtrics. Self-reports will be completed by the participant on Qualtrics.

Study Procedures

Participants will receive 16 treatment sessions over a period of 16 to 21 weeks for UP or 12 treatment sessions in 12 to 16 weeks for TC. Follow-up data will be collected 1- and 6-months post-treatment at in-clinic sessions.

We will offer parking vouchers to participants, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. Research personnel will provide up to four parking vouchers (which cost approximately $10.00 each) to every participant for completion of study assessments.

Note: As of March 18th, 2020, study staff adapted study procedures to operate remotely during the COVID-19 pandemic. These practices have continued into 2021, 2022, 2023, and the remainder of the study. This has included instituting procedures to conduct therapy sessions via telehealth (HIPAA Zoom), collecting data remotely via online services (Qualtrics, Millisecond), and conducting screenings remotely (HIPAA Zoom). IRB approval was obtained for all remote procedures. fMRI procedures were temporarily discontinued due to the COVID-19 pandemic in 2020, but study staff re-initiated scans in 2021 in accordance with BU IRB protocols.

Ecological Momentary Assessment (EMA)

The EMA component is required by all participants, unless an exception is made by the project director, Dr. Farchione. The Ecological Momentary Assessment (EMA) component will collect self-reported drinking data in real time using a smartphone app, *RealLife Exp*. RealLife Exp will send timed alerts 3-times a day at 10am, 4pm and 10pm to study participants. In addition to the scheduled EMA assessments, participants will have the option to self-initiate the survey during a drinking episode if they choose to do so. We will activate the EMA component for 5 weeks for the UP condition (1, 4, 8, 12, 16), and 4 weeks for the control condition (1, 4, 8, 12) over the course of treatment. Participants will be instructed to complete EMA for the full time period starting from the session it was activated, to when they come in for their next session, with the exception of the baseline EMA. The RA should activate EMA on the screening session, session 3, 5, 7, and 15, and deactivate EMA on session 4, 8, 12, and 16. The baseline EMA should be collected starting from screening session, and deactivated 7-days later regardless of when session 1 is scheduled.

To "activate" the survey, the RA should search for "StAR2" in the download survey section in RealLife Exp, click download, and enter in the access code ("star") when promoted. After the week of EMA has been completed, the RA should assist the participant in deactivating the survey, by swiping the downloaded StAR2 pack to the left and then pressing the trash icon. [redacted] A copy of these instructions will also be handed out to the participant at their screening session.

A smart phone (with limited functionality) will be provided to participants who do not own one themselves. The phone will be returned to study staff once participants have completed the study. Each participant will be assigned a dummy email address which will not include any identifiable information. Assigning dummy emails to the participants resolves the issue of having protected health information linked to identifiable information in any way. The list of dummy email addresses can be found at: [redacted] Once an email has been assigned to a participant, the RA must update the list with the participants' ID next to the email they were assigned.

After each participant finishes their last course of EMA (on their last session), the RA will permanently delete access to the EMA survey based on their participant ID. This will prevent the participants from attempting to continue participating in EMA after treatment has completed. The RA will also determine if the participant completed at least 80% of the EMA component. If they completed 80% or more of the EMA, they should be paid $50.

fMRI

Participants that are selected for the fMRI component will also be screened for eligibility in undergoing brain fMRI scans after completing the assessment session at CARD. All enrolled participants must be willing and able to participate in the fMRI component in order to be eligible

to participate in the trial, unless an exception is made by the project director, Dr. Farchione. About half of the eligible participants randomized to the UP condition will be asked to complete this component of the trial. We will ask all participants in the UP condition to complete the fMRI component until we have reached a sufficient number of participants (with complete scans) to evaluate the fMRI specific aims identified in the approved study protocol.

One scan will occur after randomization but before the first treatment session begins and the second scan will occur within 2 weeks after the last treatment session. Participants will be screened before each scan session for alcohol use (breathalyzers), pregnancy (urine sample, women of childbearing potential only), and illicit substance use (urine sample). Eligible participants may be asked to complete 2 fMRI sessions of 2 hours total. Thirty minutes will be allocated for BAC, pregnancy test (urine sample; women of childbearing potential only), illicit substance use test (urine sample), Alcohol Use Questionnaire (AUQ), and the CILSE safety form. Thirty minutes will be allocated for traveling to CILSE, and prepping materials for the MRI, and 1-hour and a half will be used for the 3 Tesla fMRI scan involving structural imaging (MRI) and functional imaging (fMRI). The participant should complete the AUQ both before and after the fMRI scans in Qualtrics.

The fMRI scans include a resting-state scan (no task involved), a cognitive (Stroop) task, an alcohol cue reactivity task and an Event Based Reappraisal Task. The Stroop, alcohol cue, and Event Based Reappraisal scans involve presentation of visual images to participants while they are in the scanner. No contrast agent or invasive procedures are used. Only personnel trained in working in high magnetic field environments will work on this project. Imaging data will be analyzed on secure networks using only encrypted files. All data obtained will be coded to protect participants' privacy and confidentiality.

If a participant is struggling with claustrophobia while in the scanner, the following procedures are in place: stop the task and call Dr. Farchione [redacted], the project director, for guidance on whether to continue with the fMRI. If Dr. Farchione is unavailable, call the postdoctoral fellow, [redacted]. If Dr. Eustis is unavailable, call Dr. Amy Janes [redacted] the MRI consultant. All of these phone numbers are also saved in the study phone. Signs that the participant is struggling with claustrophobia include needing an RA to stay inside the scanner room during the scan, needing frequent breaks, and/or verbally indicating they are feeling claustrophobic or want to get out.

MRI Instructions for RAs

Two RAs will accompany participants to the Center for Integrated Life Sciences and Engineering (CILSE) located at 610 Commonwealth Avenue, Boston, MA 02215. All RAs involved in MRI visits are required to complete the Level 1 MRI safety training and quiz.

Before leaving CARD the RA must:

- Administer the MRI CLISE safety screening form to the participant. This form is located in the participant's binder (MRI 1 and MRI 2 tabs)

- Administer the AUQ self-report questionnaire before and after the MRI scan
- Remember to bring the study laptop, charger, BU ID, and Eprime case (with license key)

Instructions for Scanner Room for RAs

Before Entering the Scanner Room:

Note: The screening form must be reviewed by a CILSE/MRI staff member in order for the participant to complete the scan.

- Make sure the linens on the scanner bed and pillow are new and clean
- Have the participant change into scrubs
- Ask the participant to remove ALL metal items (e.g., jewelry, belts, watches, credit cards). Lockers are provided for storage of clothing and personal items
- Use the metal detector wand and scan the participant's body for any metal that may have been missed
- The RA must remove all metal items from his/her own body

Familiarize the Participant with the Button Box:

One RA will bring the participant into the scanner room, while the other RA prepares the Eprime tasks with the MRI technician. The RA who accompanies the participant into the scanner room will familiarize the subject with the button box.

- Make sure the participant is using the button box that is labeled (R, G, Y B)
- Explain how to use the button box, as follows:

"*Please hold the button box vertically, with your dominant hand on top. Use the index and middle fingers of your dominant hand for the top two buttons, and the index and middle finger of your non-dominant hand for the last two buttons.*"

- Demonstrate how the participant should hold the box and where they should place their fingers when explaining
- Explain the order of the colors in relation to the location of the wire

Example Dialogue:

"The blue button is closest to the wire, then yellow, then green, and then red. Red is the button furthest from the wire."

- Obtain verbal confirmation that the participant understands how to hold and use the button box

Warn Participants of Loud Noises During the Scan and Provide Ear Protection:

- Warn participants again about the loud noises that will occur during the scan

- Provide the participants ear protection and instruct them on how to use it. The RA should show the participant how to roll and squeeze the ear plugs in their hand and insert them into their ears
- Confirm with the participant that the ear plugs are fully inserted and fully functional

Familiarize the Participant with the Squeeze Ball:

- Lower the scanner bed and help the participant climb on
- Inform the participant that there is an intercom that will allow research staff to talk to him/her, and that staff will be checking in periodically
- Hand the participant the button box
- Place the squeeze ball on the participant's chest and explain its function

Example Dialogue:
"I am placing a squeeze ball on your chest. If at any time during the scan you feel like you have to stop and exit the scanner, squeeze it and a loud noise will alert us outside that we need to stop the scan and check on you."

- Receive verbal confirmation the participant understands the function and usage of the squeeze ball

Reminders for the Participant

- Inform the participant again that during the first few minutes of the scan there is a small possibility they will experience peripheral nerve stimulation
- Remind the participant to try and stay extremely still for the duration of the scan
- Remind the participant to stay awake for the duration of the scan

Aligning the Head Coil

- Insert foam pads in the empty space around the participant's head in order to minimize movement during the scan
- Place the foam leg cushion underneath the participant's knees for comfort
- Retrieve the head coil and carefully place it over the participant's head; during this time please be mindful of the participant's comfort
- Raise the bed and adjust the mirror. The participants should be able to see straight back
- Tell the participant to close his/her eyes and keep them closed. Turn on the aligning laser and line up the red laser line with the white line on the head coil
- Turn off the laser and tell the participant it is now safe to open his/her eyes
- Receive verbal confirmation that the participant is comfortable and believe this will be a comfortable position for the next hour.
- Inform the participant that the bed will now be sent into the scanner

- Once the participant is fully in the scanner inform him/her that you are now exiting the room and closing the door, but you will be able to communicate through the intercom

Resting State Scan:

- Once the RA has left the participant in the scanner room, he/she must turn on the intercom and inquire about the participant's comfort. Wait for a response in order to continue
- Inquire about the positioning of the monitor screen. Fix the mirror/screen as needed
- Inform the participant that now the screen will go black for a short time. During this time, the resting state scan will take place. It will take approximately 10 minutes to complete. Remind the participant to remain awake and stay as still as possible

Example Dialogue:
"Hi X, how are you doing? Are you comfortable? Can you see the screen ok? Good. We are going to start in just a few minutes and you will hear those loud noises we talked about earlier. For right now the screen is going to go black as we collect some initial data and it will come back on for the tasks. Right now, we ask that you remain awake, with your eyes open and try not to think about anything in particular. Remember to stay as still as possible. This will take about 10 minutes to complete."

Cue Reactivity Task:

- Inform the participant that we will now run the cue reactivity task
- Receive verbal confirmation that the participant understands the task and the location of the red button
- Inform the participant that he/she will be completing this task five times with a short break in between each run
- Check in with the participant periodically about comfort level

Example Dialogue:
"Now we will run the cue reactivity task. I want you to press the red button, which is the button furthest from the wire, every time you see an animal that is not a person on the screen. As with the last scan, please stay as still as possible."

Stroop Task:

- Inform the participants that we will move on to the Stroop task
- Make sure the participant remembers the order of colors on the button box. Explain the order of the buttons to the participants again if need be (closest to the wire is blue, then yellow, then green, then red)
- Explain that first there will be a practice Stroop task. After the practice task inform the participant that they will now begin the real Stroop Task

Example Dialogue:
"As a reminder, during this task you will be asked to identify the color font of the word you see as quickly and as accurately as you can. The words will be displayed rapidly so do the best you can. We will begin with a practice version and then go into the real task. Do you have any questions?"

Event-based Reappraisal Task

- Inform the participants that we will move on to the reappraisal task
- The MRI technicians will go in there and switch to the 5-buttons buttonbox
- Explain the instructions one more time
- Ensure that you are using the correct set of images for current participant. After every five participants, we switch to a new set of images. Use same set for each participant's pre/post/

Example Dialogue:
"*In this task, what we are really interested in is people's ability to change how they are feeling. And the way we are going to ask you to change how you are feeling is by changing the way you think about something that we show you. You will see a series of pictures, and some of them are going to make you feel somewhat negative or very negative, and some pictures might not make you feel very negative at all.*"

After the Scans:

- Go into the scanner room and help the participant out of the scanner bed. Ask him/her to sit and stand up slowly, as he/she may be dizzy or weak after lying still in the scanner for an extended period of time
- The participant can then change back into street clothes and is free to leave
- Strip the linens off the scanner bed and put them in the hamper along with the participant's used scrubs
- Make a copy of the participant's screening form, give the original to the technician, bring the copy back to CARD, and file in participant's binder

Training & Certification

Training, Certification, and Supervision of Study Therapists

UP and TC therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings. Using similar procedures and scales to those currently employed across treatment outcome studies at CARD, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione. Initially, expert raters of the protocols will certify the study supervisor (Drs. Farchione) who will then be able to certify junior study therapists. All on-going adherence will be conducted by expert raters.

The adherence rating scales are designed to assess three aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). For initial certification, expert raters listen to all treatment sessions. To be certified, all therapists must receive a score of 85% or higher on at least 20% of the treatment sessions administered. Trainees who do not meet criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again.

Protocol Certification Tracking

Therapist certification status on the protocols is monitored by the Research Assistant (RA). The RA maintains the Certification and Adherence Tracking Database to track the certification cases each therapist has been assigned to ensure study integrity. The database is organized such that each therapist has their own tab within the Excel spreadsheet that contains all of the certification cases for that therapist. [redacted]

Training and Certification of IEs

Supervision

After initial training and certification (see Training and Certification Procedures), study therapists are required to meet weekly with a licensed clinician (Dr. Farchione, Project Director) who are trained and certified in the treatment protocols. These supervision meetings are expected to help maintain adherence to the treatment protocols and to help study staff resolve clinical issues that might arise during treatment.

Checks on the Integrity of Assessment Procedures

The post treatment ADIS and SIGH-A and SIGH-D will be conducted by Independent Evaluators (IEs) who are blind to treatment assignment. It is previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, research personnel will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs.

A large-scale recommendation for reducing systematic bias in the responding IEs includes having a PI and IEs who are affiliated with medical and non-medical professions and incorporating multiple sites in study. A secondary level recommendation requires training to criteria on primary outcome measures and periodic independent monitoring of evaluation implementation and scoring. The third level emphasizes using objective ratings of treatment effectiveness. Other suggestions include keeping the IEs separate from the research team and participants during their treatment sessions and making the participants aware not to reveal too much information to the IE about their treatment sessions and therapists.

The IEs for the proposed study will be Ph.D. or MA-level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow and Farchione. Dr. Elizabeth Eustis will supervise the individual training process of the IEs. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews. Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Furthermore, IEs will be asked to complete an Independent Knowledge of Treatment form (IEKNO) consistent with previous trials completed at the center, before and after conducting the post ADIS assessment, the one-month follow-up ADIS assessment, and the six-month follow-up ADIS assessment. [redacted] Copies of this form should also be stored in the Participant Binders in the proper session tabs. After the forms are completed the RA should scan both the pre, and post assessment IEKNO to the StAR 2 shared drive [redacted] This form asks the IE to reveal whether the blind has been broken by asking the IE to select the condition which they think the participant has been assigned to and provide any relevant information as to why they believe the participant has been assigned to this condition. The expected rate of guessing correctly will not be greater than chance signifying the maintained blinds. In the event that the IE learns of the condition of the participants, the IE will alert the RA who will schedule future assessment time points with the other IEs who are still blind to the participant's condition. This will only occur when an IE knows for certain which treatment a participant is receiving. If an IE learns that a participant is in treatment (i.e., by seeing them in the waiting area), but does not know which treatment they are in then the IE will not be switched.

Minimum Requirements for IE Certification

ADIS

For initial certification, IEs will listen to prior ADIS training tapes and provide CSRs for all diagnoses. These ratings will be compared to a master file (currently monitored by Dr. Todd Farchione); once the IE has "matched" on three of five assessment training tapes, the IE will conduct a mock interview with another member of the team. The five tapes are "rolling"; for example, if an IE does not match on the first three tapes, but matches on the next two tapes, he/she/they can count the last two towards the next set of five (i.e., if a match occurs on the next tape, that would suffice for certification).

During the next stage, the IE will observe an ADIS conducted by a trained IE and complete the "follow along" training ADIS in Qualtrics. After the assessment, the IE and IE-in-training will compare CSRs and discuss administration and case conceptualization. Next, the IE-in-training will administer an ADIS with a trained IE in the room for observation. The trained IE will complete a full evaluation of the trainee's administration and provide feedback (using the ADIS checklist as an objective way to assess adherence). CSRs will also be compared. Once the IE-in-training "matches" on all clinically significant CSRs with the trainer and passes adherence on the ADIS checklist, he/she/they will be certified to conduct assessments.

Once each step is completed it can be checked off on the Blank Training Checklist in the Assessment Training folder, listed above.

TLFB

In addition to achieving ADIS certification, IEs must be certified on the additional IE assessment measures. This involves the administration of Timeline Follow-Back (TLFB) for

assessment of past 90 day alcohol use. For initial certification in the administration of the Timeline Follow-back. The IEs should first read through the TLFB instructions very carefully. The instructions can be found in [redacted] Then the IEs should watch the training video at this link: https://www.youtube.com/watch?v=c5lv3gVduIc

Then the IEs should successfully administer the TLFB to Dr. Sauer-Zavala. Finally they will need to submit a recording of their first TLFB administration for review.
Once each step is completed it can be checked off on the Blank Training Checklist in the Assessment Training folder, listed above.

Note: TLFB and TIF are now administered by a trained RA.

SIGH-A & SIGH-D

The IEs must be certified in the administration of The Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A), a clinician-rated measure for measuring anxiety symptoms and their severity, and the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D), a clinician-rated measure for measuring depression symptoms and their severity. The SIGH-A & D training materials can be located in: [redacted]
The training procedures for the SIGH-A and SIGH-D are as follows:

- Read the SIGH-A Instructions and Scoring and the SIGH-D Instructions and Scoring document
- Carefully read through the SIGH-A and SIGH-D Admin Notes
- Watch the SIGH-A and SIGH-D video while scoring along on the assessment sheets
- Submit ratings for the SIGH-A and SIGH-D to Dr. Farchione

Certification Tracking

All study staff should update their Certificate and Training sheet with the dates that they became certified in each assessment. [redacted] Once filled in the form should be printed and added to the study binder.

Consensus

Certified IEs will then meet with the PD each week for ADIS consensus meetings and further supervision on intake procedures. New patients screened for the study will be presented each week to the full research and medical team to inform eligibility for study enrollment following consensus with the PD.

[redacted]

[redacted]

Training of Phone Screeners

Phone screens will be conducted by: RAs. New RAs will be trained by current RAs in conducting phone screens.

Training process: (avg = 2 weeks)

1. Observe 2 calls by current RAs
2. Conduct 2 screens with current RA observation/feedback
3. Receive approval from current RA to proceed independently

Assessment Tracking and Scheduling

The RA is primarily responsible for tracking when assessments should occur and scheduling these appointments. Independent evaluators (IEs) should be notified of an upcoming assessment via an appointment email alert containing all of the necessary information they need to complete the assessment (participant's initials, date and time of the appointment). The RA is responsible for signing out a room for the assessment on Titanium, unless the IE chooses to conduct the interview in his/her/their office.

Scheduling/Tracking Sessions

The RA schedules the first treatment session with the participant after the Screening Session appointment via phone once the full team consensus meeting has been held to determine participant eligibility. Once the participant is determined to be eligible, the RA determines randomization to treatment condition. [redacted] Only RAs, and the PI will have access to the randomization list. The RA should add participants to the list by ID number in chronological order. Next the RA should ask Dr. Farchione which therapist the participant has been assigned to. The participant should be scheduled for session 1 as soon as possible to ensure a definite start date within the first month after the screening session.

Throughout the active treatment phase, the therapist is responsible for scheduling treatment sessions with participants, and informing the RA of the treatment schedule and time of upcoming appointments (via email). When discussing the date and time of the next appointment with the patient, the therapist should also build in time for the RA portion of the assessment (e.g., an additional 30 or 45 minutes before the therapy session, depending on session number).

Therapy sessions are 50 minutes for UP participants and 30 minutes for TC participants. A urine sample will need to be collected by Bonnie or a trained RA on the screening session, MRI sessions, sessions 1, 4, 8, 12, and 16 (if applicable; for UP condition only). A blood sample will be collected by the study nurse on the screening and last treatment session. On session 1 and the last treatment session (12 for TC; 16 for UP) the RAs will need approximately 2 hours total to complete their portion of the session. Please see the table below for breakdown of how long to schedule each session for.

Note: As of March 18th, 2020, due to remote procedures, urine and blood sample collection has been reduced to the screening session and post-assessment only (after the last treatment session), at a Quest Diagnostics facility. A urine sample for pregnancy and drug testing is still collected in-person when a participant comes in for an fMRI.

Scheduling time for each session:

Session #	Time for Medical	Time with Therapist	Time with RA	Time for IE
Baseline	30 min	N/A	1.5 hours	2 hours
Session 1	15 min	50 min UP, 30 min TC	1 hour & 45 min	N/A
Session 2	N/A	50 min UP, 30 min TC	30 min	N/A
Session 3	N/A	50 min UP, 30 min TC	30 min	N/A
Session 4	15 min	50 min UP, 30 min TC	30 min	N/A
Session 5	N/A	50 min UP, 30 min TC	30 min	N/A
Session 6	N/A	50 min UP, 30 min TC	30 min	N/A
Session 7	N/A	50 min UP, 30 min TC	30 min	N/A
Session 8	15 min	50 min UP, 30 min TC	30 min	N/A
Session 9	N/A	50 min UP, 30 min TC	30 min	N/A
Session 10	N/A	50 min UP, 30 min TC	30 min	N/A
Session 11	N/A	50 min UP, 30 min TC	30 min	N/A
Session 12 (TC Post)	30 min	30 min TC	1 hour & 15 min	30 min
Session 12 (UP)	15 min	50 min UP	30 min	N/A
Session 13	N/A	50 min UP	30 min	N/A
Session 14	N/A	50 min UP	30 min	N/A
Session 15	N/A	50 min UP	30 min	N/A
Session 16 (UP Post)	30 min	50 min UP	1 hour & 15 min	30 min
1-mo Follow-Up	N/A	N/A	1 hours	30 min
6-mo Follow-Up	N/A	N/A	1 hours	30 min

Tracking treatment sessions will be done through Titanium. The therapist should also email the RA the date and time of the next scheduled session as soon as it is scheduled. The RA will check in at weekly lab meetings to make sure the calendar accurately reflects the status of each participant as this information is entered by the RA into Titanium. The RA will schedule time with Bonnie to complete any necessary procedures.

Note: As of 2020, Titanium is no longer used due to remote procedures. Treatment sessions are now tracked through the "Retention_ActivePhase" tab of the Retention Database, and a Google calendar

Scheduling Follow-up Assessments:

At the post-assessment, the RA should remind participants in the active treatment conditions of the follow-up assessment schedule (1 month and 6 months after post). These participants should expect to receive a call from the RA approximately 2-4 weeks prior to the target date of their follow-up assessments. For the 1-month, and 6-month assessments, the RA

will also contact the patient one week, and one-day, before the assessment to confirm the appointment. Follow these guidelines for attempting to reach the participant.

> Week 1 | Begin contacting patient two weeks before the assessment target date. Send an email and call patient twice during that week.
>
> Week 2 | One week before the target date, call the patient twice.
>
> Week 3 | During the week of the target date, call the patient twice and send an email.
>
> Week 4 | During the second week after the target date, call the patient twice. If the patient does not complete the assessment by the end of this week, the assessment window has expired. The RA will mail an unable to contact letter to notify the patient that she/he/they must make contact with study personnel before the next assessment target date in order to avoid being withdrawn from the study for noncompliance. If the patient does not respond by the given date she/he/they will be withdrawn from the study.
>
> Week 5 | Await the patient's response to the unable to contact letter.
>
> Week 6 | If study personnel do not hear from the patient after sending the letter, make one final call and send one final email notifying the patient of the approaching withdrawal response deadline.

Treatment Sessions

The RA is responsible for updating Titanium when a participant cancels or no-shows, and for emailing the team as soon as possible. If the participant fails to attend the scheduled session, the RA should also make a note on the front page of their Participant Binder, on the document titled Scheduled Sessions. This document has a list of all the sessions that need to be completed over the course of treatment, the date of the scheduled appointment, and the date the session was attended. Electronic copies of this form can be found in: [redacted]

Missed Treatment Sessions

While it is expected that most participants will need to reschedule an appointment on occasion during the course of treatment, repeatedly missed treatment sessions are likely to interfere with the administration of treatment procedures and ultimately lead to poorer treatment outcome. The following guidelines have been set to provide some flexibility in participant and therapist schedules while also maintaining consistency in the administration of treatment protocols across study conditions:

Allowance for Missed/Rescheduled Sessions:

- TC: Participants will receive 12 treatment sessions in 12 to 16 weeks.

- UP: Participants will receive 16 treatment sessions in 16 to 21 weeks.

Participants will have two weeks from the target date to complete each assessment. If a participant fails to contact study personnel for two consecutive weeks, he/she will be withdrawn from the study and informed of study withdrawal via letter sent to his/her home address.

Calling Procedures for No-shows and Missed Sessions

Participants will be withdrawn if there is a 2-week period of no contact and no reply after 2 calls from study staff (e.g., RA) and 2 calls from the therapist (for a total of 4 calls), using the following protocol:

On the day of a session when participant is ~15 min late for scheduled session: **1st call made by RA** to inquire about attendance:

- "We noticed that you are not here for your session, will you still be able to make it?"
- If he/she/they answers the call, plans to attend the session, and is able to arrive at the Center in time to finish all session tasks and the therapy session, the appointment will be held as planned
- If he/she/they answers and is unable to make the session, wait for therapist to provide availability for rescheduling the next session
- If he/she/they does not answer, do not call back again until the day after the missed session (or Monday if their missed session was on a Friday)

2nd call made by RA is made the day after the missed session if the participant has not been in touch. The same steps above are used for making the 2nd call.

3rd call made by the therapist 1st week after missed session and 2 RA calls:

- "You missed your session on date/time and I am calling to reschedule the appointment; I have an opening on (date/time) that I will schedule you for. Please let me know if you are unable to make it then."

4th call therapist 2nd week after missed session (and 2 RA calls and 1 prior therapist call):

- "If we are unable to schedule an appointment with you for your next session by (date that matches 2 week point of no contact), we will have to withdraw you from the study based on our attendance guidelines. Please call at your earliest convenience (or therapist can offer another date and time for session)."

Participants will be withdrawn on the date that marks 2 weeks of no contact unless the next session is scheduled and the treatment continues. Should this pattern of no contact occur 2 times during the course of treatment, the participant will automatically be withdrawn on the 3rd missed session.

On-going Adherence

Maintaining Inter-Rater Reliability

A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of supervision with the Project Director and ongoing evaluations of selected recordings of clinical assessments.

Each month an IE will listen to **one assessment** performed by another IE associated with the study and will independently complete the assessment instruments. Each IE will go through this process every other month creating one duplicate rating per month for all assessments. Further, once **every 4 months, Drs. Farchione, and/or Eustis will listen to one audio recording of an IE assessment**. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. Additionally, Dr. Eustis will meet with all IEs weekly to discuss clinical ratings and diagnostic information for new participants. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above) and inter-rater reliability (kappa) will be calculated.

Steps for Selecting Assessments

The StAR2 assessment battery was designed to:

1. Employ different methods (RA- or clinician-rated; self-report) to provide converging lines of evidence
2. Evaluate hypothesized mediators and mechanisms of change through carefully selected measures and time points

Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and participant burden.

Assessment Measures Administration

Schedule for assessments and interventions for the baseline period, each session, sessions 1, 4, 8, and 12, sessions 2, 6, 10, and 14, post treatment/session 16, and 1-month and 6-month follow-ups. Key: BL= Baseline/Screening; 1 – Collected to determine eligibility for research study; 2—To be administered before or during the fMRI scan; 3 – Excluding session 1; 4 – Only collected at session 2; 5 – Excluding sessions 8 & 12; S1—To be administered on session 1.

Assessment Schedule	**TIME OF ADMINISTRATION**

	BL	Each Session	Session 1, 4, 8, 12	Session 2, 6, 10, 14	Last Tx Session (12 or 16)	1 MFU & 6 MFU
SCREEN/MED						
Medical History & Chemical Panel/Complete Blood Count	X				X	
Urine Pregnancy Test	X[2]				X[2]	
Urine Drug	X, X[2]				X[2]	
Vitals/Weight/BMI	X				X	
Phophatidylethanol (Peth)	X				X	
Ethyl Glucuronide/ (ETG)	X		X		X	
AUD RELATED						
Blood Alcohol Concentration (BAC)	X	X				X
Alcohol Timeline Follow-back (TLFB)	X	X				X
Alcohol Dependence Scale (ADS; Skinner & Allen, 1982)	X					
Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-AR)	The CIWA-AR will be administered when the participant reports drinking 50% less than the prior assessment, as assessed by the TLFB.					
Obsessive Compulsive Drinking Scale (OCDS)			X[3]		X,	
Alcohol Use Disorders Identification Test (AUDIT)	X					
Alcohol Urge Questionnaire (AUQ)	X[2]		X[3]		X, X[2]	

Comprehensive Effects of Alcohol Questionnaire (CEOA)	X				X	X
DIAGNOSIS & CLINICAL IMPROVEMENT						
Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5)	X[1]				X	X
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy et al. 1976)	X		X		X	X
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	X				X	X
Adult Mental Healthy Continuum-Short Form (MHC-SF)	X		X		X	X
ANXIETY/MOOD						
Overall Anxiety and Depression Severity and Impairment Scales (ODSIS & OASIS)	X	X			X	X
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A & SIGH-D)	X				X	X
Inventory of Statements about Self-Injury (ISAS)	X				X	X
MEDI	X				X	X
HIGHER-ORDER & SKILLS-BASED MECHANISMS						
CERQ-Short	X				X	X
Distress Tolerance Scale (DTS)	X[S1]				X	

Anxiety Control Questionnaire Revised (ACQ-R; Brown et al., 2004)	X		X		X	X
Beliefs about Emotions Scale (BES)	X		X		X	X
Difficulties in Emotion Regulation Scale (DERS)	X		X[3]		X	X
Eysenck Personality Questionnaire Revised – Short Form (EPQR-S; Eysenck & Eysenck, 1975, 1985)	X	X			X	X
UP Cognitive Skills Questionnaire (UP-CSQ).	X		X		X	X
Personality Assessment Inventory – Borderline Features Scale (PAI-BOR)	X				X	
The Personality Inventory for DSM-5 – Brief Form (PID-5-BF)	X				X	
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez et al., 2011)	X	X			X	X
Anxiety Sensitivity Index (ASI)	X		X[3]		X	X
Southampton Mindfulness Questionnaire (Chadwick et al., 2008)	X		X[3]		X	X
POTENTIAL MODERATORS OF TREATMENT OUTCOME						
Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000)				X[4]		

Readiness to Change Questionnaire (RTCQ)-	X					
Work and Social Adjustment Scale (WSAS)	X				X	
State Hope Scale (SHS)	X		X		X	X
OTHER MEASURES						
Homework Compliance Scale (Primakoff et al., 1986)		X				
Treatment Skills Usage Questionnaire					X	X
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF)			X[3]			
NEUROCOGNITIVE ASSESSMENTS						
Stroop Task (fMRI)	X[2]				X[2]	
Alcohol Cues Task (fMRI)	X[2]				X[2]	
Continuous Performance Test (CPT)	X[S1]				X	
Go/No Go Task	X[S1]				X	
Balloon Analogue Risk Task (BART)	X[S1]				X	
Rogers Risk Task	X[S1]				X	
Computerized Paced Auditory Serial Addition Test (PASAT-C)	X[S1]				X	
Montreal Cognitive Assessment (MoCA)	X					
The Dot Probe Tasks	X[S1]				X	
Emotional Conflict Task	X[S1]				X	
Event Based Reappraisal Task	X[2]					X[2]

Description of Instruments

Below is a brief summary of the assessment measures that will be administered in this study. Unless otherwise stated, instruments selected for this study have demonstrated clinical and research utility and have reliability and validity data to support their use.

I. Assessments of Alcohol Use (AUD Related)

Alcohol Timeline Follow-Back (TLFB): The TLFB will be administered at the screening session, and at every treatment session (not including MRI sessions) and both follow-ups. The TLFB will be used to estimate participants' daily drinking. In this assessment, participants are presented with a calendar and asked to provide retrospective estimates of their daily alcohol consumption over a specified time period. It takes approximately 25-30 minutes to gather 12 months of data, and approximately 10 minutes to gather 90 days of data. The TLFB has high test-retest reliability and correlates with other established measures of alcohol use (Sobell & Sobell, 1992).

Alcohol Dependence Scale (ADS): The ADS will be administered at the screening session. Alcohol dependence will be assessed using the ADS. This 25-item scale has an internal consistency reliability estimate of 0.92 (Skinner & Allen, 1982).

Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-A): The CIWA-Ar will be administered by study nurse Bonnie Brown, when the participant reports drinking 50% less than the prior assessment, as assessed by the TLFB. If Bonnie is not available, Dr. Farchione will conduct the assessment. The CIWA-A will be used to evaluate the severity of withdrawal symptoms. This 10-item scale, shortened from the 15-item CIWA-A scale, retains significant accuracy when compared to the original CIWA-A ($r = 0.99$; Sullivan, Sykora, Schneiderman, Naranjo & Sellers, 1989).

Obsessive Compulsive Drinking Scale (OCDS): The OCDS will be administered at sessions 1, 4, 8, 12, and 16. OCDS will be used to assess alcohol craving and the urge to drink. The OCDS is a 14-item self-report questionnaire developed based on the Yale-Brown Obsessive-Compulsive Scale, an interview-based rating scale. It takes approximately 5-10 minutes to complete. The OCDS is significantly correlated with independent measures of alcohol craving and with the amount of alcohol consumed, and has a positive relationship with independent measures of the severity of alcoholism (Anton, Moak, & Latham, 1995).

Alcohol Use Disorders Identification Test (AUDIT): The AUDIT will be administered at the screening session. The AUDIT will be used to screen for hazardous and harmful alcohol consumption. The AUDIT is a 10-item questionnaire assessing alcohol consumption and alcohol-related problems. Each response is scored from 0-4, giving a maximum possible score of 40. In a study of participants in 6 countries, the overall sensitivity of the AUDIT for hazardous and

harmful alcohol use was 92% and the overall specificity was 94%, when a lower cut-off point of 8 was used (Saunders, Aasland, Babor, De La Fuente, & Grant, 1993).

Alcohol Use Questionnaire (AUQ): The AUQ will be administered before and after each MRI scan, sessions 4, 8, 12, and 16. AUQ will be used to assess alcohol craving and the urge to drink. The AUQ is an 8-item self-report questionnaire, in which participants rate their agreement or disagreement to statements on a Likert scale. AUQ scores are strongly correlated to the severity of alcohol dependence and to cognitive preoccupation with alcohol, and decline with prolonged abstinence from alcohol (Bohn, Krahn, & Staehler, 1995).

Comprehensive Effects of Alcohol Questionnaire (CEOA): The CEOA is a 38 item self-report questionnaire using a 4-point Likert scale (1 disagree to 4 agree) that assesses both positive and negative expectancies about alcohol use and its effects. Seven factors have been identified, four of which are classified as assessing positive expectancies (Sociability, Tension Reduction, Liquid Courage, Sexuality) and three assessing negative expectancies (Cognitive and Behavioral Impairment, Risk and Aggression, Self-Perception). The CEOA has demonstrated good test–retest and internal consistency reliability (Fromme, Stroot, & Kaplan, 1993).

II. Diagnosis & Clinical Improvement

Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5): This semi-structured, diagnostic clinical interview focuses on DSM-5 diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal and homicidal ideation are also part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001).

An abbreviated version of the ADIS-5 will be administered at the screening session to assess presence of current psychopathology. During treatment and the follow-up period, specific sections corresponding to those disorders identified to be clinically significant at the initial intake will be administered. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation (if applicable and at the discretion of the study team) to avoid repeating the diagnostic evaluation in this study (if completed within 1-month of the StAR2 screening date).

Clinical Global Impressions- Improvement & Severity (CGI- I & CGI-S): The CGI provides an overall clinician-determined summary measure that considers all available information, including

knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function compared to other clinical participants with similar diagnoses. The CGI comprises two companion one-item measures evaluating the following: (a) severity of psychopathology from 1 to 7, and (b) change from the initiation of treatment on a similar seven-point scale.

The CGI is administered by an experienced clinician who is familiar with the diagnoses under study and the likely progression of treatment. Consequently, the CGI rater can make an expert clinical global judgment about the severity of the illness across various time points within the context of that clinical experience. The clinician makes a judgment about the total picture of the participant at each visit: the illness severity, the participant's level of distress and other aspects of impairment, and the impact of the illness on functioning. The IE also makes CGU ratings after the post assessment, and the 1 and 6 month follow-up assessments.

Instructions: The CGI-Severity (CGI-S) asks the clinician one question: "Considering your total clinical experience with this particular population, how impaired is the participant at this time?" The clinician is asked to rate impairment using the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally impaired; 3=mildly impaired; 4=moderately impaired; 5=markedly impaired; 6=severely impaired; 7=among the most extremely impaired participants. This rating is based upon observed and reported symptoms, behavior, and function in the past seven days. Clearly, symptoms and behavior can fluctuate over a week; the score should reflect the average severity level across the seven days.

The CGI-Improvement (CGI-I) is similar in its format. Each time the clinician completes the measure (session 4, 8, 12, 16), the clinician compares the participant's overall clinical condition to the one-week period just prior to the initiation of treatment. The CGI-S score obtained at the baseline (initiation) visit serves as a good basis for making this assessment. Again, only the following query is rated on a seven-point scale: "Compared to the participant's condition at admission to the project, this participant's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline; 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment."

The CGI-I score generally aligns with the CGI-S such that improvement in one follows the other. Anchors for scoring, however, are quite different, and the CGI-I is based upon changes from the initiation of treatment in contrast to changes on a week-to-week basis. Consequently, the two CGI scores can occasionally be dissociated such that a clinician may notice changes in the CGI-I relative to baseline despite no recent changes in the overall CGI severity score or vice versa.

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q): The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains:

physical health, mood, work, household activities, social relationships, family relationships, leisure activities, daily functioning, sexual drive and interest, economic status, living situation, physical stability, vision, and overall sense of well-being. According to Ritsner et al. (2002), the Q-LES-Q has demonstrated high internal consistency and good construct validity (Endicott, Nee, Harrison, & Blumenthal, 1993).

Adult Mental Healthy Continuum-Short Form (MHC-SF): The MHC-SF is a measure of overall positive mental health which consists of 14 items. This assessment measures emotional well-being, psychological well-being, and social well-being (Keyes et al., 2008).

III. Anxiety/Mood

Overall Depression Severity and Impairment Scale (ODSIS): The ODSIS is a 5-item continuous measure assessing depression in the following domains: frequency, intensity, functional impairment in pleasurable activities, work or school, and interpersonal relationships. Items are scored on a 5-point Likert scale of 0–4. A psychometric analysis of the ODSIS scale found good internal consistency (Cronbach's alpha = .92; Bentley et al., 2014).

Overall Anxiety Severity and Impairment Scale (OASIS): The OASIS is a five-item continuous measure of anxiety-related severity and impairment. Items are coded from 0 to 4 and are summed to obtain one total score. Results from three previous psychometric evaluations of the OASIS have indicated high internal consistency, excellent test– retest reliability, and convergent and discriminant validity in clinical and nonclinical samples (Norman et al., 2006).

Structured Interview Guide for Hamilton Anxiety Scale (SIGH-A)

Purpose: The purpose of this structured interview is to assist in the reliable assessment of anxiety severity by standardizing the method of assessment and providing clear anchor points for the assignment of severity ratings. The interview items and the anchor points are meant to supplement good clinical judgment, not replace it.

Instructions: Begin the interview with an introduction, describing the scale and its purpose in a way that is relevant for the specific participant. The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for the clinician to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration of additional clarification of symptoms is necessary. The specified questions should be asked until there is enough information to rate the item confidently. In some cases, additional follow-up questions may be necessary to obtain information. For some of the items, there may be similar questions already asked about some of the symptoms (for a previous item). There is no need to repeat questions about these symptoms unless additional information is needed to rate the severity. The final score for each item should reflect an assessment and balancing of the severity and frequency of the symptom.

Rating Items: All of the items have the same anchor points. The following may be useful as guides to rating severity:

MILD: Occurs irregularly and for short periods of time.

MODERATE: Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.

SEVERE: Continuous and dominates the subject's life.

VERY SEVERE: Incapacitation.

For each item, several defining characteristics of each severity score are provided. These defining characteristics are meant as guidelines to aid in the reliable use of the severity scales and represent examples of the severity levels appropriate to the rating. Severity is defined most readily by the frequency of occurrence, and the degree of distress and interference associated with the symptom. The number of symptoms present is included in the severity rating only as it impacts distress and interference. For example, a higher rating may be achieved for a single severe symptom and for several mild or moderate symptoms. Alternatively, several mild symptoms may lead to a moderate rating of severity because of their overall impact on distress. In addition to the guidelines for each item, the interviewer should note the following conventions for boundary problems:

None to mild boundary: Most questionable cases should be rated as one, as zero is meant to be an anchor point with no symptom present.

Mild to moderate boundary: Symptoms are endorsed less than fifty percent of the time and cause little to no interference or distress; rate as one. Symptoms are endorsed less than fifty percent of the time and are rated as causing mild to moderate interference or distress; rate as two. Symptoms are endorsed more than fifty percent of the time and are rated as causing mild interference or distress; rate as two.

Moderate to severe boundary: Symptoms are endorsed less than fifty percent of the time and are rated as causing severe interference or distress; rate as three. Symptoms are endorsed more than fifty-percent of the time and are rated as causing moderate to severe interference or distress, but not both; rate as three.

Severe to very severe boundary: Questionable cases should generally be rated as a three; ratings of four are reserved for behavioral events clearly identified by the rating anchors.

To elicit the information necessary for assigning severity ratings, the interviewer must assess the frequency of occurrence, degree of distress, and degree of interference associated with symptoms. The following questions are recommended for this assessment:

Have you had the symptom every day? If NO, have you had the symptom more days than not?
How much does the symptom bother you?
How much does it interfere with your life?

NOTES: Time period. The ratings should be based on the participant's condition in the past week.

If the participant has panic attacks, this will affect the ratings of many of the symptoms. It is recommended to consider the total amount of time during the past week that the panic attack symptoms occurred, as well as their severity. For example, a participant who has few severe but short –lived panic attacks during the week, but who otherwise does not have many anxiety symptoms, would probably not have a very high total SIGH-A score.

> NOTE: When rating items 8-11 and 13 the interviewer should rate symptoms regardless of whether they did (or did not) occur during a panic attack. Simply rate the symptom as it occurred over the past week.

Scoring: Summing each individual item leads to total scores ranging from 0 to 56.

Structured Interview Guide for Hamilton Depression Scale (SIGH-D)

Purpose: To measure depression symptoms and their severity.

Instructions: The first question for each item should be asked as written. Follow-up questions are provided for further exploration or additional clarification of symptoms. The specified questions should be asked until enough information is provided to rate the item confidently. Follow-up questions may be added obtain necessary information. If the answer to a specified question is already known, it is sufficient to confirm the information with the subject (e.g., "You said that..."), make the rating, and continue. The final score for each item should reflect an assessment and balancing of the severity and frequency of the symptom. Note that participants with chronic symptoms may not be able to identify a period of normalcy or may report that "depressed" is their usual state. However, depression should not be rated as "normal" (i.e., a rating of "0") in these cases. Summing each individual item leads to total scores ranging from 0 to 53.

Example:

> **What's your mood been like this past week (compared to when you feel OK)?**
> Have you been feeling down or depressed? Sad? Hopeless? Helpless? Worthless?
> IF YES: Can you describe what this feeling has been like for you? How bad is the feeling?
> Have you been crying at all?
> **How have you been feeling about the future?** (optimistic/pessimistic) Do you feel better with encouragement/reassurance from others? Do you feel things will get better, improve, work out?
> **IF DEPRESSED: In the past week, when something good, even small things have happened, did your mood brighten up?** How long did this brighten mood last? Were there things that occurred that should have brightened your mood but did not?
> In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day?

Inventory of Statements about Self-Injury (ISAS): The ISAS was designed to measure the occurrence and frequency of 12 methods of non-suicidal self-injury (NSSI; Section I. Behaviors), in addition to assessing 13 functions of NSSI (Section II. Functions). In the present study, we are only utilizing Section I to determine presence and frequency of NSSI behaviors (current and past) among participants. The ISAS has shown good validity and reliability (Klonsky & Glenn, 2008).

Multidimensional Emotional Disorder Inventory (MEDI; Rosellini, 2013) is a 50-item self-report measure designed to assess transdiagnostic vulnerabilities consistent with a dimensional approach. The MEDI is representative of a transdiagnostic assessment approach that is well suited for treatment planning and outcome monitoring for shared mechanism treatments like the UP (Rosellini, Boettcher, Brown, & Barlow, in press). The MEDI assesses neurotic temperament, positive temperament, depression, autonomic arousal, somatic anxiety, intrusive cognitions, social concerns, traumatic re-experiencing, and avoidance.

IV. Higher-Order & Skills-Based Mechanisms

Anxiety Control Questionnaire Revised (ACQ-R): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding (Brown et al., 2004; Rapee et al., 1996).

Beliefs about Emotions Scale (BES): The BES consists of 12 items and is designed to assess negative beliefs about emotions. Responses are rated on a scale from 0 (totally disagree) to 6 (totally agree). There is empirical support for its validity, reliability, and sensitivity to change (Rimes & Chadler, 2009).

Difficulties in Emotions Regulation Scale (DERS): The DERS is a 36 item self-report measure developed to assess clinically relevant difficulties in emotion regulation. DERS items aim to measure participants' difficulties with (a) awareness and understanding of emotions; (b) acceptance of emotions; (c) the ability to engage in goal-directed behavior, and refrain from impulsive behavior when experiencing negative emotions; and (d) access to emotion regulation strategies perceived as effective (Gratz & Roemer, 2004).

Eysenck Personality Questionnaire Revised – Short Form (EPQR-S): The EPQR-S is a commonly used 48 item personality inventory that consists of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will administer the Extraversion and Neuroticism subscales, totaling 24 items (Brown, 2007).

UP Cognitive Skills Questionnaire (UP-CSQ): The UP-CSQ consists of 7 items. Participants are asked to rate the extent to which they used a variety of cognitive skills over the past week (e.g., "I looked for alternative explanations when I had distressing thoughts") on a scale from 1 (never)

to 5 (always or when needed). Items are summed to produce a total score, with higher scores indicating greater skill use. The UP-CSQ has recently been developed as a measure of cognitive skills in our research lab at the Center for Anxiety and Related Disorders. Preliminary data suggests psychometric properties of this measure are promising, however, further exploration of the validity, reliability, and use within an AUD population are necessary and will be explored in this trial (Woods, Conklin, Cassiello-Robbins, Sauer-Zavala; In Press).

Personality Assessment Inventory – Borderline Features Scale (PAI-BOR): The PAI-BOR is a 24-item measure that is based off a 4-factor model of borderline personality disorder. These factors, identified by Jackson and Trull (2001), are affective instability, identity disturbance, negative relationships, and self-harm (Morey, 1991).

The Personality Inventory for DSM-5 – Brief Form (PID-5-BF): The PID-5-BF is a 25-item personality trait assessment scale for adults age 18 or older. This measure assesses five personality trait domains: negative affect, detachment, antagonism, disinhibition, and psychoticism (Krueger et al., 2011).

Multidimensional Experiential Avoidance Questionnaire (MEAQ): The MEAQ is a self-report questionnaire that measures experiential avoidance, which is a tendency to avoid negative internal experiences, and is an important concept in numerous conceptualizations of psychopathology. Further, the MEAQ is broadly associated with psychopathology and quality of life (Gamez et al., 2011).

Anxiety Sensitivity Index (ASI): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms (Reiss et al., 1986).

Southampton Mindfulness Questionnaire (SMQ): The SMQ is a 16-item measure of mindful awareness of distressing thoughts and images (Chadwick et al., 2008).

Distress Tolerance Scale (DTS; Simons & Gaher, 2005): The DTS is a self-report index of emotional distress tolerance with 15 items and 4 subscales. The subscales include tolerance (emotional distress tolerance), attraction (attraction to negative emotions), assessment (mental assessment of distress), and regulation (regulation of measures to sooth distress). Cronbach's alpha for the scales was 0.72, 0.82, 0.78, and 0.70, respectively, with a total α of 0.82. In addition, criterion reliability and preliminary correlations were acceptable (Simons & Gaher, 2005).

Cognitive Emotion Regulation Questionnaire (CERQ-Short): The CERQ-short is a self-report measure of cognitive emotion regulation strategies used when responding to a stressful life event. The CERQ-short is a brief 18-item version of the original CERQ 36 item measure. The CERQ-

short has nine, two-item subscales. Five of the scales assess maladaptive and adaptive regulatory responses. Participants rate how often statements apply to them on a five-point scale from 1 "almost never", to 5 "almost always". Alpha coefficients for the short scales range from 0.68 (Self-blame) to 0.81 (Positive appraisal and Catastrophizing; Garnefski & Kraaij, 2006; Garnefski et al., 2006).

V. Potential Moderators of Treatment Outcome

Credibility/Expectancy Questionnaire: The Credibility/Expectancy Questionnaire is a scale for measuring treatment expectancy and rationale credibility (Devilly & Borkovec, 2000).

Readiness to Change Questionnaire (RTCQ): The RTCQ is based on Prochsaka and DiClemente's (1986) stages of change model that is commonly utilized to resolve addictive tendencies, and is comprised of three stages: precontemplation, contemplation, and action. This questionnaire is therefore commonly used with excessive drinkers to measure their readiness to change. The RTCQ shows good validity and reliability (Rollnick et al., 1992).

Work and Social Adjustment Scale (WSAS): The WSAS is a five-item measure asking participants to rate the degree of interference caused by their symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering, to 8 = severe interference). The WSAS is a descriptive measure of subjective interference in various domains of living (Marks, Connolly, & Hallam, 1973).

State Hope Scale (SHS): The SHS is a 6-item measure of state and trait forms of optimism. The SHS provides scores for agency (i.e., "perceived capacity for initiating and maintaining the actions necessary to reach a goal") and pathways (i.e., "perceived ability to generate routes to one's goals") as well as general state hope. The SHS is an internally consistent measure whose scores have demonstrated convergent and discriminant validity in relation to theoretically meaningful measures. Responses to the SHS were made on an eight-point scale ranging from definitely false (1) to definitely true (8) (Snyder et al., 1996).

VI. Other Measures

Homework Compliance Scale: At the end of each session, the therapist will evaluate the degree of homework compliance for each participant on a 0-6-point compliance scale. An overall average rating will be obtained for each participant by summing the scores for all sessions and dividing them by the number of sessions attended (Primakoff, Epstein & Covi, 1986).

Treatment Skills Usage Questionnaire: The Treatment Skills Usage Questionnaire is a 10-item questionnaire that asks each participant about the coping skills he/she/they may or may not have learned over the course of treatment. The questionnaire is specifically concerned with

determining the skills that the participants has managed to consistently utilize since ending treatment.

Working Alliance Inventory-Short Form-Therapist Version (WAI-SF): The WAI-SR is a 12-item questionnaire that assesses therapeutic alliance and is completed by the therapist: 1) agreement between participants and therapist on the goals of the treatment; 2) agreement between participants and the therapist about the tasks to achieve these goals; and 3) the quality of the bond between the participant and therapist (Tracey & Kokotovic, 1989).

VII. Biological/Medical Assessments

To assess safety-related issues, the following will be obtained from subjects: BAC (using an alcohol breathalyzer), urine drug screens at screening session and before each MRI test, urine pregnancy tests for all biological females of child bearing potential (before the fMRI scans only), blood chemistries and hematology at screening session and last treatment session, body weight and BMI, vital signs, ETG (screening and sessions 1, 4, 8, 12, 16), and Peth (pre and post). The Peth is a blood test that is used to detect prolonged or heavy alcohol consumptions within the past 2-3 weeks. The ETG test indicates the level of ethanol in urine for 1-3 days after ingestion. Most assessments will be obtained at the baseline assessment and following the Assessment Schedule. If a participant has abnormal results after analysis of the medical assessments, more tests will be ordered to ensure the safety of the participants.

Note: As of March 18th, 2020, due to remote procedures, urine and blood sample have been reduced to being collected only on screening session and after last treatment session, at a Quest Diagnostics facility. The only exception is when a participant comes in-person for an fMRI, in which a urine sample is collected for pregnancy and drug testing.

VIII. Neurocognitive Assessments

Continuous Performance Test (CPT): The CPT will be administered at session 1 and the last treatment session. The CPT measures brain damage. The CPT includes two attention tasks, the second one being more difficult than the first. In the first task, participants are presented a series of 31 letters, one letter by one letter, and are asked to click on a button when the letter X appears. In the second task, participants are presented with a series of 31 letters, and are instructed to click on the button only when the letter X appears directly after the letter A appears. The letters appear at approximately 0.92s intervals, and responses are scored correctly if the button is clicked within 0.69s after the letter appears. In both tasks, participants receive 2 trial runs before being given either a 5-minute test or a 10-minute test. Participants are scored in two ways, by dividing the number of correct responses given by the number of correct responses possible, and by dividing the number of correct responses given by the total number of responses given (e.g., how many times she/he/they clicked the button; Rosvold et al.,1956).

Go/No Go Task: The Go/No Go Task will be administered at session 1 and the last treatment session. In this online task, participants are first presented with a go or a no-go cue, and then presented with a go or no-go target. Participants are instructed to respond to a go target by clicking on a button, and not to respond to a no-go target. The cues have a high probability of signaling a correct target (valid cues), and a low probability of signaling an incorrect target (invalid cues). Incorrect responses to the no-go target are used to assess inhibitory control, which reflect impulse control. A test includes 250 trials and takes approximately 15 minutes to complete (Fillmore 2003).

Balloon Analogue Risk Task: The Balloon Analogue Risk Task will be administered at session 1 and the last treatment session. In this online task, participants are presented with a balloon. Clicking a button will pump the balloon, causing it to inflate and the participant to be awarded a certain amount of money. This happens until a threshold is reached and a pump will cause the balloon to explode, leading to loss of all money earned. At any point in time, participants can choose between pumping the balloon further, or not pumping the balloon and collecting the money they have already earned. 90 trials are conducted and the average number of pumps delivered are used to measure levels of risk-taking (Lejuez et al., 2002).

Rogers Risk Task: The Rogers Risk Task will be administered at session 1 and the last treatment session. In this online task, participants are assigned a certain number of points to begin with and are instructed to make decisions that will increase their total score. They are then presented with tasks that involve gambling their points. For example, they are presented with red and blue boxes and told that one box contains a yellow ticket. If they choose a red box that has a yellow ticket, they will gain 30 points, but if they choose a red box that does not have the yellow ticket, they will lose 30 points. If they choose a blue box that has the yellow ticket, they will gain 70 points, but if they choose a blue box that does not have the yellow ticket, they will lose 70 points. Participants' speed of decision-making and choice are used to measure their willingness to take risks (Rogers, 1999).

Paced Auditory Serial Addition Test (PASAT): The PASAT is a measure of cognitive function that assesses auditory information processing speed and flexibility, as well as calculation ability (Gronwell, 1977). The PASAT is presented using a computer software called Inquisit. Single digits are presented every 3 seconds and the participants must add each new digit to the one immediately prior to it. Shorter inter-stimulus intervals (e.g., 2 seconds or less) have also been used with the PASAT but tend to increase the difficulty of the task. Administration time is approximately 10-15 minutes, including practice sessions. The PASAT has demonstrated high split-half reliability and evidence for convergent and divergent validity (Gronwall & Sampson, 1974).

The Dot Probe Task: Two **dot-probe** tasks (500ms stimulus presentations) will be used to measure attentional bias towards and away from negative stimuli. The **Neutral-Threat (NT) Words** is the first task, which uses general anxiety and depression-related stimuli developed by MacLeod, Mathews, and Tata (1986) using a protocol developed by Bar-Haim and colleagues (2010). The second task is **Neutral-Threat-Happy (NTH) Faces**, a face-based task which displays faces with angry, happy, and neutral expressions from the MacArthur Network Face Stimuli Set. This task uses the protocol devised by Bar-Haim and colleagues (TAU-NIMH ABMT Initiative, 2012).

Emotion Conflict Task (Etkin et al., 2010; Etkin & Schatzberg, 2011): This task measures two aspects of cognitive regulation of emotional processing (conflict detection, inhibitory control) by requiring subjects to identify expression of an emotional face (e.g., happy, fearful) while ignoring an emotion word (e.g., "happy," "fear") superimposed on the face.

Montreal Cognitive Assessment (MoCA): The MoCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal (Nasreddine et al., 2005).

Note: Due to sessions being conducted remotely (including the screening session) as of March 18th, 2020, item one of the Montreal Cognitive Assessment (MoCA) is no longer administered to participants at the screening session. We will score the total score out of 29 instead of 30 to account for the change.

Measures of Study Integrity

Treatment Involvement Form (TIF; adapted from ACAP and LTS study forms): The TIF-TTS edition is a 7-item questionnaire that asks about any changes in medication, treatment, or lifestyle since the last assessment time point. At the beginning of each assessment, with the exception of the Screening Session, the RA administers the TIF to the participant and reviews it after every session. Any changes should be reported to the attending clinician. TIF is designed to assess for whether the participant has sought treatment/services outside of their study therapy sessions. It is used to determine start of treatment and/or change in treatment.

Knowledge of Treatment Form (KNO; as used in Roll et al., 2004): The IEs complete the KNO form before and after the post, 1-month, and 6-month ADIS assessment. The main functionality of the KNO is to determine whether the blind has been broken during the post assessment, or any other time leading up to the assessment. Roll et al. (2004) suggest that study integrity should try to be maintained by having evaluators who are blind to treatment condition to prevent any biases. The current version of the KNO is a 3-item questionnaire that asks the evaluator to guess which condition they believe the participants is in and how confident they are that the participant is in

that condition on a 0 to 8 Likert scale (0=Not at all, 4=Somewhat, 8=Absolutely). The last item asks the evaluator to disclose any information that may have contributed to a potential blind break.

For participants completing the MRI component of the study:
Stroop Task: The Stroop tasks will be shown to subjects using a behavioral experiment software called E-Prime. During the task, neutral words and alcohol-related words will be projected on the screen in different color fonts. Participants will be instructed to press a color button on a button box that corresponds to the color of the font of the word on the screen. There are four colors on the button box, which are red, blue, yellow, and green. The four blocks of stimuli include alcohol-related words (e.g. bar, vodka), color word (e.g. blue, green), and neutral words (e.g. years, minute). There is a practice run of the Stroop task to get participants used to using the button box, which takes about 2 minutes. The Stroop task then follows, which takes about 7 minutes to complete.

Alcohol Cues Task: The Alcohol Cues Task entails the presentation of five sets of images, with both neutral and alcohol-related images. These cues will be shown to subjects using a behavioral experiment software called E-Prime. Subjects will be instructed to look at the images on the screen in the MRI scanner. There are five runs of the task. In the beginning of each run, participant will see "Get Ready" on the screen. There are 22 pictures in each run. In each run, participant will see a fixation cross for a varied amount of time from 6000 milliseconds to 14000 milliseconds followed by the presentation of an alcohol image or a neutral image for 4000 milliseconds. In each run there are 2 images with animals in it. Participants are instructed to press a red button on a button box each time they see an animal that is not a human on the screen. The entire task takes approximately 40 minutes to complete.

Event-Based Reappraisal Task: The Event-Related Reappraisal task involves the presentation of color images selected from the International Affective Picture System (Lang, Greenwald, Bradley, & Hamm, 1993). These images will be shown to subjects using a behavioral experiment software called E-Prime. The duration of the task is 10 to 15 minutes. At the beginning of each trial, instructions to either "LOOK" or "DECREASE" will be presented on the screen, then an image will appear in the center of a black screen. Participants will be instructed to view the image, understand its content, and allow themselves to experience/feel any emotional response it might elicit. On LOOK trials, a photo will be shown and participants will be instructed to attend to and be aware of, without attempting to alter feelings elicited by the image. On DECREASE trials, participants will be instructed to reinterpret the image to alter feelings elicited by the image. Participants will rate the strength of current negative affect by pressing a corresponding button on a button box. After pressing the button corresponding to their rating, the number selected will be highlighted on the screen. At the end of the task, a "thank you for participating"

message will be presented. Participants will then be briefed upon completing the task by a study research assistant. The task takes about 12 minutes.

Therapist Assessments Procedures

The therapist is responsible for completing the Homework Compliance Scale (HCS) after each session. For the Take Control condition, there is never assigned HW, and for certain sessions of the UP there is not assigned HW. In these instances the therapist should still complete the HCS and select "0-Homework was not assigned". In addition to completing the HCS every session the study therapist should complete the Working Alliance Inventory-Short Form-Therapist Version (WAI-SFT) at sessions 4, 8, 12, and 16. The Clinical Global Impression-Improvement and Severity Scales (CGI-I and CGI-S) should be completed in Qualtrics at session 1, 4, 8, 12, and 16 (the IEs will complete the CGI and CGs at post-assessment, 1-month, and 6-month follow-ups). To complete these assessments the therapist should go into the StAR2 Qualtrics folder and select the session number. Within the session folder there is a Therapist Assessment survey battery which includes all the assessments that need to be completed for each session. [redacted]

Documenting Protocol Deviations

There are a number of protocol deviations that may occur during treatment: failing to administer key components of the treatment protocol, engaging in treatment procedures (or providing information) that may overlap with another treatment condition, and conducting treatment sessions that take longer than what is specified in the study protocol. A protocol deviation form should be completed and submitted to the IRB when a deviation occurs. The IRB's response to the deviation, and the deviation submission form, should be saved in [redacted]

When any protocol deviation occurs during treatment, the study staff should note this in the comments/protocol deviation section of the StAR2 Deviation Tracking Log in Google Sheets. If you do not yet have access to this, email the RA and they will grant you access. The RA will then document the deviation and maintain a de-identified note [redacted]

Handling Participant Requests for Booster Sessions or Additional Treatment

In general, participants will be asked not to seek additional treatment (including treatment from study therapists) during the follow-up period. In the event that a participant requests additional treatment, study staff may wish to explain the importance of refraining from additional treatment in the context of the research study's aims. It may also be helpful for participants to think about treatment as more of an ongoing process of working on the developed and learned skills that occurs even after the formal program has ended, as opposed to something which has a definitive end-point.

If a participant is planning on seeking additional treatment, contact the Project Director for additional assistance. Treatment engagement during the follow-up period will be assessed at the 1-month and 6-month follow-up assessment and may ultimately be an additional indication of treatment outcome. With that being said, the study therapist should by no means encourage study participants to seek additional treatment during the follow-up period.

At the final follow-up assessment, participants may request additional treatment. Treatment will not be provided as part of the research study, but appropriate referrals should be made. These requests, and any action taken by the IE (or RA), should also be documented as a clinical note. As the frequency of these requests may be used as a clinical outcome variable, they should be carefully documented for later review.

Managing Issues in Treatment:

Alcohol Use

If the participant's BAC is greater than 0.00% before signing the informed consent, he/she/they will have to reschedule the screening, which can be a few hours later (and BAC will be tested again) or another day. If asked to reschedule, the participant will be asked not to drive home and to make other transportation arrangements. If no one is available to take the participant home and he/she/they do not live in an area with public transportation access, a study staff member may call a taxi or car service.

For all other study sessions, participants with BAC levels greater than 0.02% will be asked to remain at the center until their levels reach below 0.02, or reschedule if necessary. Again, if a participant is under the influence and is asked to reschedule the appointment, the participant will be asked not to drive home and to make other transportation arrangements.

Note: Due to sessions being conducted remotely, a session is simply cancelled and/or rescheduled if BAC levels are above threshold.

Noncompliance

The following link describes IRB procedures regarding noncompliance:
https://www.bu.edu/researchsupport/forms-policies/noncompliance-in-human-subjects-research/

Management of Life Crises:

Determine Severity of Crisis

Major Life Crises include: death of a spouse, child, or parent; major illness or accident to spouse or child. Minor Life Crises include: car accident with physical injury, sudden impending divorce, loss of job, etc.

Major Life Crises:

If the study staff member defines the crisis as major, one full session can be devoted to a discussion of this event and its impact. The study staff member should then schedule a make-up session within one week to cover the material missed due to the crisis (Note: This would most

likely extend the length of the study by one week and is tantamount to the participant cancelling a study session). If the participant continues to need help in dealing with this crisis, a second session may be used. However, the participant must then be withdrawn from the study and given alternative treatment and/or an outside referral.

Minor Life Crises:

If the therapist defines the crisis as minor, then it does not warrant one full session of discussion. The study staff may spend approximately 15 minutes discussing the event with the participant and then should redirect the participant back to protocol material by acknowledging that such an event is likely to increase feelings of anxiety and probably would occur in anyone experiencing such an event, asking how this event affected the participant and his/her/their anxiety and/or panic, and asking how his/her/their reaction to the crisis can be discussed in the context of treatment.

If the event is not one in which the participant can be easily refocused, or requires more than 10-20 minutes of session time, the therapist should end the session after a brief discussion of the event, and schedule another full session (within a week) to cover the missed UP or TC treatment material.

NOTE: A life crisis and postponement of treatment can only occur once during treatment. If a second crisis emerges that requires postponement of treatment, it can still be addressed during the session. However, these participants will then be removed from study treatment and given alternative treatment or an outside referral.

Removal from Protocol Due to a Life Crisis

As noted above, this might occur if: 1) the participant needs additional support in dealing with the crisis, or 2) A second major crisis occurs during the course of treatment.

NOTE: A question may emerge regarding the severity of a stressor not listed above, or whether to remove a participant from the study. In these cases, the therapist should consult first with the project director. If there is any disagreement between the therapist and project director, the case may be discussed with the PI, who will make the final decision.

Premature Study Termination

Every effort will be made to keep participants in the study. Participants who drop out of or are withdrawn from the trial will be included in the data analysis as described in the Data Analysis Section of the grant. Participants who choose to end treatment prematurely will be followed for the remainder of the trial if they can still reach the post treatment session (session 12 for TC or 16 for UP) within 16 or 21 weeks from the session 1 date, respectively.

The RA should attempt to collect all self-report measures and clinician administered assessments conducted at the major time-points (4, 8, 12, 16, 1-month, and 6-month follow-up) in the event of a drop-out or withdrawal (if the participant is willing and able to continue in this

manner). Self-reports can be emailed to the participants, and the clinician-administered assessments can be conducted over the phone in order to provide flexibility to the participant if unwilling to come in. All of these sessions should be scheduled on the basis of when the last attended treatment session occurred. The payment schedule will resume, with checks issued on session 8, post, and both follow-ups.

RAs can attempt to call participants three times within two weeks after the last communication. If the participant does not call back after all three attempts, or answers/calls back but declines to continue in any capacity, study staff will make no further attempts to contact.

Participants who are withdrawn from the study by the study staff will be offered alternative care or will be assisted to find other providers upon request. It is not necessary to offer alternative treatment to participants who choose to discontinue. Every effort will be made to record reasons for study dropout or withdrawal in the Treatment Termination Form, and the Attrition tab of the Retention Database.

When to Withdraw Participants from the Study

There are two primary reasons participants are likely to be withdrawn from StAR2: 1) clinical deterioration or life crises and emergencies, and/or 2) noncompliance with study requirements and procedures.

Removal of participants from the research study should only occur in rare instances. In most cases, participants who are dropped or withdrawn from study treatment will be asked to complete a posttreatment assessment and will then be followed for the remainder of the follow-up period (beginning from the date of the posttreatment assessment). In those rare instances when a participant is completely withdrawn from the study (upon their request or at the discretion of study personnel), the project director will complete a note detailing specific reasons the participant will not continue in the trial.

Clinical Deterioration or Emergencies

In some instances, participants may need to be withdrawn from the study if they suffer clinical deterioration that warrants referral to a higher level of care or if they experience life crises (as noted above), and/or medical or psychiatric emergencies that prevent adherence to study procedures and/or make further participation in the study ill-advised.

Change in Diagnosis

Diagnostic Changes that Occur Prior to the Onset of the Study:

The diagnostic assessment (ADIS) may be administered up to one month prior to consent and treatment randomization. Participants who no longer meet the study's inclusion criteria at this pretreatment assessment will be excluded and will not be randomized to treatment.

Diagnostic Changes that Occur During the Study:

If a participant appears to have a change in diagnostic status during the study, she/he/they will not be withdrawn from study treatment. These participants will remain in the study throughout the acute treatment phase and the follow-up phase (except in cases of severe clinical deterioration) or if they drop out themselves.

Procedures for Handling Treatment Termination

Drop-Outs

If it becomes apparent that a participant is dropping out of the study, the therapist and/or RA should attempt to contact the participant by telephone to gather more information about the participant's concerns/reasons for considering dropout. Sufficient information should be gathered to complete the Termination Form [redacted] If the participant is planning on dropping out of the study, study staff can ask the participant if he/she/they is/are willing to come to the clinic for major assessment time point assessments (without completing any additional treatment sessions) at 4, 8, and 12 weeks for UP and 4 and 8 weeks for TC, and a final assessment with the IE (post-treatment). If the participant declines further assessments in person, study staff may offer telephone assessments.

NOTE: The Termination Form should be completed by the study staff member who contacts the participant. RAs please be sure to remind study therapists to document accordingly.

Treatment Termination Due to Clinical Deterioration

In these cases, the level of deterioration should be of a level such that the therapist and/or medical personnel are nearly certain that an IE will concur that withdrawal from the study is warranted. Inform the participant of the need to be evaluated by the IE. Inform the Project Director and the RA. The RA will inform the IE and schedule an appointment for the evaluation. The IE will administer the ADIS assessment. The results of this evaluation will be discussed with the Project Director and/or PI, who will then make a decision regarding removal of the participant from the study. The Project Director will inform the therapist of the final decision. The Project Director or the therapist will then inform the participant of the decision and provide appropriate referrals. These procedures should be conducted within 24-48 hours of knowledge of clinical deterioration.

Termination Due to Psychiatric Emergency

Examples of psychiatric emergencies include: suicidality and traumatic events (e.g., sexual assault, crime victimization). In these instances, the therapist has sole clinical responsibility for making decisions about the participants' status and should discuss concerns with the project director. An IE evaluation, involving the ADIS, SIGH-A, and SIGH-D, is always preferable before termination; however, if this clearly would not be in the participant's best interest, an IE evaluation is not required. Regardless, the Project Director should be notified, and the Termination Form completed by either the therapist or IE (whoever has the most complete information).

Termination Due to Medical Emergency

Examples of medical emergencies include: acute illness, appendicitis, hospitalization for a medical condition or accident. In these instances, a termination evaluation involving the ADIS, SIGH-A and SIGH-D, should be conducted by an IE, if possible, and can be done via telephone. The Project Director should be notified and a Termination Form completed.

Study Protocol: Data Collection & Storage

Data Collection

Qualtrics

The current study utilizes the Qualtrics Research Suite for online data collection, as developed and distributed by Qualtrics Labs Inc. (www.qualtrics.com). This data collection program is used by over four hundred colleges and universities around the world, and procedures for maintaining the security of research data are well established. The Qualtrics Research Suite is specifically designed to meet and exceed industry standards for Internet security as well as IRB standards for the protection of research participants. Their servers, database, and web presence employ multiple forms of enterprise-level security features to accomplish these goals. Qualtrics Labs Inc. has SAS 70 certification and meets the privacy standards imposed on health care records by the Health Insurance Portability and Accountability Act (HIPAA).

No identifying information will be collected using the Qualtrics Research Suite online data collection software. Research participants will access the online questionnaires using an assigned ID number, which will be assigned when the participant has been approved by the PD for enrollment. As with traditional paper-and-pencil assessments, these online research data will not be directly linked to data containing individual identifiers, which are sorted in a separate location. Also, as IP addresses represent a form of potentially indirect identifying information about a participant, these will be excluded from data collection.

Raw data will be exported from Qualtrics into SPSS databases for analyses. The data will be collected when the participant completes the online surveys designated by a specific link that will be e-mailed to the participant by the RA from the study-specific Gmail account. Once the participant completes the surveys, the data is automatically saved to the designated Qualtrics account, and ready to be exported. [redacted]

After each session, the RA running a given participant will go back to Qualtrics to make sure the data for that session were properly recorded. If the data was not properly recorded or the participant left the session early before completing all of the self-reports, the RA should email the link to the self-report battery to the participant and ask them to complete them as soon as possible.

Inquisit

Inquisit 5 Lab is a tool for designing and administering psychological tests and experiments on dedicated computers, provided by Millisecond. There are four neurocognitive tests used in this trial: Balloon Analogue Risk Task (BART; Lejuez et al., 2002), Continuous Performance Test (CPT; Rosvold et al., 1956), Go/No-Go Task (Fillmore et al., 2006), Millisecond Gambling Task (Rogers et al., 1999). No identifying information will be collected using the Inquisit lab software. The Inquisit Lab is installed [redacted] at CARD. There is a shortcut named "Bart_CPT_Go_Rogers.iqx" on the desktop. When administering the test, open the shortcut, enter participant ID (and group number), and the four tests will run in a row. The data manager RA should be responsible for uploading the output data to the shared drive [redacted] in corresponding tasks folders before 5 pm of the following work day, and should also ensure the data is complete.

E-Prime

E-Prime is a behavioral experiment software, provided by Psychology Software Tools. There are two emotion regulation tasks based on E-prime used in this trial: the Dot Probe Task (face and word version; TAU-NIMH ABMT Initiative, 2012) and the Emotion Conflict Task (practice and actual task; Etkin et al., 2010; Etkin & Schatzberg, 2011). No identifying information will be collected using the Inquisit lab software. E-prime is installed [redacted] When administering the test, open the shortcuts, enter participant ID and session number, and administer the task. The RA who is administering the task should sit with the participant during the emotion conflict tasks (practice and actual task), read the instructions to him/her/them, and make sure he/she/they understand the task. For the dot probe tasks, the RA can leave the room after entering the participant ID and session number. The data manager RA should be responsible for uploading the output data [redacted] in corresponding task folders before 5 pm of the following work day, and should ensure the data is complete.

Note: Due to sessions being conducted remotely as of March 18th, 2020, participants are no longer administered the neuropsychological battery at their session one or post-assessment.

Study Databases

Multiple databases have been created for data management. [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Data Management

[redacted] For the hand-entered data, one RA will enter the data, a second RA will check every entry, and a third RA will randomly check 30% of the data entered. Research volunteers supervised by RAs may also help enter and check data. Should the RAs have *specific* concerns about data integrity, they should immediately alert Dr. Eustis for consultation. If necessary, the Project Director will be contacted to discuss appropriate actions. Should any more *general* abnormalities arise, the RAs are responsible for bringing such issues to the group in the weekly lab meeting. Any necessary changes to data will be saved [redacted] Upon completion of the trial, such changes will be incorporated into the SPSS final database.

Data Storage

[redacted]

Data Reporting

The Data Manager, [redacted], is responsible for updating the group once a month at the Monday lab meeting. These updates will be provided [redacted] Data reports will reflect all surveys completed before the prior business day.

Quality Control

Maintaining Confidentiality

Maintaining confidentiality of study participants is the responsibility of all members of the research team and should be observed in accordance with the APA guidelines on Ethical Principles of Psychologists and Code of Conduct. Standards for maintaining privacy and confidentiality can be found here: http://www.apa.org/ethics/code/index.aspx

A number of specific procedures have been developed for this study to help maintain confidentiality:

1) All data entered into the data pool are strictly confidential and should not contain any identifying information.
2) Computerized research data (including digital audio recordings) are stored [redacted] The PI, study therapists, RAs, and volunteers working on data entering and checking have access to it. The data manager RA is in correspondence with BU CAS IT to give additional access and/or remove non-active users whenever changes in that nature need to be made.
3) Data from participants who complete, drop, or withdraw from the study will be saved in the shared drive [redacted]
4) Only key study personnel (i.e., the PIs and trained study staff) will have access to research data.
5) A link between the participant's ID number and name will be kept in a separate locked folder in the shared drive, and can be accessed by RAs and Dr. Farchione: [redacted]
6) No identifying information will be revealed in the presentation or publication of any results from the project.
7) All data will be destroyed seven years following the conclusion of the study. Audio recordings will be erased within one year after study completion.

Certificate of Confidentiality (CoC)

For this study, a Certificate of Confidentiality from the National Institutes of Health has been obtained. With this Certificate, the researchers cannot be forced to disclose information that

may identify the participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the participants. The Certificate of Confidentiality does not prevent the researchers, however, from disclosing voluntarily, without the individual's consent, information that would identify them as a participant in the research project under the circumstances described below, in the limits of confidentiality section.

A CoC does not prevent the participants or a member of their family from voluntarily releasing information about themselves or their involvement in the research study. If an insurer, employer, or other person obtains the participant's written consent to receive research information, then research personnel may not use the Certificate to withhold that information. Additional information of CoCs can be found at: http://grants.nih.gov/grants/policy/coc/.

Limits of Confidentiality

Massachusetts law requires that confidentiality be broken by any of the study staff if they learn in the interview or during the course of treatment of likely current abuse of children, elders, or disabled individuals. Further, if the participant tells anyone associated with the study information that leads him/her/them to believe that the participant might be at risk for hurting themselves or others, members of the study staff are obligated to break confidentiality and take action to prevent harm. Also, because this research is sponsored by NIAAA, and monitored by the Institutional Review Board for Human Subject Research of the Boston University Charles River Campus, staff from these agencies may review records that identify the participants for audit or program evaluation. They, too, will protect the participant's privacy.

Institutional Review Board (IRB): Charles River Campus

To ensure the integrity of the current study and protect all involved in participation, The Charles River Campus Institutional Review Board (CRC IRB) must approve all aspects of recruitment, assess any potential risks and benefits of undergoing treatment, and ensure that study procedures are carried out properly. The CRC IRB follows federal regulations that govern research on human subjects.

The CRC IRB is part of a shared IRB system that also includes the BU Medical Campus and Boston Medical Center. Three boards serve on the Medical Campus and one serves on the CRC. The CRC IRB typically meets every third Tuesday of each month. The board reports to the "Institutional Official," currently Mellouk, Kathryn M.; Assoc VP, Research Compliance. For more information, visit: http://www.bu.edu/researchsupport/.

The Charles River Campus IRB is located on Boston University's main campus at One Silber Way, 8th floor, Boston, MA, 02215. The office phone number is: 617-353-2595. *Contact person*: Please contact Shayne C. Deal with any questions at 617-358-6116 or sdeal101@bu.edu (This is accurate information as of July 2018 but may be subject to change over the duration of the study).

BU/BMC IRB Policies on Human Subjects

Boston University is committed to conducting human subjects research following the ethical principles as outlined in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. The basic ethical principles are: respect for persons, beneficence, and justice. All individuals (IRB, investigators, students, and staff) involved in conducting human subjects research must adhere to these principles.

The CRC IRB is established in compliance with regulations of the Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), as well as other applicable federal regulations, and state and local laws. This includes the following; this list is not all inclusive and may change depending on current funding sources:

1. Office for Human Subjects Research (OHRP)
2. Food and Drug Administration (FDA)
3. Department of Defense (DOD)
4. Department of Education (DOE)
5. State and local laws

Human subjects research being conducted by members (faculty, students, or employees) of Boston University's Charles River Campus must be reviewed and approved by the CRC IRB. The CRC IRB adheres to the DHHS and FDA definitions when determining if research activities are human subjects research.

The CRC IRB has the authority to approve, require modifications to secure approval, and to disapprove research activities being conducted by members of Boston University's Charles River Campus. Officials of Boston University cannot approve research that has not been approved by the CRC IRB.

The CRC IRB does not have oversight over research conducted by members when they are acting independently of their official BU roles and responsibilities. This research will be determined to be independent of their official roles and responsibilities and not subject to IRB review if:

1. The research is conducted on their own time and not reimbursed by Boston University or through Boston University accounts,
2. The research is conducted without the use of Boston University space, materials, supplies, or staff support,
3. Any research publications, reports, or presentations will not list the member's position and affiliation with Boston University.

Investigators are responsible for determining if research projects involve human subjects and therefore require review by the CRC IRB. If an investigator is unsure if a project is human subjects research, he/she/they should contact the IRB for consultation. The IRB Director or IRB

Analysts have the authority to make the determination of whether a research project meets the definition of human subjects' research. Investigators who would like a written determination about whether the project is human subjects research can contact the IRB office with this request. More information about the IRB policies can be found at: https://www.bu.edu/researchsupport/forms-policies/research-involving-human-subjects/

IRB Binder

A binder containing IRB materials for the StAR2, including the tracking of upcoming deadlines and all correspondence between the StAR2 research lab and the Charles River Campus IRB (CRC IRB) is located in [redacted]. Materials are organized chronologically by relevant section. The RAs are responsible for maintaining the IRB binder. The binder contains the following sections:

IRB Correspondence List

At the front of the binder is a list that tracks upcoming IRB deadlines and correspondences. Whenever the PI receives an IRB notice regarding any aspect of the project, the letter is filed by the RA in the appropriate section and the list is updated to reflect when the correspondence occurred, what section of the binder it is in, and who filed it. *For each section of the binder, any IRB correspondence is placed before all other materials.* For example, the IRB approval letter would be filed in front of the initial submission materials (i.e., the application, consent form, etc.) in the *Initial Submissions* section of the binder by the RA, who would then write the date of the letter and his/her/their initials in the appropriate columns on the list. [redacted] This should also be updated whenever the hard copy is updated.

If the letter includes a project deadline, then the date of the correspondence is highlighted on the list to indicate importance. The correspondence list is used for documenting submission of study renewal, amendments, deviations, and unanticipated problems and the IRB's response to these submissions. It is crucial to highlight the initial and yearly submission dates and to note expected re-submission dates on the list, as it acts as a quick reference for important deadlines. For example, renewal applications should be submitted at least *eight weeks prior to expiration*; including this date on the checklist is important. Please see the following sections for further directions.

Initial Submission

Following the deadlines list is the initial submission of the UP study to the IRB. This is a research application that provides the IRB with the contact information of UP project investigators, managers, and other assistants, a background for the study, and a detailed outline of the project and its procedures.

The initial submission approval was made on September 13, 2017. At the beginning of the initial submission section of the IRB binder is the IRB's response to the initial submission. It contains approval of the study. The list at the front of the binder is updated to reflect submission

and the date of IRB approval. The date of approval must be highlighted on the list in order for the study renewal submission to occur on time.

Annual Renewals

Each year, approval of the research study must be renewed. The renewal application is reviewed by the IRB, which then approves the application for continuation. Requirements for continuing review are provided to the PI in the IRB approval letter. The PI is responsible for submitting a Progress Report and updated Informed Consent Form(s) (when applicable) to the IRB for review and approval prior to expiration of the study. Many research protocols only require annual review but some research projects (e.g., those with higher risks or at the request of the DSMB) may require more frequent review. The required frequency of review is determined by the IRB and is specified in the IRB approval letter.

The Progress Report contains the following information: the complete and approved IRB protocol, protocol status (pending/no accrual, active, closed to accrual, completed, open for data analysis, open for long-term follow-up only), accrual information, accrual categories, reports of unanticipated problems and adverse events, subject complaints, amendment information, protocol exceptions, protocol deviations, protocol findings, and any presentations or publications of study findings. In addition, any information concerning the state of knowledge about the study question (particularly other information that might change the assessment of clinical equipoise or the risk: benefit assessment) is presented as part of the progress report. **A Progress Report form is sent to the IRB *eight weeks* prior to study renewal**. Failure of the PI to receive the renewal notice does not excuse the PI from his/her/their responsibility for submitting Progress Reports on time. Any protocol modifications (not included in amendments made during the study) are listed here to be reviewed. Copies of the submitted Progress Report and the IRB's response are kept in the Annual Renewal section of the binder and on the shared drive. The correspondence list is updated to reflect communication between the study and the IRB.

Based on the information provided in the Progress Report and as allowed by the regulatory guidance, the staff in the IRB office determines whether the progress report can be reviewed by a board member who is a designated expediter or whether it must be reviewed by a convened IRB panel. Progress Reports submitted for continuing review may be expedited when the research is:

1. Approved by expedited review (as an expedited study) on initial approval and no changes in risks have occurred
2. Approved by convened IRB but the research is now closed to enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects
3. Approved by convened IRB but no subjects have been enrolled and no additional risks have been identified
4. Approved by convened IRB but now the remaining research activities are limited to data analysis

The continuation of research after expiration of IRB approval is a violation of the federal regulations. If the IRB has not received and approved continuation of a research study by the study's current expiration date, all study related activities must cease (including recruitment, enrollment, study interventions, long-term follow-up, and data analysis) unless the IRB has decided that it is in the best interest of the subject(s) to continue.

The Annual Renewal section of the binder is broken down into yearly sections. As with all IRB correspondences, the IRB response to the annual renewal (included requested modifications) is placed in front of the initial renewal application. Yearly correspondences with the IRB are noted on the list and dates of re-approval are highlighted as a reminder for the next year's renewal.

Amendments

After the initial IRB application is approved by the IRB, changes to the research protocol require a submission of an amendment to the IRB stating the intended changes. These proposed changes must be approved by the IRB *before* they can be implemented. A copy of the amendment is placed under the Amendments section in the binder. The IRB's approval of the changes to protocol should be kept at the front of this section. As with initial submission and approval, the dates of submission and approval should be noted on the list at the front of the binder. The Amendment Request form can be found at this link: https://www.bu.edu/researchsupport/formsandpolicies/form-library/.

Once the changes have been approved, the PI must initiate the amendment(s) and update the consent forms to reflect a change in protocol (i.e., replace the outdated consent with the new IRB approved form). Until approval has been received, all procedures must be done according to the initial application unless subjects are at risk for harm. For subjects whose participation began prior to protocol modification, re-consent is not necessary unless the nature of the study has changed. For instance, a change in scheduling does *not* require that subjects who consented prior to this change be notified.

The addition of new personnel to the study requires IRB notification, as it is considered an amendment. A letter must be sent to irb@bu.edu explaining the role of the individual and reasons for the addition. Also, new personnel must complete the Human Subjects Protection Training, which can be found at *http://www.bu.edu/irb/crc-irb-forms/.* Certification of completion is sent to irb@bu.edu. A BU Conflict of Interest form, also found at the above site, must be given to the individual and returned to the IRB.

The determination as to whether expedited review or full board review is required is based on how the change affects the risk level of the study. Amendments to full board protocols are reviewed by the full board unless the amendment reflects only minor or administrative changes. When full board amendments are reviewed, the findings are documented in IRB minutes. The IRB's decision regarding the amendment is provided to the PI. The IRB may conduct an audit of any research protocol if there is reason to suspect changes have been made to the protocol prior to or without the approval of the IRB.

Protocol Deviations

Protocol deviations represent incidents, circumstances, or processes that occur during the research protocol that are not part of or are inconsistent with the approved IRB protocol, with the policies and procedures outlined in this manual, or with the Federal regulations. For example, if a participant does not fill out a consent form prior to participation in the study, protocol has been violated. Investigators are required to follow the IRB approved protocol. Once the PI or any member of the study team identifies an instance where the approved protocol has been seriously altered this must be promptly reported to the CRC IRB within 5 days. Minor changes, such as study visits/procedures that are either omitted, conducted outside of the visit window, or in a different order than specified in the protocol that do NOT affect or have the potential to affect subject safety or data integrity, should be submitted within 20 working days of the incident. A Deviation Report form must be submitted to the CRC IRB for review. The submitted form and the IRB's response is kept in the Protocol Deviations Submissions folder in Dropbox [redacted]

Protocol deviations are reviewed by a member of the IRB staff. PIs are required to provide the IRB with CAPs (corrective action plans) for all deviations which explain how the PI will prevent the deviation from recurring. The IRB may approve, request modifications to, or disapprove CAPs. Frequent or serious protocol deviations can cause the IRB to institute an audit of a research protocol and referral to the appropriate institutional research oversight committee. A listing of all protocol deviations is available to the board at the end of each annual progress report. The board uses the information in the protocol deviations report and the Corrective Action Plan (CAP) in making its determination as to whether continuation of the research is appropriate.

Unanticipated Problems and Adverse Events.

The CRC IRB requires that any unanticipated problem be reported using the Adverse Events found on the shared drive. The following information defines what unanticipated problems are and explains how to manage them:

Upon submitting an Adverse Events form to the CRC IRB and receiving a response letter, an update to the binder list stating the date of the correspondence should be [redacted] the RA. Copies of the submitted form and the response letter are also kept [redacted]

Reporting Unanticipated Problems to the IRB

Effective immediately, BU/BMC investigators will no longer individually report all SAEs to the IRB. Instead, only those events that meet **all three** of the following criteria: 1) is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents (such as the IRB-approved research protocol and informed consent

document), and (b) the characteristics of the subject population being studied; AND 2) is related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND 3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, OR are by definition SERIOUS (Note: all incidents, experiences, or outcomes that are unexpected AND related or possibly related AND are SERIOUS are automatically unanticipated problems). Based on the above definition, many (if not most) AEs and SAEs that are currently reported to IRBs are NOT by definition *unanticipated problems* and, therefore, do NOT--according to the regulations--have to be reported to the IRB.

The "Unanticipated Problems and Summary of Events Report" (UPSER) should be used to report all events that meet the definition of *unanticipated problems* to the IRB. The UPSER may be submitted by any member of the study staff at any time, even when an amendment or progress report is pending. These *unanticipated problems,* whether they are internal or external, must be reported to the IRB **within two business days** of the investigators learning of the event. Internal events are those experienced by subjects enrolled by BU/BMC investigators no matter where the "event" occurs. For single site studies, all events are internal events. Only those internal events that meet the definition of *unanticipated problems* need to be individually reported to the BU/BMC IRB.

External events are those that occur to subjects enrolled at other (non-BU/BMC) sites. Investigators in multi-center trials receive SAE reports of all external SAEs from all sites. These external SAEs no longer have to be routinely reported to the BU/BMC IRB on individual SAE reports. Instead, external SAEs will ideally be reviewed by a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, a DSMB/DMC, an AE monitoring committee) or the investigators, in accordance with a monitoring plan described in the IRB-approved protocol. These entities should make the determination as to whether the SAE represents an *unanticipated problem*. Instances when external SAEs are determined to be *unanticipated problems* should be rare; when they occur, they must be submitted to the IRB. The submission must include an explanation from the investigator or sponsor as to why the event is considered an *unanticipated problem*, and a description of the proposed protocol changes or other corrective actions to be taken [Note: Problems that are unexpected, related, or possibly related and represent a greater risk to subjects will almost always require modification to the protocol and consent].

Managing IRB Content

The RAs are primarily responsible for managing content related to the IRB and for informing the study team of submission/revision deadlines. The RAs will construct necessary IRB documents and provide them to Drs. Farchione or Eustis for review before submission. Copies of all IRB correspondence sent or received to the PD or PI should be given to the RA so

these documents can be filed in the IRB folder [redacted]

The IRB [redacted] consists of a folder for each amendment submission, an Adverse Events folder, Approved Documents folder, Protocol Deviation Submissions folder, and Continuing Review folder. Each Amendment folder is titled with the date it was submitted, the amendment number, and the approval status (i.e., submitted, approved, rejected, in-progress). In each amendment folder, is the Amendment form, the approval letter/IRB response letter, and the submission materials.

Adverse event management and report

Definitions

OHRP guidance on unanticipated problems and adverse events:
https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/advevntguid.pdf

Guidelines and FAQs: http://www.bu.edu/researchsupport/compliance/human-subjects/

Adverse Event (AE)

AE is defined at this institution as, "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research."

Serious Adverse Event (SAE)

SAE is defined at this institution as, any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in in participant's hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization).

Unexpected Adverse Event

Definition: Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either: 1) the known or foreseeable risk of adverse events associated with the procedures involved in the

research that are described in (a) the protocol related documents, such as the IRB approved protocol, any applicable investigator brochure, and the current IRB approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts, or 2) the expected natural progression of any underling disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Adverse event tracking

All Adverse events submissions and IRB responses to the submission should be saved in the BU Dropbox folder: Dropbox (BOSTON UNIVERSITY)/UP-AUD/IRB/Adverse Events. When adverse events come up throughout the course of the study they should be logged in The Adverse Event Tracking Log in Google Sheets. Here is the link: https://docs.google.com/spreadsheets/d/1CdxXESTvWHNcWOqDNgfScTMzdvnbhdAo6aKv729VK-o/edit#gid=0
This link is shared with the bostonstar2study@gmail.com account.

Data and Safety Monitoring Plan

The following procedures will be followed in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study a DSMB will be used.

Data and Safety Monitoring Board (DSMB)

Functions of the DSMB

A Data Safety Monitoring Board (DSMB) will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these 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 and will monitor enrollment to ensure that the study conclusion is not delayed.

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 mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues.

Members: Drs. Todd Farchione (Project Director), Barbara Kamholz (DSMB Chair), John Otis, and Kristen Ellard

Barbara Kamholz, PhD, ABPP, DSMB Chair
Kamholz Clinical Psychology Services LLC
[redacted]

John Otis, PhD, DSMB Member
Assistant Professor
Department of Psychiatry
Boston University
National Center for PTSD
Boston VA Medical Center
[redacted]

Kristen Ellard, PhD, DSMB Member
Department of Psychiatry
Massachusetts General Hospital
[redacted]

Functional Organization of the DSMB

The Chairperson of the DSMB will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. 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.
2. 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 treatment groups. This includes treatment retention rates and reasons for dropout.

3. 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, an event requiring or prolonging hospitalization, or any congenital anomaly. Included is any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE, including information about the event and its outcome, and the subject's medical history and current conditions. If the SAE is considered an unanticipated problem (for more information see the above section on Unanticipated Problems) then reporting to local IRBs will be completed within 2 business days of the unanticipated problem. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study, as indicated by the grant and in accordance with the CRC IRB, 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.
5. 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.
6. 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.

Monitoring of Data Quality by the DSMB

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. These reports are prepared by the Data Manager, in collaboration with other members of the research team, and at a minimum, will include an overview of the progress of participant intake and retention; summary reports describing participant compliance with treatment visits and study evaluations, as described in the protocol, and a summary of the completeness and quality of key data elements needed to characterize participants, and primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Data Safety Monitoring Plan

Because all BU CILSE procedures are nonsignificant risk in nature, the co-investigator at BU CILSE will execute a Data Safety Monitoring Plan (DSMP) covering BU CILSE procedures.

This DSMP includes monitoring and regular reporting of accumulated study data to Drs. Barlow and Farchione. DSMP procedures covering subject safety will be executed if necessary to protect the safety of human subjects. Subject safety and adverse events will be monitored and assessed by study staff during each study visit. If any adverse events should occur, the subject can withdraw voluntarily or, if a contraindication to fMRI scans or other disqualification from study eligibility becomes apparent, at the discretion of the BU CILSE co-investigator.

Adverse events related to BU CILSE study procedures will be reported to Dr. Barlow. Serious adverse events, non-serious unexpected adverse events that are related or possibly related to the study, and unanticipated problems involving subjects or others will be reported to Dr. Barlow as soon as possible and within 5 working days/7 calendar days. Within 10 working days of this notification, a full written report regarding events will be submitted to Dr. Barlow. Events that do not fall into the above categories will be reported to Dr. Barlow in summary format for inclusion into the annual IRB continuing review report.

Annual DSMB Report to NIAAA

Annually during the course of the study, the DSMB will prepare a summary report of its findings regarding safety and quality based on data received. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve participant safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report. The report will be stored in the DSMB folder in the StAR2 Dropbox folder.

Study Materials

Audio Recorders

Model: Sony ICDPX370 Mono Digital Voice Recorder with Built-in USB, black

For the current trial, multiple audio recorders will be obtained for certification, adherence, and training purposes. There are a total of 6 audio recorders currently assigned to assessors, therapists, and RAs [redacted] Each person is responsible for maintaining and keeping track of the recorder at all times throughout the study. Each person must store the recorder in a safe, locked area when not in use (if participant recordings are still being stored on it). However, study staff should always attempt to upload the audio recordings to the recordings folder of the StAR2 shared drive directly after every session and clear the original audio file from the recorder. If a recorder is lost before the uploading process, the PI must be notified immediately.

Recordings of the clinical interview portion of the in-clinic screening session (ADIS, SIGH-A, and SIGH-D) will be digitally recorded to ensure adherence to the screening protocol

and inter-rater reliability for the administration of the clinical assessments. In addition, digital recordings will be collected during the RA administered assessments (TLFB, MoCA) and health assessments with Bonnie Brown (study nurse), occurring throughout treatment.

The digital recordings will be stored [redacted] The digital recordings will be destroyed along with the other study data, after 7 years following the end of the study.

Study Computer

The study computer will be used throughout the study for questionnaires on Qualtrics. [redacted] If the computer is occupied, the RAs may use the study laptop or check out a room with a computer in Titanium to administer the Qualtrics surveys.

Accounts & Server Access

BU Server (Active Directory Shared Drive)

Each study member has access to the shared drive through their own Kerberos Active Directory log in information. See below for instructions on how to log into the Shared Drive. [redacted]

In the StAR2 study, audio files of treatment recordings will be shared with expert raters for therapist certification and adherence purposes. Immediate and secure access to the audio files is required. The BU shared drive server is utilized to share the audio files with the experts with access to the folders. Each therapist will only have access to their personal recording folder. Dr. Farchione is the expert rater and will have access to all the recording folders. According to the BU shared drive security overview, everything saved to the server is encrypted upon transmission and storage allowing only the permitted parties involved to access to the files. While the audio files will not contain any identifying information, maintaining recording folders on the shared drive ensures that employees have access only to file names and locations, not file content. Given the number of files that the experts will listen to, the BU shared drive offers a safe and efficient means for sharing the audio files.

How to Access the Shared Drive

Access on CARD network computers:

[redacted]

[redacted]

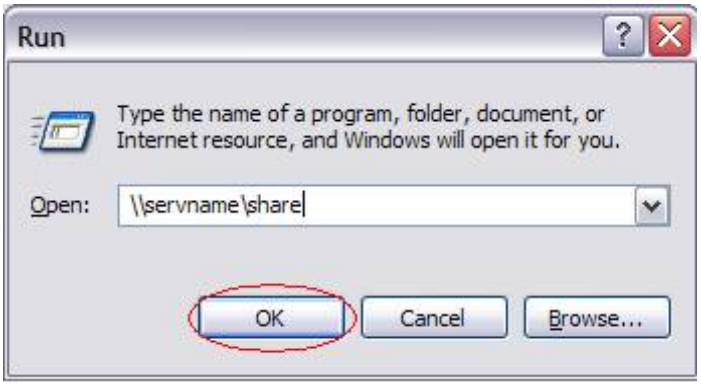
Access by Internet:

[redacted]

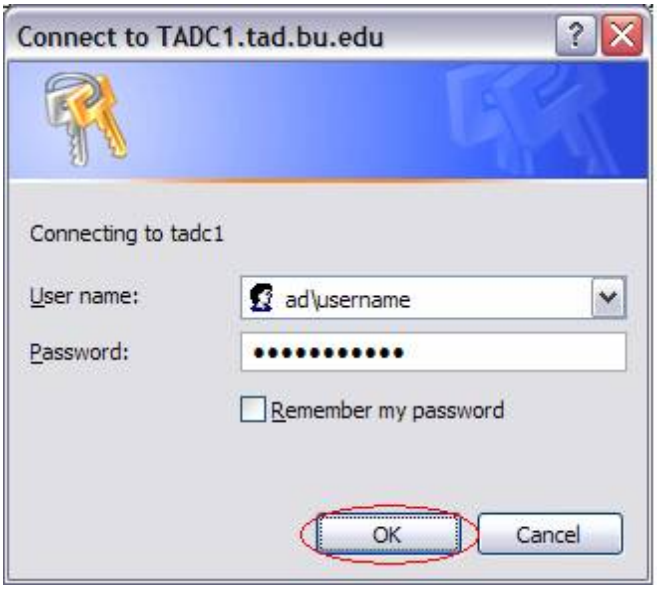
Access on Personal Computers:

[redacted]

3. [redacted]



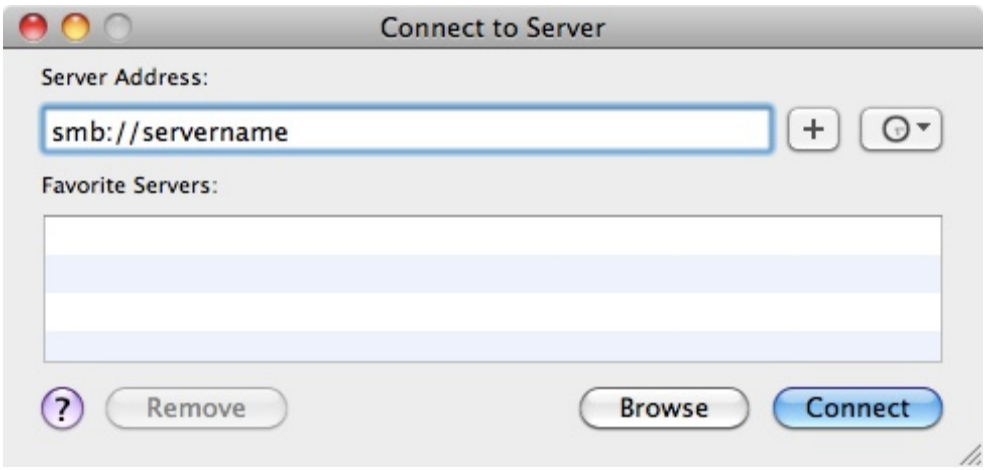
4. [redacted]



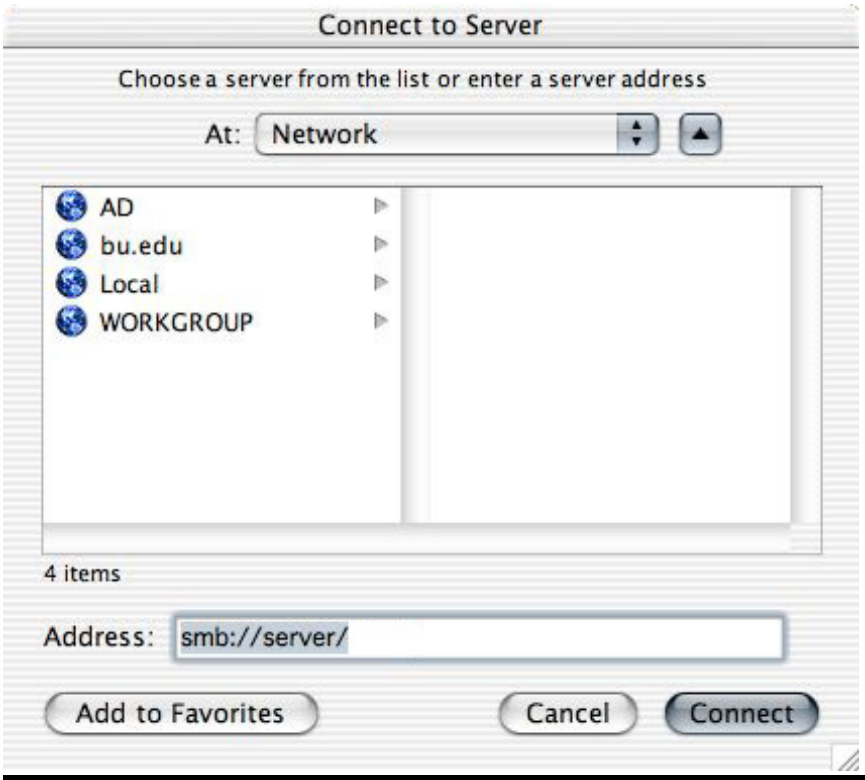
Connecting to Active Directory Resources Using Mac OS X

[redacted]

In OS X 10.5 or later:

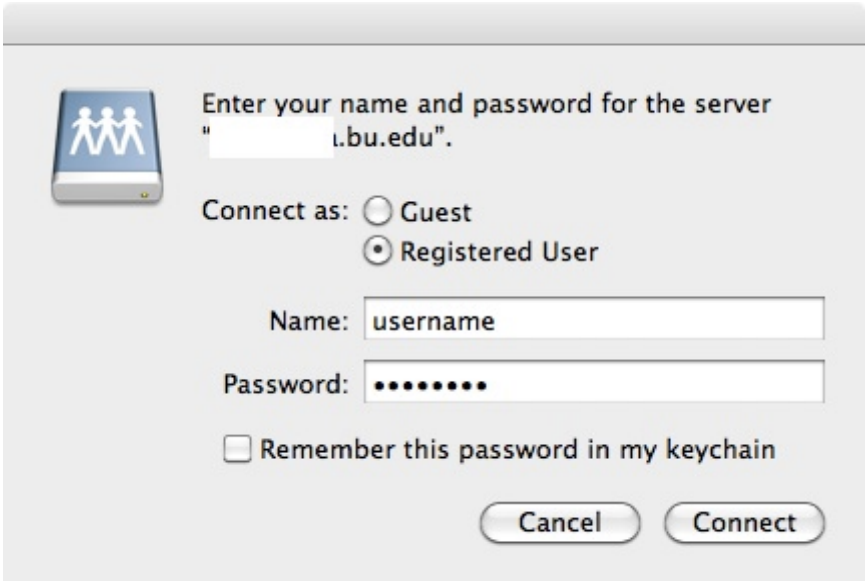


Earlier versions of OS X:

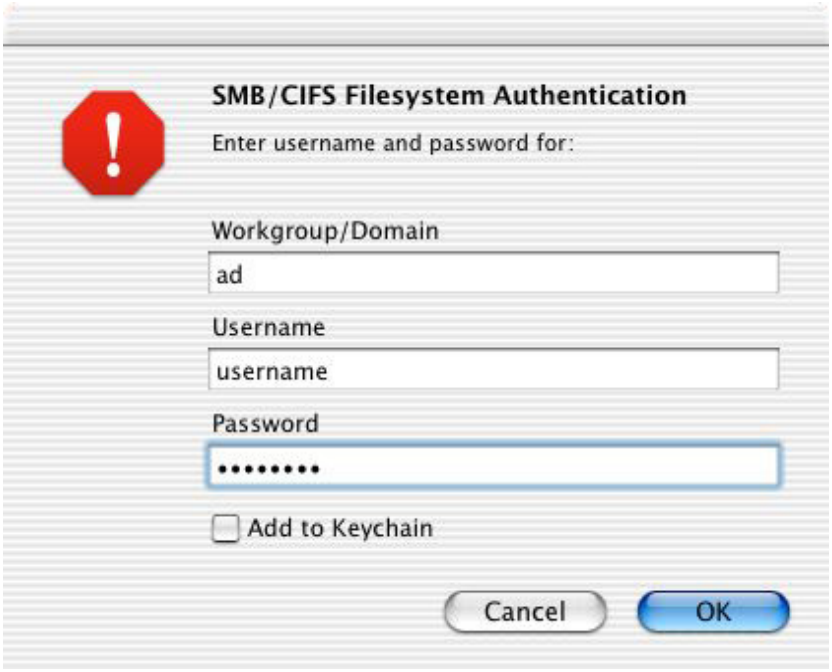


5. [redacted]

OS X 10.5 or later:



Earlier versions of OS X:



[redacted]

Gmail

Scheduling Participants using Gmail

In order to maintain an open line of communication throughout the completion of the StAR2 study, a Gmail account has been created for the lab. This Gmail account is mainly used for communicating with participants who prefer email to phone. The RA will oversee the general management of the Gmail account.

Study Gmail Account Login Username and Passwords

[redacted]

How To Log a Treatment Session in Titanium

1. On the calendar screen, right click in the time slot/schedule where you want to add the appointment (Note: By default, weekend days are not displayed but this setting can be changed by your center administrator. To navigate to days not displayed from the calendar screen, click the Go To button on the menu bar and use the calendar pop-up window to select the desired day, or use the arrow navigation icons)
2. Click Add > type of appointment to be added and select **"Other"**
3. Enter Appointment Information: Choose an appointment code. In the description write StAR2, participants ID number, and session number. Also be sure to mention the RA and type of visit (health/med or ADIS).
   (Note: Do not put confidential information in these fields.)
4. Click the Scheduling tab to add the **room number** so the appointment is added to this schedule
5. Click Save (Note: Depending on the settings chosen by your center administrator, you may see prompts to add the appointment to your schedule, that either you or the client has a conflicting appointment, or assign a new client to yourself).
6. After making the appointment for the participant, make sure to add it to the calendar of the person overseeing the visit:
   a. If **RA** portion, add the appointment to the RA's calendar.
   b. If **ADIS** screening or post-assessment add appointment to the IE's calendar.
   c. If **health/med** portion add appointment to Bonnie Brown's calendar and schedule a medical room under the "Scheduling" tab.
   d. If **therapy** appointment, add to the therapist's calendar.
7. Click Exit.

If a Client Cancels/No Shows to Appointment:

If a client reschedules their treatment session, notify the rest of the study staff by e-mail immediately. Timely rescheduling of participants' treatment sessions is vital because different assessments may need to be distributed depending on the session number.

How to Log a Rescheduled Treatment Session:

1. Log into Titanium
2. Locate the scheduled treatment session that has been cancelled and click on it
3. Change the attendance of the appointment from "scheduled" to "canceled" and mark in the notes section of the event why the participant cancelled. If participant 124 canceled the appointment, the title would change from "124_T8" to "124_C8".
4. This same procedure should be followed for participants who do not notify study staff about their inability to complete the treatment session. The title of the appointment should indicate NS for "no-show". If participant 124 did not show up to the appointment, the title would change from "124_T8" to "124_NS8".
5. If the participant has rescheduled the treatment session, please create a new treatment appointment as described above. In this case the rescheduled appointment should be marked as RTS such that if participants 124 ended up rescheduling their cancelled appointment, the new appointment's title would be "124_RTS8".
6. Should the participant cancel a rescheduled session, the Project Director should be notified of the reason the participant is providing for their inability to complete the treatment session. If the participant misses more than 3 scheduled, consecutive treatment sessions, the lab should be notified as the participant may be withdrawn from the study.

Miscellaneous

Documenting Participants Contacts

All contact between study staff and participants will be documented [redacted] Additional contact between study staff members and participants outside of treatment will also be documented on a specific Additional Contact form. This form will be completed if the participant calls, e-mails, or comes in person to CARD with the intent of speaking with their therapist.

[redacted] Completed forms are given to the RA to be filed in the "Study Binder" which contains "Additional Contact" forms for all study participants.

Instructions for Payment

The nurse administrator at CARD, will be responsible for issuing checks to the RA, who will then either provide the check to the participant directly (immediately after completing the study assessment) or by mail, sent within 3 business days of the payment session. Following completion of a paid assessment, the RA should request payment from the administrator by writing "StAR2", the session number, date of session, participant's name, and amount on a piece of paper (please hand the slip directly to the administrator in person). The administrator will write a check for the amount requested. The RA should make two copies of each check. One

copy is placed in the participant's Med binder. The other copy is placed in the check copies drawer at the front desk (front desk staff can orient study staff to this drawer).

Participants are paid at MRI 1 (UP only), session 8, last session (12 or 16), for at least 80% completion of EMA (added to the last session check), MRI 2 (UP only), and the 1-month and 6-month follow-ups. The RA can give the participant the check in person on the session compensated for. If it is the MRI 1 session or session 8, it can be given no later than the next session. The RA should document when the payment has been provided to the participant [redacted]

This database contains information on who has been paid for which assessment, when the check was given to the participant, and any problems that may have occurred.

Compensation Schedule:

The total possible amount earned by the participant if all components are completed in the study is $450 for UP participants and $250 for Take Control participants.

- fMRI Scan 1 (UP only)- $100
- Week 8- $50
- Week 12 or Week 16 (depending on condition) $75
- EMA Component- $50 for at least 80% completion (paid at post)
- Scan 2 (UP only)- $100
- 1 month FU- $100
- 6-month FU- $100

Should any questions or concerns arise, please do not hesitate to contact Drs. David Barlow or Todd Farchione [redacted]

Thank you for your continued cooperation!

Appendix A: Consent Form

Protocol Title: Efficacy Evaluation of Transdiagnostic CBT for Comorbid Alcohol Use and Anxiety Disorders
Principal Investigator: Todd Farchione, Ph.D
Description of Subject Population: Adults seeking help for alcohol use disorder and an anxiety disorder
Version Date: 3/16/2022

Consent Statement

You are being asked to participate in this research study on the treatment of anxiety and alcohol use disorders. About sixty subjects will take part in this study.

Before agreeing to participate, please read this form carefully. The purpose of this form is to provide you with important information about taking part in this research study. If any of the statements or words in this form are unclear, please let us know. We would be happy to answer any questions to be sure that you understand what your participation would involve.

The goal of the study is to compare a psychological treatment (the Unified Protocol) designed to be used for a variety of different types of psychological disorders, including anxiety disorders and alcohol use disorders, to a modified, therapist-directed version of *Take Control,* a program designed by the National Institute of Alcohol Abuse and Alcoholism to help individuals moderate their drinking. The Unified Protocol teaches skills for managing emotions like anxiety, fear, sadness, or anger while Take Control targets drinking behaviors more directly. In order to compare these two treatments, this study will compare the symptoms and functioning (e.g., how someone is doing in different areas of life) of study participants who receive each type of treatment. The study will include a number of different assessments that will be completed before, during, and after treatment. Both the treatment and assessments will be free of charge.

The researcher in charge of this study is Todd Farchione, Ph.D. Dr. Farchione can be reached at Center for Anxiety and Related Disorders (CARD) at 617-353-9610 between 9 AM and 5 PM. We will refer to them as the “researchers” throughout this form. For emergencies after hours, please call the 24-hour emergency number of the study nurse Bonnie Brown, R.N. at 617-835-1840.

As you are considering participating in this study, we would like to help you think through the participation by stating that if you are considering any change in your current drug or therapy program, this might not be the time to participate in a study like this. During this study, you will be asked to contact staff if you start any outside therapy and/or change the dose of any current medication you are taking for your psychological well-being. However, you may participate in self-help groups such as Alcoholics Anonymous. So, if you anticipate change in medications or therapy, you probably do not want to participate right now in this study. Of course, you are always free to visit your doctor for any psychological help or make any choices that you wish, but you should know that this may cause you to become ineligible to continue in the study.

If you have any questions about the research or any portion of this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, we will ask you to sign this form. We will give you a copy of the signed form.

Sponsor

This study is being funded by the National Institute on Alcohol Abuse and Alcoholism.

What will happen if I take part in this research study?

If you agree to take part in this study, we will ask you to sign the consent form before we do any study procedures. The study procedures are listed below.

Please note that at each study visit, including the screening visit, you will be asked to complete a breathalyzer test. If the breathalyzer test reveals an alcohol level higher than 0.02% blood alcohol concentration or if you appear under the influence of another drug, you will not be able to attend the appointment. You will be provided with a breathalyzer, which is yours to keep following completion of the study. You will be asked to complete a breathalyzer test and report the result to study personnel during each study session.

This study consists of two screening visits, 12 to 16 treatment sessions, a 1-month follow up session, and a 6-month follow up session. Study sessions will be conducted remotely via Zoom. We will be using Boston University's secure Zoom account. Zoom requires the use of a browser but does not require any software download. For more information about Zoom security and privacy, please see: ZOOMcare.com.

Screening visit:

The purpose of the screening visit is to determine if you are eligible for this study. A recent diagnostic evaluation or recent research study screening evaluation, conducted at CARD, may be used as part of the screening visit in this study. This visit will take up to four hours. It will be done through Zoom and is split over the course of two visits. During the screening visits, we will ask you to do the following:

- Provide information about yourself such as your birth date, race, ethnicity, and gender.
- Answer questions about your medical and psychiatric history, medication and illnesses.
- Fill out questionnaires about general psychological complaints such as anxiety, depression, and substance use.
- At the time of your screening session and upon completion of the study treatment (weeks 12 or 16 depending on which treatment you receive), we will ask you to go to a Quest Diagnostics facility to complete your medical testing (a urine sample for a drug screen and a blood sample via injection by needle). We will provide you with a testing form prior to your visits that you will give to a medical professional at Quest. We are also able to Uber you to a Quest Diagnostics testing facility near you at your convenience.
- Blow into an alcohol breathalyzer.
- We will ask you to report your height, weight, and the most recent blood pressure reading you received from a medical professional.
- Answer questions about current treatments you are receiving for alcohol use disorder or anxiety disorders.
- Be asked to participate in a neuropsychological test, administered by the research assistant

If you are eligible to participate in this study, we will assign you by chance (like the flip of a coin) to one of two study groups. One group will receive the Unified Protocol. The other group will receive Take Control. Neither you nor the researchers can choose your study group.

Weekly Study Sessions

You will receive 12 to 16 weekly study sessions following the initial screening. The weekly study session will be between approximately 60 and 90 minutes long except for session 1 and the last treatment session, which will take approximately 3 hours to complete. During these sessions, you will:

- Be asked to complete several self-report measures asking about your mood, alcohol use, cravings, quality of life, and mental and emotional health.
- Be interviewed by a researcher about your drinking since the last visit.
- Be asked to breathe in a breathalyzer to assess your blood alcohol level at every session.
- Be asked to take blood and urine tests, to assess your general health and alcohol and drug use.
    - Blood tests will occur at the screening session and on the last treatment session.

  .
- Be asked to participate in some form of therapy treatment, either the Unified Protocol or Take Control.
- Be asked to participate in some neuropsychological tests. Neuropsychological testing will happen at session 1 and the last treatment session. These tests will take approximately 30 additional minutes to complete.

EMA Component

The Ecological Momentary Assessment (EMA) component to this study will collect self-report drinking data in real time. The software we will be using is called Life Data. Life Data is a downloadable smart phone application which will send timed alerts 3-times a day (between 10am and 10pm) for up to 5, 7-day periods. In addition to the 3 times throughout the day you will have the option to self-initiate the survey during a drinking episode if you choose to do so. The drinking survey will consist of 5-6 questions To protect your privacy, your EMA responses will not be electronically linked to your identifiable information in any way.

fMRI Scans

You must be willing, and able to participate in the fMRI component in order to be eligible to participate in this trial. However, not all eligible participants will be asked to complete this component of the trial. If you are selected, we will ask you to undergo two brain magnetic resonance imagining (fMRI) scans during the study. These scans will take up to 1.5 hours each. One will take place during the screening session and the other will take place at the end of the trial. These scans will take place at Boston University's Center for Integrated Life Sciences (CILSE). Results from these scans may be shared with research personnel at McLean Hospital who are working with us on this study.

fMRI scans will be scheduled after completion of the assessment session at CARD, at which point you will be screened for pregnancy (women of childbearing potential), recent smoking or alcohol use, and illicit drug use. We will also ask you about any metal within your body. If you undergo the scans, you will need to remove all metal objects (such as hearing aids, dentures, jewelry, watches, and hairpins) from your body because these objects may be attracted to the powerful magnet used for the test.

The fMRI scans include four components. The first is a resting-state scan, in which you are asked to lay still so we can evaluate your brain activity when you are not performing any particular tasks. The next task will display alcohol words on a screen and you will be asked to indicate the color of the font of the words you see. The following task will involve the presentation of two sets of images, those consisting of images of alcoholic beverages and a neutral set of cues. In the final task you will be shown a series of

images and asked to either sit with or alter the emotion the image evokes, and make ratings on the intensity of feeling experienced.

We will ask you to lie still on a table that slides into a tunnel-shaped machine. The machine is slightly wider than your body. The top and sides of the tunnel will be very close to your body. The MRI machine makes loud noises as it take pictures of your brain. We will give you earplugs to reduce the noise. You will be able to hear and speak to the research staff at all times during the MRI procedures. We can stop the procedure at any time.

We will obtain physiological measures such as skin conductance, heart rate, pulse, and brain images. We will attach small sensors to the surface of your skin on your hand and/or torso to collect physiological data. These measures are completely safe and do not involve any physical discomfort.

You will be notified if the results of your MRI examination are abnormal. If you choose to share your results with your primary care physician, results can be forwarded when the CARD's Medical Records Release Form is signed.

Post-Treatment Assessments:
We will ask you to complete additional assessments one month and six months after the treatment sessions have ended. These assessments will be completed remotely via Zoom. During these interviews, you will be asked questions about your current alcohol use and anxiety and will be asked to complete some self-report questionnaires. These assessments will last approximately one hour.

Reporting Sexual Misconduct, Sexual Harassment and/or Sexual Assault:
If you are a member of the Boston University community and you report sexual misconduct to study personnel, including as part of study procedures, we are mandated to report the misconduct to the Boston University Title IX Coordinator. Members of the Boston University community include students, faculty, staff, affiliates, visitors, applicants for admission or employment, and independent contractors. Sexual misconduct includes sexual assault, sexual harassment, dating violence, domestic violence, stalking, and sexual exploitation. If you have questions, please review the BU Title IX policy, contact the Title IX coordinator, the Study Investigator, or the IRB Office.

Confidentiality:
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer,

medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

A description of this clinical trial is available on http://www.ClinicalTrials.gov. This website will not include any information that can identify you. At most, the website will include a summary of the results from this study. You can search this website at any time.

In order to maintain confidentiality, data with participants' identification information will be stored offline, on a password-protected external hard-drive, and locked in a drawer in CARD, which is only accessible to study personnel. Other study data, without any identifiable information of the participants will be stored online in Google sheets, under a Google account specially created for this study, which is only accessible to study personnel.

We will make every effort to keep your records confidential. Of course, there are times when federal or state law requires the disclosure of your records. The instances in which your information may be shared are listed below:

- **Reporting child/elder abuse:** If, during your participation in this study, we have reasonable cause to believe that child/elder abuse is occurring, the researcher must report this to authorities as required by law. The researcher will make every reasonable effort to protect the confidentiality of your research information. However, it might be possible that a civil or criminal court might demand the release of identifiable research information.
- **Reporting suicidal risk:** If, during your participation of this study, we have reason to believe that you are at risk for being suicidal or otherwise harming yourself, we are required to take the necessary actions. This may include notifying your doctor, your therapist, or other individuals. If this were to occur, we would not be able to assure confidentiality.
- **Reporting intent to harm:** If, during your participation in this study, we have reasonable cause to believe that you intend to threaten or harm another person, the researcher must report this to authorities as required by law. The researcher will make every reasonable effort to protect the confidentiality of your research information. However, it might be possible that a civil or criminal court might demand the release of identifiable research information.
- **Other:** Records from this study could be subpoenaed by a court of law under certain conditions. We would also not be able to assure confidentiality if there is criminal or civil legal action related to sanity or competence, if you initiate legal action or ethical charge against the research, or if you request or allow disclosure of this information by signing a release of information form. Also, because this research is sponsored by the National Institute on Alcohol Abuse and Alcoholism, and monitored by the Institutional Review Board for Human Subject Research of the Boston University Charles River Campus, staff from these agencies may review records that identify you for audit or program evaluation. All of these agencies will protect your privacy.

The following people or groups may review your study records for purposes such as quality control or safety:

- The Researcher and any member of his research team.
- The Institutional Review Board at Boston University. The Institutional Review Board is a group of people who review human research studies for safety and protection of people who take part in the studies.
- The sponsor of this study, the National Institute of Alcohol Abuse and Alcoholism.

- Federal and state agencies that oversee or review research
- Central University Offices

In accordance with Boston University's policy, we will store your data for seven years following the end of the study. The results of this study may be published or used for teaching. We will not put identifiable information on data that is used for these purposes.

If you choose to sign the current consent form, you may be asked to participant in a supplemental study entitled "Assessment Supplement to Alcohol Use Studies." If you choose to participate and subsequently sign the consent form for that study, you are also consenting to have data from this study combined with data from that study. Should you choose to not participant in the supplemental study, that decision will have no impact on your enrollment in the current study and your data will not be shared with the supplemental study.

Alternative to Participation
You may choose not to take part in this research study. You do not have to take part in this research study in order to receive treatment for alcohol use or anxiety disorders. Other treatments available for these symptoms include therapy that is not part of a research study and psychiatric medications. If you would like referrals to another type of treatment, please ask a study staff member.

Compensation for Research Related Injury
If you are injured as a result of taking part in this research study, we will assist you in getting medical treatment. However, your insurance company will be responsible for the cost. Boston University does not provide any other form of compensation for injury.

Potential Risks:
The primary risks involved in this study are those associated with treatment for anxiety in general and those associated with alcohol withdrawal. You will not be forced to do anything you do not want to do. You can also stop study procedures at any time. If you experience any adverse reactions, you can contact CARD personnel at 617-353-9610 during office hours (9AM-5PM) Monday through Friday. For emergencies after hours, please call the 24-hour emergency number of the study nurse Bonnie Brown at 617-835-1840. If an emergency arises during the course of the study and you are unable to contact study staff, you should go to the closest emergency room immediately. However, no special provision will be made for compensation or for payment for treatment solely because of your participation in this experiment. This paragraph is a statement of Boston University's policy and does not waive any of your legal rights.

Alcohol Withdrawal
You may experience symptoms associated with alcohol withdrawal during the study. These symptoms include shakes or tremors, chills, nausea and/or vomiting, agitation, sleeplessness, seizures, and delirium (disorientation, altered sensorium, and hallucinations).

You may experience moderate to severe withdrawal symptoms if you stop drinking abruptly or if you attempt to steadily reduce your drinking. If you need treatment for withdrawal we will refer you to another treatment center for detoxification and you will be withdrawn from the study.

Risks of fMRI
There is a possibility of damage associated with magnetically sensitive metals being attracted to the magnetic field of the fMRI device. There are no known harmful effects from the strong magnetic field used for fMRI. But the magnet is very powerful. The magnet may affect pacemakers, artificial limbs, and

other medical devices that contain iron. The magnet will stop a watch that is close to the magnet. Any loose metal objects have the risk of causing damage or injury if it gets pulled toward the strong magnet.

You should not have an fMRI if you have claustrophobia (fear of small spaces). The top and sides of the machine will be very close to your body. Because of this, you may feel anxious while inside the fMRI machine. If you do feel anxious during the procedure, you can ask us to stop the fMRI at any time. If you are pregnant or suspect you are pregnant, you should inform the study staff before the fMRI examination. Although there is no known risk of using fMRI in pregnant women, the safety of fMRI during pregnancy has not been established. Therefore, you cannot have an fMRI for this study if you are pregnant or think that you are pregnant.

We are doing the fMRI in this study to answer research questions, not to give you medical care. This fMRI is not the same as one that your own doctor would order. It may or may not show problems that would be found on a regular fMRI. If we do see something that looks like a medical problem, we will tell you and forward the results to your primary care physician or help you get follow-up care.

Risks of Psychological Discomfort
You may experience discomfort and anxiety when answering questionnaires and when responding to tests evaluating your mood states and alcohol cravings. In addition, you may experience some discomfort or anxiety from discussion of personal information. You may find questions about your history distressing or uncomfortable. You may feel nervous when answering psychological questions. You will not be forced to do anything you do not want to do. You may get tired during the tasks. You can rest at any time.

Loss of Confidentiality

The main risk of allowing us to use and store your information for research is a potential loss of privacy. To protect your privacy, the storage of research data will be maintained using the suggested methods from the BU CAS Information Technology group. These methods involve labeling your information with a code and keeping the key to the code in an encrypted online storage created by the BU CAS Information Technology group, which is only accessible to the principal investigator. Physical copies of data without identifiable information will be stored in a locked cabinet at CARD, only accessible to study personnel. Study data collected and maintained online including but not restricted to assessments, interviews, progress tracking will be de-identified, only distinguishable by study ID.

Risks of Phlebotomy:
Risks associated with having blood drawn may include: excessive bleeding, fainting or feeling lightheaded, hematoma (blood accumulating under the skin) and infection (a slight risk any time the skin is broken). The likelihood of these risks will be minimized by having blood drawn by a trained phlebotomist, nurse, or physician.

Potential Benefits
You may or may not benefit from this study. Study procedures may help you obtain relief from anxiety symptoms and associated disabilities. Study procedures may also help you reduce your drinking. However, benefits from these procedures cannot be guaranteed for any particular participant. As an indirect benefit, you will be providing information that will be helpful in expanding scientific knowledge about anxiety disorders and alcohol use disorders. Others may benefit in the future from information that is learned in this study.

Compensation

You will earn up to $575 including $100 per fMRI assessment and an additional $50 for completing at least 80% of the EMA component. The remaining $325 will be distributed during the treatment and follow-up periods. You will receive $50 for completing all study procedures up to session 8, $75 for completing all study procedures associated with the post session (either 12 or 16), $100 for completing all study procedures associated with the 1-month follow-up, and $100 for completing all study procedures associated with the 6-month follow-up. To be eligible for payment, you must complete all study procedures associated with a compensated time point, which may include completing self-report questionnaires, completing labs, and/or completing neurocognitive tests.

If you have any questions regarding the research or your participation in it, either now or anytime in the future, you are free to ask the research team. The research team can be reached at 617-353-9610 and will be happy to answer your questions. If any problems arise as a result of your participation in this study, including research related injuries, you should immediately call the Principal Investigator (Todd Farchione) at 617-353-9610.

If you have questions about your rights as a research participant, or if you have any complaints or concerns and want to speak with someone independent of the research team, you may contact the Boston University Charles River Campus IRB at 617-358-6115. The IRB Office webpage has information where you can learn more about being a participant in research, and you can also complete a Participant Feedback Survey.

Statement of Consent

I have read the information in this consent form including risks and possible benefits. I have been given the chance to ask questions and my questions have been answered to my satisfaction. My signature means that I understand the information, am 21 years old or over and agree to participate in this study.

SIGNATURE

_____
Name of Subject

_____ _____
Signature of Subject Date

I have explained the research to the subject and answered all his/her questions. I will give a copy of the signed consent form to the subject.

_____
Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

Additional Consents:

Consent to Use CARD Clinical Evaluation

You consent for use of your CARD clinical evaluation to provide diagnostic and symptom severity information for this study.

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Obtaining Consent Date

Digital Audio Recording Consent
We would like to audiotape your sessions during this study. In order to protect your confidentiality, we will refrain from using your name or any other identifiable information while you are being audiotaped and we ask that you do the same. We will store these tapes on an encrypted volume created by BU CAS Information Services and Technology on a sever within a secure data center and only approved study staff will be able to access the tapes. We will label these tapes with a code instead of your name. The key to the code connects your name to your audiotape. The researcher will keep the key to the code in a password-protected computer file. All tapes and associated computer files will be stored for seven years.

These audio recordings will be reviewed by members of the study staff for the purposes of supervision and consultation. Sometimes study session recordings will be made temporarily available to select study investigators via a secure online server so that they can be reviewed for these purposes. Once the recordings have been evaluated, they will be removed from the server and stored on a secure hard drive, as described above.

By signing my name below, I give permission to have any session audio recorded throughout the study.

_____
*Name of Subject (*please print)

_____ _____
Signature of Subject *Date*