Developing and Evaluating a Positive Valence Treatment for Alcohol Use Disorder with Anxiety or Depression.

Protocol Number: 2022-003

National Clinical Trial (NCT) Identified Number: <Number, once assigned by CT.gov>

Principal Investigator: Robin Aupperle, PhD

Sponsor: Laureate Institute for Brain Research

"Sponsor" indicates an institution, foundation, or individual who takes responsibility for and initiates a clinical investigation; often times this is the university with which the Principal Investigator is affiliated.

Grant Title: Developing and Evaluating a Positive Valence Treatment for Alcohol Use Disorder with Anxiety or Depression.

Grant Number: R34 AA030688

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

Study investigators and staff who are responsible for the conduct, management, or oversight of this clinical trial have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name: Robin Aupperle, PhD

Title: Principal Investigator, Laureate Institute for Brain Research (LIBR)

Investigator Contact Information
Affiliation: Laureate Institute for Brain Research (LIBR)
Address: 6655 S. Yale Ave., Tulsa, OK 74136
Telephone: 918-502-5744
Email: raupperle@libr.net

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Developing and Evaluating a Positive Valence Treatment for Alcohol Use Disorder with Anxiety or Depression

Grant Number: *R34 AA030688 (NOA not yet received)*

Study Description: The proposed study consists of two phases. During Phase 1, we will recruit a small sample of participants to complete a psychosocial intervention termed Affective Modulation of Positivity (AMP) for individuals suffering from comorbid depression or anxiety disorders and alcohol use disorder (AMP-A). These participants will be asked to provide both qualitative and quantitative input about the AMP-A intervention. Based on their input and clinician input, the AMP-A manual will be modified for use in Phase 2. The goal is to recruit up to 20 participants in order to ensure we have at least 8 participants who complete all sessions of AMP-A. Phase 2 is a randomized clinical trial (RCT) protocol in which individuals suffering from comorbid depression or anxiety disorders and alcohol use disorder will be randomized to complete AMP-A or a more traditional cognitive-behavioral therapy (CBT) intervention. We will recruit up to 100 participants in order to reach a target of N=60. Assessed outcomes will include participant acceptability and completion rates, participant compliance with the intervention, positive and negative affect, substance use- and depression and anxiety-related symptom severity, functional disability, and neural reactivity to reward and alcohol cues during functional magnetic resonance imaging (fMRI).

Objectives: Primary Objective: For Phase 1, the primary objective is to assess participant and clinician feedback on acceptability and satisfaction of the AMP-A intervention. For Phase 2, the primary objective is to assess for potential clinical utility of AMP-A utilizing an RCT comparison of AMP-A and CBT interventions. The primary outcome for the RCT will be positive affect at the post-treatment time point.

Secondary Objectives: Secondary outcomes for the RCT include social connectedness and psychological well-at the post-treatment time point.

Tertiary/Exploratory Objectives: Exploratory outcomes for the RCT phase include anticipation, responsiveness, and recall of positive (non-drug) experiences and positive reinforcement motives to use alcohol, level of alcohol use and anxiety and depression symptoms, as well as neural reactivity to reward and alcohol cues during fMRI.

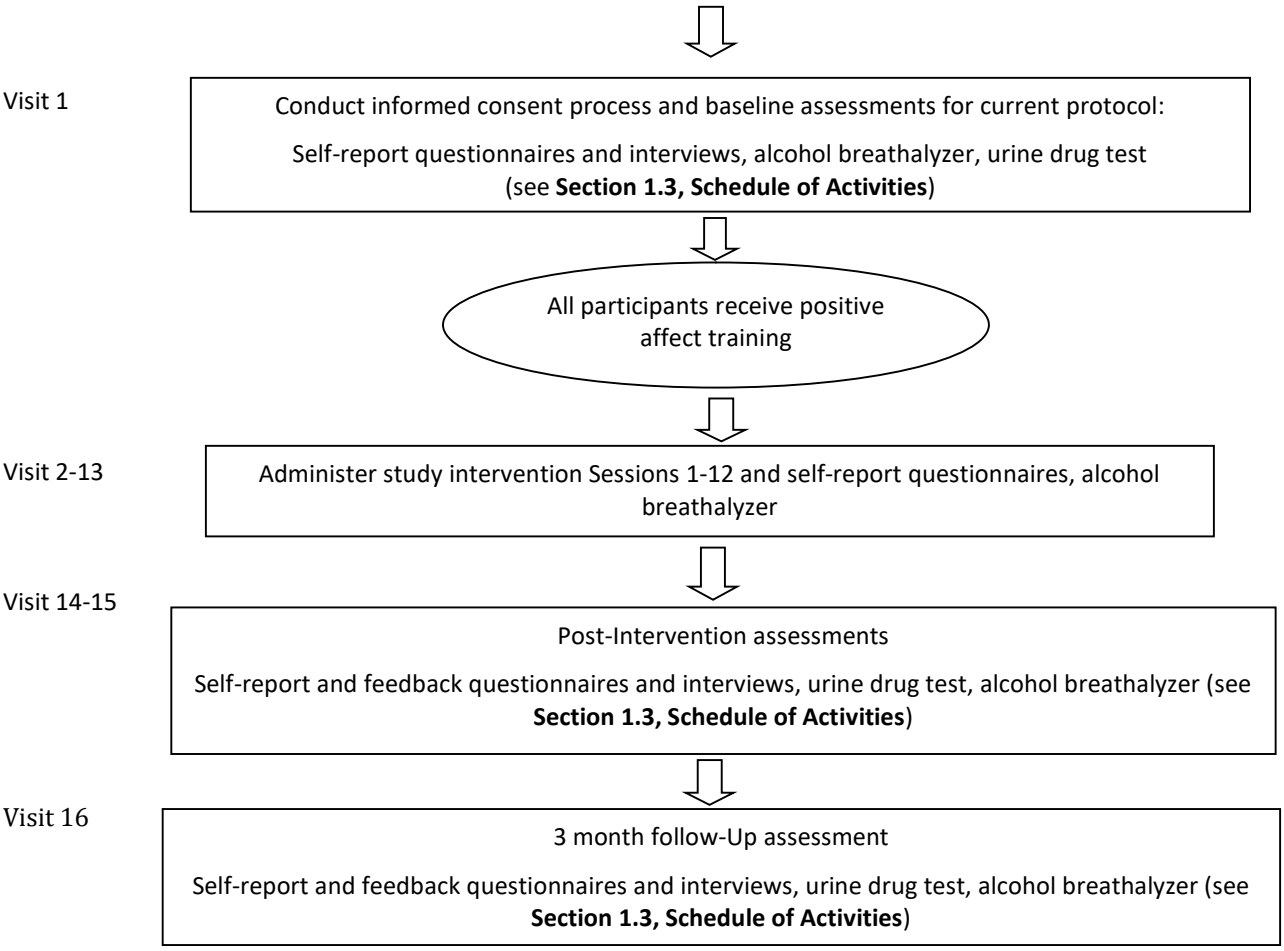
Endpoints: Primary Endpoint: Post-treatment (i.e., within two weeks of completing the intervention).
Secondary Endpoints: Three month follow-up (i.e., 12-15 weeks after completing the intervention)

Study Population:	For Phase 1, the goal is to recruit up to 20 participants in order to ensure we have at least 8 participants who complete all sessions of AMP-A. Participants will be adults, age 18-65, meeting diagnostic criteria for alcohol use disorder and elevated anxiety or depressive symptoms. All genders, races, and ethnicities will be included. Phase 2 will include up to 100 participants to be enrolled and randomized to AMP-A versus CBT, using the same inclusion/exclusion criteria as Phase 1. Participants who meet additional safety criteria for being able to complete MRI will also be offered the opportunity to complete these aspects of the Phase 2 protocol.
Phase or Stage:	Phase I/II
Description of Sites/Facilities Enrolling Participants:	Laureate Institute for Brain Research (Tulsa, OK) is the only site enrolling participants in this study.
Description of Study Intervention/Experimental Manipulation:	In Phase 1, the study intervention will consist of 12 sessions of AMP-A conducted in individual sessions. Each session will last approximately 1 hour in duration and sessions will be scheduled once or twice weekly. In Phase 2, the study interventions will consist of 12 sessions of either AMP-A or CBT conducted in individual sessions lasting approximately 1 hour in duration and scheduled once or twice weekly.
Study Duration:	24 months
Participant Duration:	18 – 24 weeks

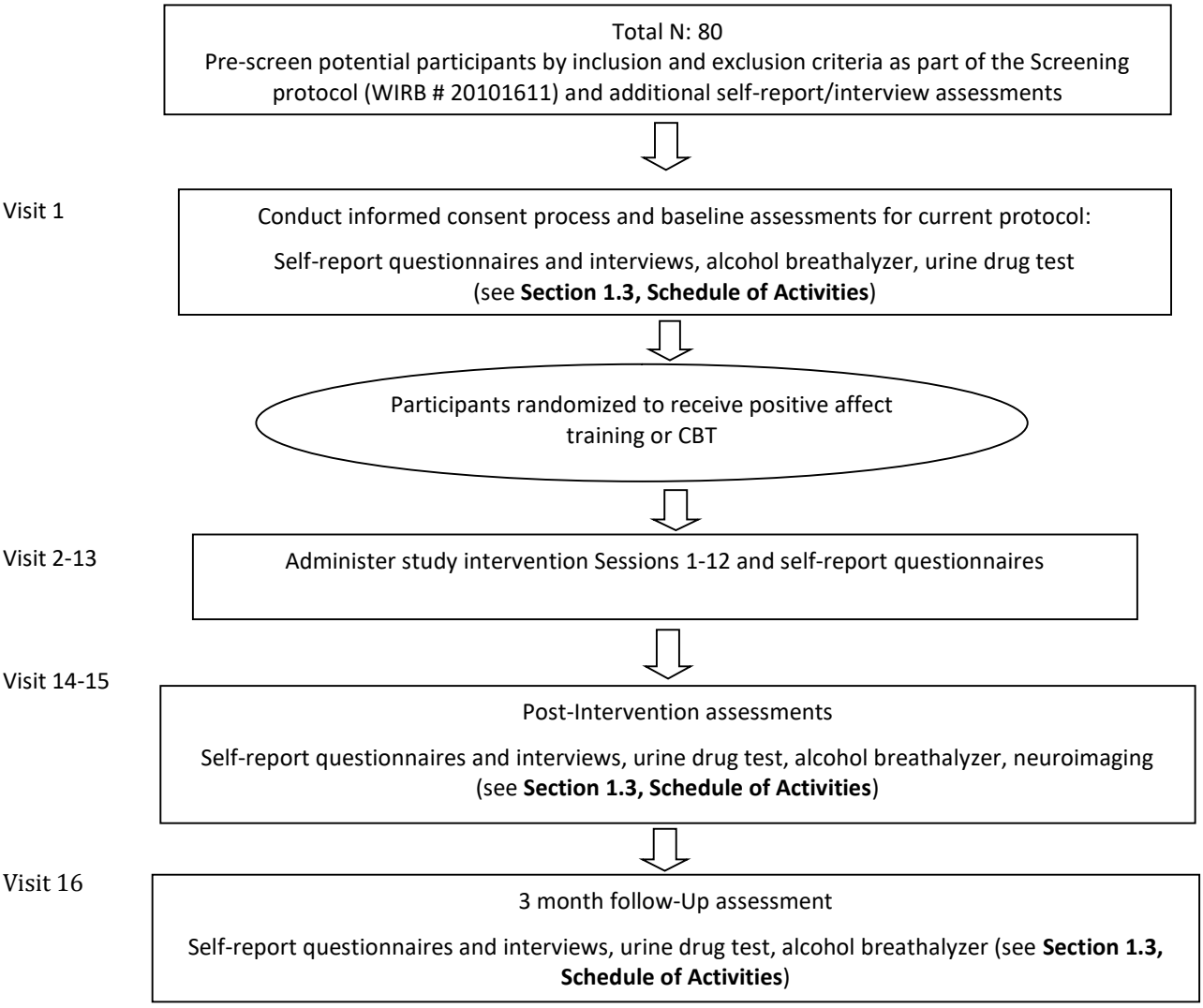
1.2 SCHEMA

Phase 1

Total N: 8 completers (up to 20 enrolled)
Pre-screen potential participants by inclusion and exclusion criteria as part of the Screening protocol (WIRB # 20101611) and additional self-report/interview assessments


Visit 1
Conduct informed consent process and baseline assessments for current protocol:
Self-report questionnaires and interviews, alcohol breathalyzer, urine drug test
(see **Section 1.3, Schedule of Activities**)
All participants receive positive affect training
Visit 2-13
Administer study intervention Sessions 1-12 and self-report questionnaires, alcohol breathalyzer
Visit 14-15
Post-Intervention assessments
Self-report and feedback questionnaires and interviews, urine drug test, alcohol breathalyzer (see **Section 1.3, Schedule of Activities**)
Visit 16
3 month follow-Up assessment
Self-report and feedback questionnaires and interviews, urine drug test, alcohol breathalyzer (see **Section 1.3, Schedule of Activities**)

Phase 2


Total N: 80
Pre-screen potential participants by inclusion and exclusion criteria as part of the Screening protocol (WIRB # 20101611) and additional self-report/interview assessments
Visit 1
Conduct informed consent process and baseline assessments for current protocol:
Self-report questionnaires and interviews, alcohol breathalyzer, urine drug test
(see **Section 1.3, Schedule of Activities**)
Participants randomized to receive positive affect training or CBT
Visit 2-13
Administer study intervention Sessions 1-12 and self-report questionnaires
Visit 14-15
Post-Intervention assessments
Self-report questionnaires and interviews, urine drug test, alcohol breathalyzer, neuroimaging
(see **Section 1.3, Schedule of Activities**)
Visit 16
3 month follow-Up assessment
Self-report questionnaires and interviews, urine drug test, alcohol breathalyzer (see **Section 1.3, Schedule of Activities**)

1.3 SCHEDULE OF ACTIVITIES

Phase 1:

	Pre-screening (Pre-consent)	Visit 1 (pre-training)	Visits 2-13 (training)	Visit 14-15 (post-training)	Visit 16 (3 month follow-up)
Review Eligibility from LIBR Screening Protocol (includes demographics, clinical history)	X (as part of Screening protocol)				
MINI/PHQ/OASIS/PHEN-X 30 Day	X	X			
Informed Consent		X			
Outcome Evaluation					
PROMIS Alcohol Use, Positive Affect, Depression, Anxiety, and Meaning and Purpose, NIH Toolbox Loneliness, Sheehan Disability Scale, Homework Rating Scales, Working Alliance Inventory, adherence and acceptability scale, Distress/Endorsement Validation Scale, Timeline Followback		X	X	X	X
All other self-report measures		X		X	X
Feedback Questionnaires		X	X	X	X
Qualitative feedback interviews				X	
Intervention – AMP-A			X		

Phase 2:

	Pre-screening (Pre-consent)	Visit 1 (pre-training)	Visits 2-13 (training)	Visit 14 (post-training)	Visit 15 (3 month follow-up)
Review Eligibility from LIBR Screening Protocol (includes demographics, clinical history)	X (as part of Screening protocol)				
MINI/PHQ/OASIS/PHEN-X 30 Day	X	X			
Informed Consent		X			
PRISM-5 to confirm AUD diagnosis		X			
Columbia Suicide Severity Rating Scale		X		X	
Outcome Evaluation					
PROMIS Alcohol Use, Positive Affect, Depression, Anxiety, Sheehan Disability Scale, Homework Rating Scales, Working Alliance Inventory, adherence and acceptability scale, Distress/Endorsement Validation Scale, Timeline Followback		X	X	X	X
All other self-report measures		X		X	X
Structural and functional neuroimaging		X		X	

	Pre-screening (Pre-consent)	Visit 1 (pre-training)	Visits 2-13 (training)	Visit 14 (post-training)	Visit 15 (3 month follow-up)
Intervention – AMP-A or CBT			X		

2 INTRODUCTION

2.1 STUDY RATIONALE

Substance use disorder is a problem that impacts 21.6 million people in the United States, with prevalence rates of the disorders and associated mental health outcomes (i.e., suicide) increasing significantly over the past decade[1-6]. The 12-month prevalence of alcohol use disorder specifically is approximately 9%[7]. Substance use disorder, including alcohol use disorder, is characterized by enhanced neural responsivity to drug (alcohol) cues, but reduced neural responsivity to non-drug reward cues[8-11]. These effects may be exacerbated by comorbid major depressive disorder (MDD) or symptoms of anhedonia[12], comorbidities which are particularly high amongst alcohol use disorder[7]. Response rates for current interventions with alcohol use disorder are rather poor, with only 58% experiencing benefits greater than control conditions[13]. There is a need to identify interventions that may target reward responsivity in a way that would promote recovery, reduce affective disturbance, and support better long-term functioning for individuals suffering from alcohol use disorder and comorbid depression and anxiety disorders. Positive affect interventions have recently been developed and tested in other populations (i.e., HIV, anxiety/depression) as a way of enhancing positive valence and reward processing[14 15]. These interventions have shown significant promise in these populations, but have yet to be examined in the context of alcohol use disorder. The current pilot study would test the feasibility and acceptability of an 12-session protocol of positive affect training with populations suffering from comorbid alcohol use disorder and depression or anxiety disorders, and explore the impact of the intervention on positive affect, negative affect, alcohol use and craving, and neural response patterns during reward and drug cue processing. The primary outcome for the current study is completion rate, with secondary outcomes including participant acceptability ratings. Exploratory outcomes include self-reported positive affect symptoms, negative affect symptoms, anhedonia, Sheehan Disability Scale, alcohol breathalyzer use, time til first use, frequency of use, and striatal and OFC activation in response to alcohol cues and non-alcohol reward (monetary). Primary endpoint is the post-intervention time point (within 2 weeks of completing intervention), with secondary endpoint being the three month follow-up.

2.2 BACKGROUND

Often considered to be the foundation of drug and alcohol treatment, psychosocial treatments can serve as stand-alone treatment or used in combination with pharmacological intervention while being implemented individually or within groups[16 17]. A strong evidence base exists for several psychosocial treatments or interventions including cognitive-behavioral therapy (CBT), contingency management (CM), and motivational enhancement/motivational interviewing (MI)[16 17]. A recent meta-analysis demonstrated that nearly 2.5 times as many substance- or alcohol-users achieved post-treatment and/or clinically significant abstinence when an intervention program included an evidence-based psychological treatment[17]. However, response rates for substance and alcohol use treatment are usually only small to moderate in effect and produce improvement over control conditions in only about 58% of cases[13]. Given this and the increased rates of substance and alcohol use, and the detrimental and catastrophic mental health outcomes (i.e., suicide), it is clear that novel treatments are needed that may target specific neural and behavioral deficits and that may improve rates of treatment response in both substance use and mental health domains.

One of the hallmark characteristics of substance and alcohol use disorders involve increased desire for the drug, with the drug being excessively salient at the expense of other, more natural, reinforcers or rewards (i.e., social relationships, goal attainment, etc.[9-11]. Addiction across various substances is accompanied by alterations in blood flow and activity within reward processing regions (i.e., dopamine-dependent sites), such as the striatum, amygdala, orbitofrontal cortex (OFC), and other prefrontal sites (i.e., anterior cingulate cortex [ACC], dorsolateral prefrontal cortex [dlPFC])[18]. However, substance and alcohol use disorder has also been found to relate to decreased neural sensitivity (i.e., within striatum, OFC, and amygdala) to non-drug reward, such as monetary reward or verbal feedback[19-24]. Appropriate valuation of natural reinforcers is known to be important for goal selection and action, and likely for motivating choices that are supportive of an individual's future well-being…and thus important for recovery from addiction[25]. Indeed, there has been some indication that reward-related behavioral responses or brain activation/metabolites may be predictive of treatment outcome for substance use disorder, including alcohol use disorder specifically[26-30]. In addition, individuals with alcohol use disorders are at least 2 – 3.5 times more likely to be diagnosed with mood or anxiety disorders; with up to about 40% of patients meeting criteria for MDD or an anxiety disorder[7 31]. Mood and anxiety disorders, and the hallmark symptom of anhedonia, are also associated with reduced responsivity within reward circuitry, including striatum, OFC, and ACC regions[32-34]. Thus, enhancement of non-drug reward responsivity could be beneficial not only for addiction but also for comorbid symptoms of anxiety and depression.

The positive affect system is thought to guide people toward situations with reward potential, and is characterized by positive emotions (e.g., joy, excitement, happiness), cognitions (e.g., attentional bias for reward-relevant stimuli), and approach behaviors (e.g., curiosity, social initiation) that together facilitate the acquisition of psychosocial resources that promote overall health and well-being[15]. Manualized positive affect interventions used in other populations are often conducted using either 5- or 10-session protocols that focus on enhance positive affect in several ways, including amplifying response to positive events, gratitude expression, acts of kindness, affirming values, engaging in meaningful activities, optimism, etc. There is mounting evidence that it is possible to enhance positive

affect across a variety of populations, including normative populations[35], depression[36], anxiety[15], and chronic health conditions (e.g., heart disease, HIV[14 37]. There is also initial evidence that interventions targeting aspects of positive affect (i.e., compassion training) may alter activity in reward circuitry, including the OFC and striatum[38]. While there has been a few studies using very specific interventions (e.g., gratitude exercises[39]) or more traditional cognitive-behavioral interventions that may enhance approach motivations (e.g., behavioral activation[40]), there have been no studies utilizing comprehensive, manualized interventions for enhancing multiple facets of positive affect with substance or alcohol use disorders. The current study would examine (1) the feasibility, acceptability, and potential utility of conducting an 12-session positive affect intervention (AMP-A) nwith populations experiencing comorbid alcohol use disorder and depressive or anxiety disorders and (2) the feasibility of a randomized clinical trial (RCT) protocol comparing a 12-session positive affect intervention (modified based on Phase 1) to a more traditional cognitive-behavioral therapy (CBT) intervention.

We have conducted a prior study with AMP-A (LIBR Protocol # 2019-010-02), which was instrumental in helping us develop and refine the treatment manual, and provide rationale for application for grant funding. Thus, the current proposed, 2-phase study will further this work, developing the AMP-A intervention based on further piloting and examining initial clinical utility through an RCT.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential Risks

Risks associated with MRI (Phase 2 only): MRI scanning uses powerful magnetic fields and weak radio frequency pulses (electromagnetic radiation), neither of which has been associated with adverse effects in patients or laboratory animals when studied under clinical imaging protocols. However, as in the clinical setting, subjects must be free of any external or implanted ferrous material. People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Additionally, fast switching of the magnetic field gradients in some MRI pulse sequences may occasionally cause peripheral nerve stimulation that in some subjects produces muscle twitching or paresthesias, especially in the torso. Because MRI is performed in confined quarters, the feeling of being isolated or confined may cause physical discomfort, anxiety, or claustrophobia. It is expected that a very low percentage of subjects will be unable or unwilling to complete participation. The noise from the scanner is loud enough to damage hearing to the unprotected ear.

Risks associated with treatment: It is possible that participants may experience adverse effects to treatment in the form of worsening mental health or substance use symptoms or behaviors.

Risks associated with screening, interviewing, and assessments: The risks of the screening evaluation and assessments are minimal and most likely risks include fatigue and discomfort or irritability with the nature of questions and/or testing procedures. Some of the questions in the interviews may be distressing or uncomfortable to answer and the most likely risk is psychological distress.

Risks associated with Alcohol Cue Exposure:

Risk: Alcohol cue exposure is a conventional method in experimental addiction studies. Functional neuroimaging with MRI (fMRI) with alcohol cue exposure tasks is a routine method to activate and depict neurocircuits involved in alcohol craving. There are over 300 published studies indexed at the National Library of Medicine's website (www.pubmed.com) with alcohol cue exposure fMRI among alcohol users. The only risk that is associated with these paradigms other than minimal risks associated with fMRI in general is the increased level of alcohol craving among participants.

Strategies for protecting against or minimizing all potential risks identified:

Risks associate with MRI (phase2 only): A safety-screening questionnaire will be completed by each subject prior to entering the MR environment. The safety pre-screening questionnaire probes for subjects for possible occupational exposure to metal slivers or shavings remnants of which may remain lodged in the subjects head or neck. Subjects with surgical clips or shrapnel, cochlear implants, or any other form of ferrous metal body implanted in or on their body will be excluded. All subjects with any form of implant wires or electronic device implants will be excluded. All persons involved in this protocol will receive MR safety training conducted at LIBR by the Institute's MR safety officer.

To minimize the effects of peripheral nerve stimulation, we will employ MRI sequences that have been used at LIBR in thousands of scans with only a few reports of mild peripheral nerve stimulation. Additionally, subjects will be provided a squeeze ball by which they can notify the research team that the scan should be stopped should they experience muscle twitching.

Pregnancy testing with immediate results will ensure that no pregnant participant receives an MRI. Any positive pregnancy test results would be discussed with the participant, and counseling will be provided should the participant indicate distress concerning the result.

We intend to minimize claustrophobic problems using a series of procedures: 1) by giving a detailed explanation of the environment prior to scanning, 2) allowing subjects the opportunity to habituate to the scanner environment by resting in LIBR's mock scanner prior to their real scan, 3) maintaining voice contact with the subjects at all times, 4) maintaining visual contact of the patient in the scanner using observational cameras placed inside the scanner room, and 5) providing subject an emergency squeeze ball to signal the MRI technician to stop.

To minimize the risk of hearing damage, all participants will be fitted with hearing protection and be required to wear the hearing protection for the duration of the MRI scanning.

Plans for handling incidental findings:

Incidental scan findings: In addition to standard T1-weighted MP-RAGE and functional fMRI EPI sequences used for the research component of the study, we will also obtain T2-weighted FLAIR images which are sensitive to CNS and white matter abnormalities. For each subject, a set of T1- and T2-weighted images will be sent via PACS and evaluated by a neuroradiologist (Integris Radiology Group, Oklahoma City, OK) for the presence of unanticipated abnormalities (e.g., tumors). The neuroradiologist will recommend referral to a physician if incidental findings are discovered which warrant follow-up evaluation. Upon detection of such incidental findings during MRI scanning, a physician researcher from LIBR will verbally communicate the discovery to the subject. The physician researcher will also provide written communication of the incidental finding to the subject. The written communication will guide the participant to make the discovery known to their primary-care physician. In addition, once the participant provides written consent authorizing the release of his/her medical records and MR images, LIBR will provide a digital copy of the MRI scans to the primary-care physician. Additionally, detection and disclosure of incidental findings will be documented in a database contained on LIBR's computer cluster.

Strategies to manage and protect the privacy of participants and confidentiality of research data:

We have instituted the following measures to protect the privacy of participants and confidentiality of research data:

- Data will be collected by LIBR staff who completed training in human subjects' research, HIPAA, and research integrity, on research data management, confidentiality and mandatory reporting, and project specific training on the protocol.
- To protect confidentiality, no personally identifying information will be coded on questionnaires, interviews, brain imaging data, or other study records. Further, subjects will not be identified in any reports or publications. All de-identified hard-copy data will be stored in locked file cabinets in a locked office. A unique subject identification number is assigned to each participant, and linked to the study participant name in an electronic file managed in accordance with ISO 27000 standards as specified below with access limited the PI, Study Psychiatrist or Physician, and designated Study Coordinator.
- The original signed consents, screening form, locator form with contact information, the Research Privacy Form, and any other forms or papers containing personally identifiable information (PII) will be stored in a secured medical records room with access granted only to authorized study personnel.
- Electronic data will be stored securely on servers and databases accessible only to study personnel.

Plans for ensuring necessary medical or professional intervention in the event of psychological distress, or worsening of mental health or substance use symptoms/behaviors:

The researchers are trained to frequently inquire the subjects about their willingness and ability to continue with testing. If the subjects express concerns about continuing with testing, the research assistants will stop testing, offer a break, or, in case the subject is not willing to continue, terminate the testing session. If subjects report psychological distress, suicidal ideation, or intent to harm self or others, Dr. Aupperle, Dr. Paulus, or their licensed designee, will be contacted immediately to ensure appropriate care and compliance with mandated reporting to authorities. Subjects may be referred for professional intervention, as deemed appropriate, including calling emergency personnel (911) if needed. A current list of local mental health treatment programs will be provided to all subjects at screening. Information reported will be kept in confidence with the exception that disclosure of suicidality, homicidality, or child or elder abuse warrant reporting to appropriate authorities.

Risks associated with Alcohol Cue Exposure:

We will assess the level of craving after the cue exposure sessions inside or outside MR scanner to ensure that subjects will not leave the center with a significant level of craving. Different craving reduction methods, such as relaxation, distraction or reappraisal will be instructed to the study staff to help participants to reduce any potential craving.

Risks Associated with Intervention:

All subjects will be informed of the procedures/strategies involved in the intervention protocol during the informed consent process. Anxiety and depressive symptoms (including suicidal ideation) and substance use behavior will be monitored weekly throughout the intervention by using validated symptom questionnaires. This will allow for detection of any worsening of symptoms during completion of the study. This will be supplemented by observation by the clinician working with each participant. If symptoms worsen during the course of the study, the subject will be assessed individually by Dr. Aupperle, Dr. Paulus, or their licensed designee as needed. If symptoms worsen significantly such that additional evaluation, emergency services, or other clinical treatments is needed, appropriate referrals will be made (as described in the contingency plan for suicidality, below). If a subject has a clinical issue in between treatment sessions that does not reflect a psychiatric emergency, they will be able to reach a LIBR clinician during official hours (weekdays between 0800 and 1700). On weekends and off-hours (evenings and nights) they will be able to call a 24-hour per day on call service for LIBR, which is provided through the Call Center of Laureate Psychiatric Clinic and Hospital. In case of clinical emergency between sessions, subjects will be instructed to contact 911 or Tulsa Community Outreach Psychiatric Emergency Services (COPES – 918 744 4800).

Contingency plans for monitoring suicidality, worsening clinical symptoms, or other mental health emergencies

All volunteers who are deemed a serious suicide risk will be excluded from the study. All research volunteers will undergo routine, state-of-the-art screening and diagnostic assessments at LIBR. The screening will be conducted by a clinician interviewer (who holds either a nursing or MD degree, or a MA or PhD degree in clinical or counseling psychology, and has received extensive training and experience in the evaluation and management of patients with major psychiatric disorders). In the evaluation of suicidal risk, we specifically will exclude from participation any volunteer who endorses having developed a plan to attempt suicide and has intent to attempt suicide in the near future (i.e., in the next month). Any volunteer who is excluded from participation for these reasons will be referred for emergency care according to written LIBR policies for managing potentially suicidal patients, as described below.

While the participants are in this study they will be monitored for the development of suicide risk or for worsening in their clinical illness by a clinician. This will be conducted using the weekly self-report assessments and clinical observation, as described above. If concerns arise when the participant is physically present at the Laureate Institute for Brain Research, psychologist Robin Aupperle, PhD is available on site to address any concerns that arise. If Dr. Aupperle is unavailable or further evaluation is deemed necessary, psychiatrists Dr. Martin Paulus, and Sahib Khalsa will be available.

For patients who are at the LIBR facility and are deemed to constitute a serious risk for suicide, the LIBR policy requires that they be escorted by two clinicians to the onsite, 24-hour emergency facility at Laureate Psychiatric Clinic and Hospital (which is located about 100 yards from the LIBR facility). If participants refuse to be escorted to this facility and leave the LIBR premises, the study clinician will contact the Community Outreach Psychiatric Emergency Services (COPES – 918 744 4800), which is available 24 hours per day to send a mobile unit to the person's home.

For participants who develop serious suicidal ideation while not on the LIBR premises, these participants will be instructed to call 911 or to go to the nearest emergency room if they feel they are a threat to themselves or others. They will also be given the contact details of the Tulsa Community Outreach Psychiatric Emergency Services (COPES – 918 744 4800). If they report serious suicidal ideation while in another treatment center (e.g., 12&12 or WIR), they will be connected with emergency support staff at those treatment centers as well.

For participants who have clinical issues that do not reflect a psychiatric emergency, they will be given a telephone number where they can reach a LIBR clinician during those hours when LIBR is officially staffed by clinicians (weekdays between 0800 and 1700) and encouraged to call their treatment providers external to the study (e.g., treatment providers at 12&12 or WIR). For weekends and off-hours (evenings and nights) they are provided a second telephone number where they can reach the 24-hour per day on call service for LIBR, which is provided through the Call Center of Laureate Psychiatric Clinic and Hospital.

Upon study completion, patients who are currently under treatment by an external provider will be referred to their own clinician. Subjects who are dropped from study participation, or patients who complete the study and are not under the care of a clinician, will be provided a referral to a

psychiatrist or other mental health professional at one of the following clinics (regardless of the reported level of post-treatment symptoms):

Outpatient (insured)
Laureate Psychiatric Clinic and Hospital
6655 South Yale Ave
Tulsa OK, 74136
(918) 481-4000

Department of Psychiatry (sliding scale)
University of Oklahoma College of Medicine
Tulsa OK, 74136
(918) 619 4400

Outpatient (uninsured)
Tulsa Center for Behavioral Health (sliding scale)
2323 South Harvard Ave
Tulsa, OK, 74114
(918) 239 2100

Counseling and Recovery Services (sliding scale)
7010 South Yale Ave, Suite 215
Tulsa OK, 74136
(918) 492 2554

Family & Children's Services
650 S Peoria Ave
Tulsa, OK 74120
918-587-9471

CREOKS
4103 S Yale Ave Ste. B
Tulsa, OK 74135
918-382-7300

Inpatient
Laureate Psychiatric Clinic and Hospital
6655 South Yale Ave
Tulsa OK, 74136
(918) 481 4000

Individually tailored referrals will be made for participants who reside outside of the Tulsa region, so that they will be referred to psychiatric or substance use services that are located near their home or workplace.

2.3.2 KNOWN POTENTIAL BENEFITS

The interventions being utilized in the study (Positive Affect training; CBT) have been shown by previous research to enhance positive affect and/or to decrease negative affect for some people and we hypothesize that it may also be helpful for individuals suffering from substance use. All participants in this study will be assigned to receive an active intervention. Therefore, there is a possibility that participants will benefit from participation in this study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risk in this study is low, given that the assessment procedures are non-invasive and have minimal risks, all participants will receive the active intervention. The study will be the first to examining the feasibility and potential utility of targeting positive affect for individuals suffering from substance use and the intervention may benefit participants in the study. Thus, the minimal risks involved in the study are outweighed by the potential benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Phase 1: Examine the feasibility and acceptability of conducting AMP-A with individuals suffering from substance use disorder. Primary outcomes will include treatment completion rate and participant and clinician feedback on acceptability and feasibility and input from qualitative interviews with participants and clinicians.	Primary endpoint: post-intervention (within approximately 2 weeks after completing training). Secondary endpoint is approximately 3 months after completing the intervention.	Outcome to assess feasibility and acceptability.	N/A
For Phase 2, primary objective is to assess the impact of AMP-A versus CBT	Primary endpoint: post-intervention (within	Outcomes to assess potential clinical benefit of positive affect training.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
on positive affect.	approximately 2 weeks after completing training). Secondary endpoint is approximately 3 months after completing the intervention.		
Secondary			
The secondary objective(s) if Phase 2 is to explore the potential impact of AMP-A versus CBT on psychological well-beng and social connectedness.	Primary endpoint: post-intervention (within approximately 2 weeks after completing training). Secondary endpoint is approximately 3 months after completing the intervention.	Outcomes to assess potential clinical benefit of positive affect training.	Neural and behavioral responsivity to reward and positive affect processing (as assessed in the tertiary objectives)
Tertiary/Exploratory			
A tertiary objective is to explore the potential impact ofAMP-A versus CBT on self-reported anticipation, responsiveness, and recall of positive (non-drug) experiences and positive reinforcement motives to use alcohol, levels of alcohol use and anxiety and depressive symptoms, and neural responses during processing of positively valenced or alcohol-related cues.	Primary endpoint: post-intervention (within approximately 2 weeks after completing training).	Outcomes to further assess the clinical potential of AMP-A and the potential neural and behavioral mechanisms of clinical effects.	N/A

4 STUDY DESIGN

4.1 OVERALL DESIGN

Phase 1 of this study is a non-randomized, single-arm, single-site Phase I/II clinical trial conducted at Laureate Institute for Brain Research (LIBR) in Tulsa, OK. The primary objective for this study is to examine the feasibility and acceptability of conducting positive affect training with individuals suffering from substance use disorder. Primary outcome will include treatment completion rate; secondary outcome will include the score on a participant feedback questionnaire. We hypothesize that the majority of participants (>60%) will complete all 12 sessions of the intervention and that participant feedback concerning the intervention will be at least moderately favorable on average. Secondary outcomes will include qualitative input from participants and clinicians concerning the AMP-A protocol, which will be used for informing modifications to the intervention protocol. The exploratory objectiv is to explore the potential impact of training on positive and negative affect, symptom severity, and functional disability. We hypothesize that positive affect will significantly increase from baseline to post-intervention, while negative affect, alcohol-related craving, and functional disability will significantly decrease.

Phase 2 of this study is a randomized, two-arm, single-site Phase I/II clinical trial conducted at Laureate Institute for Brain Research (LIBR) in Tulsa, OK. The primary objective for this study is to examine the feasibility of conducting an RCT comparing positive affect training (AMP-A) to cognitive-behavioral therapy (CBT) with individuals suffering from co-occuring alcohol use disorder and depression or anxiety symptos. Primary outcome will include positive affect; secondary outcomes will include psychological well-being and social connectedness. Exploratory outcomes include self-reported anticipation, responsiveness, and recall of positive (non-drug) experiences and positive reinforcement motives to use alcohol, levels of alcohol use and anxiety and depressive symptoms, and neural responses during processing of positively valenced or alcohol-related cues. We hypothesize that activation with striatal and orbitofrontal cortex (OFC) regions to alcohol-UNrelated reward cues will increase from baseline to post-intervention, while striatal and OFC response to alcohol-related cues will decrease from baseline to post-intervention. Primary endpoint is post-treatment, secondary endpoint is 3 months post-treatment for self-report measures (neuroimaging will only be completed at pre- and post-treatment).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The current study is focused on further developing the AMP-A manual through piloting and clinician and therapist feedback, assessing the feasibility and acceptability of AMP-A, and examining the potential clinical utility of AMP-A through an RCT design with CBT as the comparator intervention. We hypothesize that AMP-A could have clinical utility for co-occuring alcohol use disorder and anxiety/depression symptom due to its direct targeting of reward and positive valence processing, which has often been identified as dysfunctional for individuals with substance use and mood and anxiety disorders. Given our primary objective of assessing feasibility and acceptability of the intervention in the Phase 1, we are not including a control group and all participants will receive AMP-A. In Phase 2, we will assess clinical utility of AMP-A through an initial RCT comparing AMP-A to CBT. The

results will be used to inform larger RCTs comparing the efficacy of AMP-A and CBT for comorbid AUD and depression/anxiety.

4.3 JUSTIFICATION FOR INTERVENTION

The positive affect intervention protocol employed in Phase 1 is based on previous work showing that a 12-session AMP-A training is sufficient for exerting clinical benefit in various populations, including HIV and anxiety populations (as well as a recent pilot we conducted with individuals experiencing co-occuring alcohol use disorder and depression/anxiety symptoms). The protocol is based specifically on the protocol used in these previous studies. Clinicians in the study will be trained by investigators (Dr. Charles Taylor) who have implemented this protocol in previous studies.

The 12-session AMP-A intervention to be employed in Phase 2 will be a slightly modified version of that used in Phase 1, as it will be modified based on quantitative and qualitative feedback from participants and clinicians. CBT interventions for comorbid AUD and anxiety or depression have been found to have small but significant beneficial affects compared to treatment as usual [41]. The CBT intervention used as a comparison is a modified version of a protocol being used for comorbid substance use and anxiety by collaborator, Dr. Wolitzky-Taylor at UCLA (R34-AA025364).

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, at least 7 intervention sessions, and the 3-month follow-up assessment.

The end of the study is defined as completion of the 3-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.]

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria (for both Phases 1 and 2):

(1) Age between 18 and 65 years old.
(2) Meeting diagnostic criteria for alcohol use disorder [42] according to the DSM-5.
(3) Significant depression or anxiety symptoms as indexed by scoring Patient Health Questionnaire (PHQ-9) ≥ 10 and/or Overall Anxiety Severity and Impairment Scale (OASIS) ≥ 8.
(4) Below normative levels of positive affect as indexed by PROMIS Positive Affect <50.
(5) Able to provide written informed consent.
(6) Have sufficient proficiency in the English language to understand and complete interviews, questionnaires, and all other study procedures.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

(1) Unwillingness or inability to complete any of the major aspects of the study protocol, including self-report or behavioral assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (i.e., being unwilling to answer individual items on some questionnaires or being unwilling to complete a behavioral task). In addition, the neuroimaging portion of the protocol will be optional.
(2) Non-correctable vision or hearing problems.
(3) No telephone or easy access to telephone.
(4) Diagnosis of Schizophrenia spectrum, other psychotic disorders, or bipolar I disorder.
(5) Active suicidal ideation with plan and intent to attempt suicide within the next month.
(6) Has a history of unstable liver or renal insufficiency; glaucoma; significant and unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.
(7) A positive test for drugs of abuse, including alcohol (breath test), cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, methadone, and oxycodone at the time of baseline assessments. Participants will be asked to refrain from using alcohol within 24 hours prior to assessment sessions and to refrain from using marijuana within 48 hours of assessment sessions.
(8) Current use of a medication or change in the dose or prescription of a medication within the 6 weeks prior to enrolling in the study that could potentially affect brain functioning (e.g., stimulants, anxiolytics, antipsychotics, mood stabilizers, anti-hypertensives). The current use of antidepressants (i.e., SSRIs) will not be excluded as long as the dose has remained consistent for 6 weeks prior to baseline assessment sessions. While individuals reporting use of benzodiazepines will be excluded; individuals with sporadic use (i.e., less than once per week) may be included, but will be asked to refrain from using within 72 hours prior to assessment sessions. Inclusion of individuals reporting other types of medications or supplements not listed or considered this far will be at the discretion of the PI according to evidence in the literature of it affecting brain function or brain blood flow.
(9) Taking drugs that affect the fMRI hemodynamic response (e.g., methylphenidate, acetazolamide, and excessive caffeine intake > 1000 mg/day) – Phase 2 only
(10) Concurrent engagement in psychosocial treatments that specifically target alcohol use disorder or mood/anxiety symptoms and began within 12 weeks of baseline assessments. Individuals concurrently receiving psychosocial treatments for other symptoms, or that are not specifically targeting symptoms (e.g., ongoing support groups) will not be excluded as long as the dose of treatment (i.e., frequency of sessions) has not changed significantly within 6 weeks prior to enrolling in the study.
(11) MRI contraindications (for those in Phase 2 opting into this portion) including: cardiac pacemaker, metal fragments in eyes/skin/body (shrapnel), aortic/aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio-stimulators (TENS unit),

persons who have ever been a professional metal worker/welder, history of eye surgery/eyes washed out because of metal, vision problems uncorrectable with lenses, inability to lie still on one's back for 60-120 minutes; prior neurosurgery; tattoos or cosmetic makeup with metal dyes, unwillingness to remove body piercings, and pregnancy – Phase 2 only

(12) Moderate to severe traumatic brain injury (>30 min. loss of consciousness or >24 hours posttraumatic amnesia) or other neurocognitive disorder with evidence of neurological deficits, neurological disorders, or severe or unstable medical conditions that might be compromised by participation in the study (to be determined by primary care provider).

(13) Severity of alcohol use disorder requiring more intensive treatment (i.e., intensive outpatient or residential), as determined by baseline assessments conducted by licensed clinicians.

(14) Given the current study involves development of the positive affect intervention, we will not enroll any special vulnerable populations (pregnant women, fetuses, neonates, prisoners, children).

5.3 LIFESTYLE CONSIDERATIONS

Other than the target of increasing positive affect related activities and decreasing use of alcohol, no additional changes in health lifestyle (i.e., diet) are implemented with patients as part of this protocol. Participants will not be asked to discontinue any current/ongoing medical care.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful treatment of a comorbid mental health disorder being excluded, or a change in treatment status. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment of study participants: Study participants will be recruited through other protocols ongoing at LIBR (Screening protocol (WIRB # 20101611; schedule Visits for NeuroCAPS protocol (WIRB #20183208), which recruit through community advertisements and referral from mental health and substance use clinics. Additionally, they will be recruited through study-specific radio and Facebook advertisements. The recruitment materials are provided with this protocol. We anticipate screening approximately 150 individuals to obtain the targeted 90 (20 in phase 1; 100 in Phase 2) participants that meet criteria for the study. Potential participants will be screened by phone or in-person using the WIRB screening protocol 20101611 to determine initial eligibility and baseline symptom severity. Patients will accordingly complete a diagnostic interview with study personnel using an abbreviated version of the Mini International Neuropsychiatric Interview (MINI V7.0)[43] and the computer-assisted Psychiatric Research Interview for Substance and Mental Disorders (PRISM-5)[44]. From the MINI, we will include

sections on Panic Disorder (PD), Social Anxiety Disorder (SAD), Posttraumatic Stress Disorder (PTSD), Generalized Anxiety Disorder (GAD), Obsessive-Compulsive Disorder (OCD) and Major Depressive Disorder (MDD) and several modules to provide further clinical information (Suicidality, Manic/Hypomanic Episode, Eating Disorders, and Psychotic Disorders). The PRISM-5 will be conducted to confirm in more detail the diagnosis of alcohol and other substance use disorders. In addition, the Overall Anxiety Severity and Impairment Scale (OASIS[45]), Patient Health Questionnaire (PHQ-9[46]) are conducted as part of the LIBR screening protocol to be used in identifying individuals meeting criteria for the current study. These questionnaires may be repeated in the current protocol to confirm that participants still meet criteria for the study. They additionally will complete screening to determine that sensory processing (i.e., vision, hearing) are sufficient to complete the study protocol. All participants (whether or not they meet eligibility criteria following the baseline session) will be provided with community mental health referrals as needed.

Provisions for recruiting non-English speaking participants: Non-English speaking subjects will not be recruited.

Gender/Minority/Pediatric Inclusion for Research: Women and minorities will be included in the study without prejudice according to their representation in the study population. All efforts will be made to ensure that our subject population closely resembles the gender, ethnic and racial composition of the Tulsa region and the programs we are recruitingfrom (i.e., Women in Recovery and 12&12 programs.) Children are not included in this protocol due to its focus on identifying the feasibility of this intervention for adults with SUDs.

Measures to increase retention:

- At the baseline visit, we will collect detailed contact information for each enrolled subject, including email, home/work/cell phone, and permanent address. In addition, for each subject we will collect contact information for 1-2 relatives, partner, and/or friends.
- Transportation (e.g., cab fare) will be provided to/from sessions for those who indicate this is an obstacle to participation.
- Subjects will be offered their brain pictures printed on a keepsake item (e.g., mousepad, t-shirt, mug) at study completion.
- All follow-up time points will be preferably completed in person. However, if absolutely necessary, subjects will be offered the opportunity of completing them over the phone rather than having them withdraw from the study.
- Participant will be asked during baseline assessment the likelihood of being able to complete all study sessions. The assessor will then discuss ay obstacles identified that may prevent completion and troubleshoot solutions. All participants will be provided text or voicemail reminders about each study session.

Payment for Participation. For baseline, post-training, and followup procedures, study compensation will involve $25 per hour for completion of self-report and behavioral assessment and $50 per hour for completion of neuroimaging procedures. For neuroimaging procedures in Phase 2, participants will be provided an additional $0-$55 per session based on MRI task performance. Participants will be compensated $30 for completion of each follow-up assessment session. Compensation will be prorated per half hour for those who do not complete all aspects of the protocol. Participants will not be compensated for their time spent in treatment sessions, only for the assessments completed.

Payments will be provided to subjects via the ClinCard System, a global electronic payment technology (similar to a debit card). After each visit, subjects will have their account credited with the amount paid for their participation in the study.

For compensation of assessments and feedback questionnaires completed at the intervention sessions, participant will be provided $5/session. This will be provided regardless of whether the participant attends a session (as surveys may be sent via a link to be completed online). No compensation will be provided for procedures associated with the intervention itself.

For completion of focus groups, therapy participants will be provided $50 and be provided snacks during the focus groups.

Clinicians will be recruited from external clinics to review the manual and provide input during continuing education seminars we provide. Food and beverages will be provided but no payment will be provided to clinicians.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Following completion of baseline assessments, participants in Phase 1 will be asked to complete 12 sessions of the positive affect intervention (AMP-A), conducted once or twice weekly and with each session lasting 1 - 1.5 hours. If the content of sessions is too much to cover for any one client, the intervention may be extended to 14 sessions as needed. Participants in Phase 2 will be randomized to complete either (1) a slightly modified 12 session AMP-A intervention or (2) a 12-session CBT intervention, each conducted once or twice weekly and with each session lasting 1 - 1.5 hours.

In both phases, participants will be expected to complete all intervention sessions within 16 weeks of starting the first session. Each session will be completed as individual therapy sessions (i.e., one-on-one with a therapist). Therapy sessions may be delivered via videoconferencing (e.g., using Zoom, GoTo, or similar technologies). Participants will be informed that confidentiality of information shared during videoconferencing cannot be guaranteed. Participants will be allowed to participate via audio only connections as requested.

AMP-A will involving positive emotion enhancement exercises established in prior studies, including noticing and amplifying positive emotions, practicing gratitude, engaging in acts of kindness, and pleasurable or meaningful activities, identifying strengths and values, being optimistic, engaging in activities meant to make others happy, and living life to its fullest[15]. We will use the protocol developed by Taylor et al.[15] with modifications to specifically address alcohol use, based on previous work[47], and further modified based on our prior pilot study. The general structure of each session will follow standard cognitive behavioral treatment regimens as follows: (1) meet with clinician to review completion of the prior week's exercises, including self-monitoring forms of emotions and exercise completion; (2) identify and troubleshoot any issues that arose during exercise completion; (3)

introduce material about a new positive emotion enhancement activity; (4) identify concrete exercises to implement for the upcoming week. The manual to be used in this study is included with the protocol. The intervention manual is provided with this submission.

The CBT intervention to be implemented in Phase 2 will consist of 12 sessions that include motivational interviewing and cognitive-behavioral strategies established in prior studies[41], including evaluating the consequences of alcohol use, discussing high-risk situations and triggers, conduct self-monitoring of the relationship between thoughts, emotions and alcohol use, identification and building of useful lifestyle changes, problem solving strategies, communication skills, and social support.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The interventions will be delivered by a licensed doctoral or master's level clinician or a therapist in training (i.e., clinical psychology post-doctoral fellows or graduate students). Each therapist will complete in-person or video-recorded workshops in each intervention (conducted by Charles Taylor, PhD for AMP-A; by Kate Wolitzky-Tayzlor, PhD for CBT), read articles and manuals related to the treatment, and watch videos of previous therapy sessions conducted as part of the study as they are available. Each therapy session is video and audio recorded and at least 20% of sessions will be randomly selected for fidelity ratings by Drs. Taylor, Wolitzky-Taylor or their trainees. Skill acquisition and fidelity will be assessed by a fidelity form created by Drs. Wolitzky and Taylor specific to the intervention being delivered. Each therapist will attend weekly consultation and supervision with the PI and/or consultants, Drs. Taylor and Wolitzky-Taylor. Therapists will also be asked to complete surveys concerning therapist allegiance and expectancies.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Phase 1, all participants will receive the active intervention protocol focused on the positive valence system. Thus, there is no blinding or randomization.

For Phase 2, participants will be randomized to receive the positive affect intervention or CBT. Randomization will be stratified by sex (male/female). Assessors and participants will remain blind to intervention until after all baseline assessments have been completed.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

The participants will be asked to complete the Homework rating scale (HRS) at each intervention visit. In addition, copies of any homework sheets will be copied and kept with their research records to allow for evaluation of how well individuals complied with homework instructions. The therapists will also be asked to rate compliance to and engagement in the intervention after each session.

6.5 CONCOMITANT THERAPY

All participants will be permitted to continue their ongoing pharmacologic or therapy treatments. However, participants for whom changes in medication or therapy "dosage" are planned for the one week duration of the study will be excluded.

6.5.1 RESCUE THERAPY

Include content in this section if applicable, otherwise note as "N/A."

List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions about administration of rescue medications.

Example text provided as a guide, customize as needed:

The study site will not supply rescue therapy. In the case that participants experience significant worsening of symptoms over the course of the proposed intervention, their participation may be terminated and the participant would be referred to their current clinicians external to the study and/or be provided additional referrals to supplement the current treatments they are receiving external to the study.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Participants will be informed that participation is completely voluntary and they are allowed to withdraw from the study at any time. If a participant indicates they are unwilling to do the primary aspects of the study (e.g., neuroimaging or neurofeedback sessions), they will be excluded from participation. However if a subject discontinues from the neuroimaging session (after having begun the scanning session) but does not withdraw from the study – for example, due to experiencing psychological distress during scanning – they will be allowed to complete the remaining study as indicated by the study protocol.

Over the course of the study (each intervention session), suicide risk will be assessed using the QIDS[48] or BDI suicide ideation item, substance use severity will be monitored using PROMIS Substance Use[49], and anxiety and depressive symptoms will be monitored using the PROMIS Anxiety and Depression scales. If a participant reports any increase in suicidal ideation, use of substances of abuse, or significant worsening of mental health symptoms (i.e., increase of >5 on the PROMIS total T scores), referrals will be provided as needed and further assessment will be conducted to determine whether it is in the participant's best interest to withdraw from the study.

At the time of study intervention discontinuation or study withdrawal, the reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue will be documented. If a participant withdraws, they will be asked to complete the Withdrawn Questionnaire to indicate reasoning for withdrawing.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance (attends less than 7 of the therapy sessions; is unable to attend a therapy session for more than 2 weeks consecutively)
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study (see previous section for description of assessments to monitor for potential increase in suicide risk and worsening clinical symptoms).
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a scheduled follow-up visit and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return for a follow-up assessment session:

- The site will attempt to contact the participant, ascertain if the participant wishes to and/or should continue in the study, and as needed, reschedule the missed visit (within one week of the originally scheduled date).
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls, 3 text messages, and, if necessary, an email or certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- If there is any concern about the safety of a participant lost to follow-up (e.g., due to previously recorded suicidal ideation) and study staff are unable to reach the individual, then confidentiality may be broken and the COPES hotline (918-744-4800) may be called to help ensure safety of the participant.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Self-report and Interviewer Measures:

Participants will be asked to complete interview and pencil-and-paper questionnaires related to clinical symptoms, traits and personality characteristics, daily life function, and medical and mental health history. These questionnaires are listed below. The time points in which all measures are administered is provided in Section 1.3, Schedule of Activities. Pre-intervention self-report and interviewer-based assessments are estimated to take approximately 3-4 hours to complete in total. Post-intervention self-report assessment is estimated to take approximately 2-3 hours total, as will th 3-month time point. Weekly assessment measures are estimated to take 15-20 minutes to complete. If there are participants who are only able to complete part of the intervention (i.e., only able to attend a few of the sessions) either due to their own wish to terminate or due to exclusion criteria or clinical concerns (described above), they will only be asked to complete survey sessions for weeks that they attend. In addition to the measures listed in Table 1, participants in Phase 2 of the study will be asked to complete the therapy preferences questionnaire (submitted with protocol) to ascertain which therapy they would have preferred to receive (AMP-A or CBT). Participants will also be asked to completed the Withdrawn Questionnaire and Cultural Acceptability of Treatments Survey (CATS) and the Withdrawn Questionnaire after they complete or withdraw from treatment. If treatment is conducted via zoom, participants will also be asked to complete the TeleHealth Feedback Form.

For Phase 1, focused on furtherdeveloping and refining the AMP-A protocol, we will also will include open-ended questions for focus groups conducted with participants who completed the preliminary version of AMP-A in our prior feasibility study (LIBR Protocol #2019-010-02), participants who complete AMP-A as part of Phase 1 of the current study, and substance use clinicians (N=5-10 that have implemented AMP-A; N=5-10 who are current clinicians in outpatient substance use disorder clinics and have been familiarized with AMP-A). The focus groups will use open-ended questions to obtain information concerning what was most/least helpful and what could be modified to optimize clarity and relevance for AUD+ANX/DEP (including content, materials, and sequencing). Focus group questions are included with this IRB application. The “End of Session” questionnaire[50] will also be completed by all participants in the proposed Phase 1, after each therapy session, which will ask them to rate what was most/least helpful during that session, whether the session content was clear, and how the session content could be made more helpful.

For phase 2, participants will also have the option of completing pre- and post-neuroimaging sessions, each of which is estimated to take approximately 3 hours total (1.5 hours of scanning, with ~.5 hours before and after for preparation and instructions and post-task ratings).

Table 1. Self-Report measures for each time point (Phase 1 and 2)

Domain	Measure	Screening	Pre Therapy	During Treatment	Post Treatment	Follow-Up Time Point (3 mo)
Demographic Update	Demographics Form - Update		X		X	
	Medical History Update		X		X	
	Tulsa Life Chart – web-based application		X		X	
	Patient Health Questionnaire (PHQ-9[51])	x	X			
	Overall Anxiety Severity and Impairment Scale (OASIS [51]	X	x			
	Psychiatric Research Interview for Substance and Mental Disorders (PRISM-5)[44]		x			
	Mini-International Neuropsychiatric Interview (MINI)[43]	X				
	Columbia Suicide Severity Rating Scale (CSSR)[52]		x	As needed	x	
Substance Use	Customary Drinking and Drug Use Record (CDDR)[53]					
	Michigan Nicotine Reinforcement Questionnaire (MNRQ[54]; adapted for alcohol)		X		X	
	Alcohol Craving Questionnaire Short Form (ACQ-SF)[55]		X	Each Week	X	X
	Timeline Follow-Back[56]		X	Each week: # of drinks/ day	X	X
	PROMIS Alcohol Use[49]		X	Each Week	X	X
	PROMIS Alcohol Use – Negative Consequences[49]		X		X	X
	PROMIS Alcohol Use – Positive Consequences[49]		X		X	X
	PROMIS Alcohol Use – Negative Expectancies[49]		X		X	X
	PROMIS Alcohol Use – Positive Expectancies[49]		X		X	X
	PROMIS Nicotine Dependence[49]		X		X	X
	PROMIS Substance Use Severity[49]		X		X	X
	Alcohol Breathalyzer		X	Each Week	X	X
	Urine drug test		X		X	X
	PhenX Alcohol 30 Day Quantity and Frequency[57]	X				
Mental Health, Positive and Negative Valence	NIH PROMIS Scales for Positive Affect, Meaning and Purpose, Depression, Anxiety scales[49]		X	Each Week	X	X
	Quick Inventory of Depressive Symptomatology (QIDS)QIDS-SR[48]		X		X	X
	Mood and Anxiety Symptom Questionnaire-Short form (MASQ)[58]		X		X	X
	Traumatic Events Questionnaire (TEQ)—update[59]		X		X	
	PTSD Checklist (PCL)[60]		X			
	PROMIS Anger, Perceived Stress, Self-Efficacy, and General Life Satisfaction scales[49]		X		X	X
	Sheehan Disability Scale (SDS)[61]		X	Each Week	X	X
	UPPS Impulsive Behavior Scale[62]		X		X	X
	Columbia Suicide Severity Scale[52]		X		X	
	Positive and Negative Affective Schedule (PANAS-X)[63]		X		X	X
	Approach Avoidance Temperament Questionnaire[64]		X		X	X
	NIH toolbox Friendship and Loneliness[49]		X	Every 2-3 sessions	X	X
	Snaith—Hamilton Pleasure Scale (SHAPS)[65]		X		X	X
	Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)[66]		X		X	X
	Temporal Experiences of Pleasure Scale (TEPS[67]		X		X	X
	Social Connectedness Scale – Revised (SCS-R)[68]		X		X	X
	Patient Health Questionnaire (PHQ)[46]	X				
	Overall Anxiety Severity And Impairment Scale (OASIS)[45]	X				
	Savoring Beliefs Inventory (SBI)[69]		X		X	X
	Responses to Positive Affect Scale (RPA)[70]		X		X	X
	Emotion Values[71]		X		X	X
	MINI Checklist[72]		X			

Health-related questionnaires	Pittsburgh Sleep Quality Index[73]	X		X		
	International Physical Activity Questionnaire (IPAQ)[74]	X		X		
Intervention	Session Attendance		Each Week	X		
	Credibility/Expectancy Questionnaire[75]	X	Session 2			
	Homework Rating Scales – Patient[76]		Each Week			
	Homework Compliance Rating – Therapist[76]		Each Week			
	Working Alliance Inventory[77] (therapist and client)		Every 3-4 sessions			
	Withdrawn Questionnaire (included)		if withdraws			
	Adherence and Acceptability Scale (AAS)[78]	X	Every 3-4 sessions	X		
	Distress/Endorsement Validation Scale (DEVS)[79]	X	Every 3-4 sessions	X		
	Therapy Improvement Scale (included)			X		
	Treatment Follow-up Form (included)					X
Feedback Surveys	Telehealth Usability Questionnaire [80]			X		
	End of Session Questionnaire – Participant		Each week			
	Study Feedback Survey	X		X		
Minority stress and discrimination	Racism and Life Experiences Scales – Daily Life Experiences (RaLES-DLE) [81]	X				
	Multigroup Ethnic Identity Measure – Revised (MEIM-R) [82]	X				
	Cultural Acceptability of Treatment Surveys (CATS)[83] [84] - modified			X		
	Heterosexist Harassment, Rejection, and Discrimination Scale (HHRDS) [85]	X				

Neuroimaging Session

Scanning procedures will be conducted at two time points (pre- and post-intervention) for the current study. Prior to scanning, each subject will complete (1) self-report assessment of sleepiness (Karolinska Sleepiness Scale[86]) and state affect (Positive and Negative Affect Schedule [PANAS][63]), (2) review of fMRI procedures and MRI safety screen and assessment of handedness (Edinburgh Handedness Inventory[87]), (3) the participant last use summary (PLUS; provided with this submission). In addition, all participants will complete urine drug tests and breathalyzer tests to confirm they are not under the influence of alcohol or recreational drugs at the time of assessment and all females of child-bearing age will complete a urine pregnancy test. Participants will be scanned in a GE Discovery MR750 3.0 Tesla scanner (GE Medical Systems) at the Laureate Institute for Brain Research. The scanner is equipped with system-standard 8- and 32-channel brain coils. The multi-element brain arrays are highly sensitive MRI signal detectors offering vastly improved sensitivity for the detection of functional activation induced signal changes at high spatial and temporal resolutions, as well as anatomical MRI at very high spatial resolutions. The receivers allow for shorter readout times and reduced signal distortions and ventromedial signal dropout.

MRI preparation: MRI eligibility will be confirmed prior to entry into the scanner. The subject will be asked to remove all ferromagnetic items. The subject will be trained on all fMRI tasks and given time to practice. If the subject requires vision correction, he or she will be fitted with plastic glasses closely matching his optic prescription. A urine sample will be collected for a pregnancy test (for female participants). Earplugs will be inserted prior to entering the scanner. The audio system will be explained so the participant will know how to communicate with the scanner operator and headphones will be placed over the ears. The subject will be reminded of the importance of staying still in the scanner. To

minimize motion, the participant's head will be stabilized with a specially designed pillow under the neck and wedge-shaped cushions between the sides of the head and head-holder. Padding will be arranged to maximize comfort and a pillow will be placed under the knees to provide lower back relief. The MRI operator will put the head coil in position over the participant's head, localize the head position on the scanner, and ensure that the subject can fully view the display screen at the end of the scanner gurney, where task images will be displayed, by looking in the mirror directly above their eyes. The response box will be positioned in the subject's dominant hand and the subject will test the buttons. In the subjects' non-dominant hand, the pulse oximeter is placed on one finger and the subject is provided the emergency squeeze ball. Once the subject is comfortable, the gurney will move into the magnet. The MRI technician will secure the scan room door, dim the scan room lights, and communicate with the participant through the console. In addition to the functional scans listed below, there will be localizer, anatomical, and diffusion tensor imaging scans to obtain data concerning white/gray matter structure and volume, as well as white matter integrity. In addition, there will be one "resting state" scan in which participants are asked to look at a fixation cross on the screen and to not think about anything in particular. At the completion of the MRI session, subjects will complete the Karolinska Sleepiness Scale (KSS)[86] and Positive and Negative Affect Schedule – short form (PANAS)[63].

Physiological measures:

Physiological noise estimation and correction will be acquired through physiological monitoring of pulse rate using a finger-tip pulse oximeter throughout the MRI session. An elevated pulse rate will generate a query from the scanner operator. Pulse rates above 90 beats per minute will prompt the scanner operator to ask participant if they are okay. The pulse oximeter sensors are connected to an In Vivo physiological monitoring system. Collection of physiological data during the scan will be linked to the behavioral tasks by a pulse marker generated by the magnet console and recorded on the physiological tracings. The concurrent information on pulse rate will be used to remove physiological fluctuations from the fMRI data.

Tasks to be conducted during fMRI:

Reward Processing Task: To measure behavioral and neural responses to rewards and losses, participants will complete the monetary incentive delay task (MID), a well-established measure of reward processing[88 89]. This task dissociates anticipatory and consummatory phases of reward processing and has been shown to reliably activate brain regions implicated in regulating approach-related response tendencies and reward sensitivity (e.g., ventral striatum). On each trial, participants are given a cue indicating potential reward (circle), loss (square), or no reward/loss (circle or square). In order to receive a specified reward or avoid a loss, participants are required to press a button within a certain duration of time (adapted for individual participant reaction times) following presentation of a white square (target cue). Task difficulty, based on reaction times collected during a practice session, is set such that each participant should succeed on ~66% of trials. The degree of potential reward or loss is varied on three levels indicated by the number of horizontal lines in a cue, i.e., one line indicates the lowest reward value (no reward), two lines an intermediate reward, and three lines the highest reward. For the MID task, participants can gain or lose points and earn an average of $30 (up to $55). The

primary outcomes of interest will be: (1) anticipation of reward vs. no-reward, (2) receipt of reward outcomes vs. no-reward outcomes, (3) anticipation of loss vs. no-loss, and (4) receipt of loss outcomes vs. no-loss outcomes. The Monetary Incentive Delay Task will take about 18 minutes to complete.

Alcohol Cue Reactivity Task: In the Alcohol Cue Reactivity (DCR) paradigm, participants are presented with blocks of cues that are either alcohol-related (beer, wine, and/or liquor) or neutral. Images are taken from the previously validated databases[90], International Affective Picture System (IAPS[91]), or stimuli used in previous fMRI studies related to alcohol cue processing[92]. Each image will be presented for approximately 5 seconds, with fixation cross presented on the screen in between. After each block of pictures (i.e., 20-30 seconds of pictures, or 4-6 pictures), participants are asked to rate their craving for alcohol on a one to four scale, with one being "No Urge" and four being "Strong Urge" to use. Total scan time for this task is approximately 10 minutes. At the beginning and end of the imaging sessions, subjects will complete a Karolinska Sleepiness Scale (KSS)[86].

8.2 SAFETY ASSESSMENTS

Safety and tolerability of the intervention will be assessed using the participant feedback and acceptability questionnaires mentioned above (DEVS[79], AAS[78]), and the clinical symptom measures and interviews discussed in previous sections. Any spontaneously reported events will also be recorded by study staff.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A serious adverse event will be considered any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. requires inpatient 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. any other adverse event that, 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.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no additional treatment and do not interfere with the participant's daily activities to a greater degree than when enrolled in the study.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning that is somewhat greater in degree than when enrolled in the study.
- **Severe** – Events interrupt a participant's usual daily activity and may require a modification in their current treatment plan external to the study. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by the PI, Dr. Aupperle (licensed clinical psychologist) or Dr. Paulus (board-certified psychiatrist), based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Expected adverse reactions are AEs that are known to occur for the study procedures being studied and The PI, Dr. Aupperle (licensed clinical psychologist) or Dr. Paulus (board-certified psychiatrist) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event may come to the attention of study personnel during study visits and interviews or electronic surveys. All AEs, not otherwise precluded per the protocol, will be captured on an adverse event form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates significantly at any time during the study, it will be recorded as an AE (see above sections concerning monitoring of suicidal ideation and mental health symptoms).

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The PI will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Unanticipated, serious adverse events will be reported to the IRB within 24 hours of the time project staff become aware of the incident. In addition, at yearly intervals throughout the course of the study, the IRB will receive a summary of all other safety-related reports including safety-related protocol deviations, treatment retention, and reasons for dropout. Should the protocol or data collection plans be amended as a result of adverse events or subsequent data review, the IRB will be notified and the

amendment approved prior to study amendment implementation. In addition, the participants will be notified of any significant new findings that develop during the course of research (e.g., other potential risks) that may affect their wish to continue participation in the study.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events will be reported to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

8.3.8 EVENTS OF SPECIAL INTEREST

Participants will be informed that study personnel are mandated reporters of child, dependent, or elder abuse and that confidentiality may be broken in these instances, or in the instance in which the participant is considered to be of danger to themselves or others.

8.3.9 REPORTING OF PREGNANCY

Individual participants will be informed of a positive urine pregnancy test and participation in the study will be discontinued.

8.4 UNANTICIPATED PROBLEMS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB, and to the funding agency within 48 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the funding agency within 7 days of the investigator becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

See above sections.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The proposed project would support the final stages of intervention development, including (1) incorporating qualitative and quantitative input from AMP-A participants and clinicians and (2) conducting a pilot randomized clinical trial (RCT) with the resulting, modified AMP-A intervention with N=60 individuals with AUD+ANX/DEP. The *central hypotheses* for the RCT are that (1) AMP-A will enhance functioning of the PVS compared to CBT—a first-line treatment for AUD that has small effects on the PVS—and (2) PVS improvements will be associated with reductions in alcohol use.

Aim 1: Further develop and refine AMP-A (Stage 1a) using an iterative process, guided by prior work and feedback from AUD+ANX/DEP patients who complete AMP-A (N=8) and clinicians who have experience in treating the target population and/or with delivering AMP-A. H1: Participant and clinician feedback will reflect a high level of acceptability and satisfaction with AMP-A.

Aim 2: Determine the effects of AMP-A vs. CBT on the PVS (Stage 1b). Based on preliminary data and extant findings, we hypothesize that compared to CBT, AMP-A will result in greater increases in self-reported positive affect (primary outcome; H1A) and social connectedness, psychological well-being

(secondary outcomes; H1B). Exploratory PVS outcomes expected to improve following AMP-A vs. CBT include anticipation, responsiveness, and recall of positive (non-drug) experiences and positive reinforcement motives to use alcohol (H1C).

Aim 3: Relate changes in PVS function to the degree of clinical improvement. Because PVS dysfunction is implicated in the maintenance of AUD and ANX/DEP, we hypothesize that increases in the PVS (e.g., positive affect) will be associated with reductions in alcohol use (primary clinical outcome; H2A) and anxiety and depression symptoms (secondary clinical outcomes; H2B).

9.2 SAMPLE SIZE DETERMINATION

Because this project focuses initially on the development of an intervention, sample size determination (N=60 randomized) was primarily guided by appropriateness for pilot study objectives and ability to inform future fully powered studies[93 94]. Our proposed N=60 conforms to guidelines in the literature for pilot studies (typical recommendation is 30/group[93 94]) and should provide (a) useful data regarding intervention feasibility and (b) data characteristics/distributions appropriate to examining data- and analysis-related procedures, variability, and potential effect sizes. The minimum effect size detectable in the proposed study was calculated based on a 2-sample, 2-sided t-test to compare differences in mean change in positive affect by treatment arm (alpha=0.05). Assuming N=52 evaluable participants (26 per group; assuming 10% lost to follow-up; i.e., subjects who provide no post-randomization outcomes), we have 80% power to detect a Cohen's d=0.79 effect size of change between the treatment arms. Our ability to detect medium to large effect sizes in the proposed study is supported by observations that prior CBT trials for AUD found small within-CBT improvements in positive affect (d range = 0.10-0.14)[95 96], whereas our preliminary work in ANX/DEP samples found large within-AMP improvements in positive affect (d range = 0.89-1.16).

9.3 POPULATIONS FOR ANALYSES

Both intent-to-treat analyses (including all participants with baseline and at least one post-baseline time point completed) and completer anlaysis (including all participants who completed the AMP-A or CBT interventions) will be completed.

9.4 STATISTICAL ANALYSES

Aim 1: Protocol Development and Acceptability.

For focus groups, analysis will be conducted as has been done in Co-I Dr. Wolitzky-Taylor's prior treatment development studies with co-occurring substance use and ANX/DEP[97]. Themes described in the focus groups will be identified in transcripts[98]. After separately examining portions of the transcripts for examples that suggest processes, actions, assumptions, and consequences to extract these themes[98 99], we will reach consensus about which themes to examine in detail and a codebook will be developed[100]. Text management software will be used to mark instances where each theme occurs.[101] To increase confidence that all instances of a theme have been identified, 2 independent coders will read the material and mark codes[102]. Once themes have been marked, all text that pertains to each

theme will be summarized. For survey data ("End of Session" Questionnaires, AAS, DEVS), total and subscale scores will be summarized using descriptive statistics.

Aim 2: Outcome Analysis of PVS Outcomes.

Analyses will incorporate the modified intent-to-treat (mITT) principle. Participants who are randomized and attend at least one treatment session will be included in the mITT population. We expect missing data will be minimal for our primary outcomes, which will be assessed during each visit (<10% lost to follow-up), but higher (15-20%) for outcomes assessed only at pre- and post-treatment in the event that subjects who discontinue early are lost to follow-up or decline to complete post-assessments. Missing data will be evaluated. If the missingness is not random (non-ignorable), multiple imputation and/or propensity weighting will be considered, but will not be applied without extensive sensitivity analysis (for more details see Section 4.3 of the Clinical Trials Protocol Synopsis: Statistical Design and Power). As a sensitivity analysis we will report associations from complete- and imputed-data analyses. All results will be reported as point estimates (means and standard deviations) and interval estimates (95% confidence intervals). All tests of significance will be 2-sided. A *p*-value of 0.05 will be considered statistically significant. Analysis will be conducted using R statistical package. Demographic and baseline characteristics will be compared between study arms using Fisher's exact test for categorical variables, and a 2-sample t-test for continuous variables. Non-parametric alternatives will be considered, if parametric assumptions fail.

We will employ longitudinal modeling to measure trajectories over time, namely the MMRM approach. The primary dependent variable in the MMRM model is change from baseline in positive affect at each post-baseline visit. Independent variables in the MMRM model include treatment arm, visit (as a categorical variable), arm-by-visit interaction, positive affect at baseline and potential covariates of clinical interest (e.g., sex) that are simultaneously unbalanced at baseline (univariate $p<0.10$) and associated with the outcome (univariate $p<0.15$). To avoid inflation of Type I error, we will use permutation tests for inference. Hypothesis: Participants assigned to AMP-A will display greater increases in positive affect compared to CBT. Analagous methods will be applied to secondary and exploratory positive valence outcome measures, including NIH Toolbox Loneliness and PROMIS Meaning and Purpose (secondary) and TEPS, and SBI, MNRQ Positive Reinforcement from Alcohol, SHAPS, NIH Toolbox Friendship, and PROMIS General Life Satisfaction, (exploratory), to compare AMP-A vs. CBT from baseline to post-treatment. We will use Holm's adjustment to correct for multiple testing of secondary outcomes. There will be no correction for exploratory outcomes.

Aim 3: Relate changes in PVS function to Changes in Alcohol Use.

The primary clinical outcome of interest is alcohol use (TLFB number of drinking days in the past month). Linear regression models will be performed within the full sample to examine the association between change in positive affect (primary target engagement outcome) and change in alcohol use from baseline to post-treatment. We will explore whether the magnitude of the correlation differs by treatment arm - i.e., if the clinical outcomes of AMP-A seem to have a stronger relationship to changes in PVS as has been seen in our prior work in ANX/DEP[103]. Secondary clinical measures include TLFB average drinks per

drinking day (past month), PROMIS anxiety and depression; exploratory measures include TLFB percent of heavy drinking days (past month), PROMIS Alcohol Use, MNRQ Negative Reinforcement from Alcohol, ACQ-SF, and SDS. Methods analogous to the primary analysis will be applied to examine the association between change in primary (positive affect) and secondary target engagement outcomes (NIH Toolbox Loneliness; PROMIS Meaning and Purpose measures) and change in anxiety and depression, and secondary alcohol use outcomes.

Exploratory Aim: Explore the potential impact of training on neural reactivity during reward processing and alcohol cue processing.
Hypothesis 1a: Participants will have increased striatal responses during the MID task, from pre to post intervention. Hypothesis 1b: Participants will have decreased striatal responses during the processing of alcohol cues, from pre to post intervention. Analyses will include linear mixed models to investigate the time*treatment effects on average percent signal change in regions of interest (striatuma, vmPFC, anterior insula, anterior cingulate cortex, amygdala, and dorsolateral prefrontal cortex).

9.4.1 SAFETY ANALYSES

Acceptability and tolerability of the intervention will be assessed using the Adherence and Acceptability Scale[78] [104] and on the Endorsement and Discomfort Scale[79] and symptom rating scales described above. Spontaneously reported adverse events will also be documented by study staff. Adverse events will be recorded on the Adverse Event Form.

9.4.2 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.3 PLANNED INTERIM ANALYSES

9.4.4

N/A, other than the interim safety analysis described above.

9.4.5 SUB-GROUP ANALYSES

The impact of age and sex will be considered during analyses; given the small sample size, this will be evaluated more qualitatively than through specific subgroup analyses.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.7 EXPLORATORY ANALYSES

Exploratory analyses will be conducted to examine changes on the self-report measures, brain activation and connectivity, being collected that are not specified in the aims and hypotheses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The consent materials are submitted with this protocol, along with a "communication methods preferences form" that all participants will be asked to complete immediately after consent.

10.1.1.2 PROCESS AND DOCUMENTATION OF CONSENT.

Informed Consent will be obtained by members of the research team that have received training from the PI to obtain consent for this study. All participant interactions including consenting will be conducted in private interview/exam rooms.

Documented Consent: If the individual appears eligible, we schedule the documented informed consent process in order to conduct the Clinical Interview. Documented informed consent will be obtained once the consent has been reviewed and the individual agrees to participate using the appropriate approved informed consent document. Participants are provided a copy of the consent. All volunteers are of legal age and will be asked to give fully informed documented consent following consent procedures already approved. Care is taken to appropriately describe IRB-approved consent forms as documented by signature of the person giving permission and person obtaining informed consent. We review consents for completeness and file them in a locked file cabinet in a locked office. Consent may be obtained electronically using tablet computers, in which case a full copy of the informed consent will still be provided to the participant.

Measures to decrease coercion of participants: The researcher will remind the subject that participation is strictly voluntary and remind them that they have the right to withdraw at any time without penalty. In addition, it will be emphasized that their decision to participate or not participate in the research study will have no impact on their treatment and care provided by external treatment providers. Family members will be allowed to be present and discuss the consenting process with the participant if requested.

Subject Capacity: All subjects enrolled in this study will have the capacity to consent.

Subject/Representative Comprehension: During written informed consent, subject's understanding of the study protocol will be assessed using open-ended questions (e.g., Q: "Approximately how long will you be followed for the purposes of this study?" A: "approximately 10-16 weeks"). If they are unable to communicate understanding of the protocol, they will not be enrolled in the study.

Debriefing Procedures: None of the procedures used in this study involve withholding information from the subject.

10.1.1.3 CONSENT PROCEDURES AND DOCUMENTATION

See previous section.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Strategies to manage and protect the privacy of participants and confidentiality of research data:

We have instituted the following measures to protect the privacy of participants and confidentiality of research data:

- Data will be collected by LIBR staff who completed training in human subjects' research, HIPAA, and research integrity, on research data management, confidentiality and mandatory reporting, and project specific training on the protocol.
- To protect confidentiality, no personally identifying information will be coded on questionnaires, interviews, brain imaging data, or other study records. Further, subjects will not be identified in

any reports or publications. All de-identified hard-copy data will be stored in locked file cabinets in a locked office. A unique subject identification number is assigned to each participant, and linked to the study participant name in an electronic file managed in accordance with ISO 2700 standards as specified below with access limited the PI, Study Psychiatrist or Physician, and designated Study Coordinator.

- The original signed consents, screening form, locator form with contact information, the Research Privacy Form, and any other forms or papers containing personally identifiable information (PII) will be stored in a secured medical records room with access granted only to authorized study personnel.
- Electronic data will be stored securely on servers and databases accessible only to study personnel.

The Life Chart application, developed by LIBR, is accessed only within the LIBR network by participants and members of LIBR's research team. Life Chart data is stored behind a firewall through a password protected database on a secure server managed by LIBR that undergoes weekly security dynamic and static analysis scans through Veracode's platform under the HIPAA/Omnibus Act/HITECH/HITRUST policy. Veracode is used by over 2000+ companies in the world in making secure software (*www.veracode.com*).

A Certificate of Confidentiality will be obtained from NIH to further protect the subject.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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Co-investigators include: Martin Paulus, MD (LIBR Scientific Director and board-certified psychiatrist), Jennifer Stewart, PhD (LIBR Principal Investigator), Charles Taylor, PhD (collaborator and Associate Professor, University of California – San Diego), Kate Wolitzky Taylor, PhD (collaborator and Associate Professor, University of California – Los Angeles), and Evan White, PhD (LIBR Associate Investigator).

10.1.6 SAFETY OVERSIGHT

Given the low level of risk involved in this study, safety oversight will be under the direction of the PI and co-investigator and LIBR Scientific Director, Dr. Martin Paulus.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The Project PI and Dr. Martin Paulus (board-certified psychiatrist, LIBR Scientific Director) will have primary responsibility for monitoring the safety of the study and complying with the reporting requirements.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

The PI will be responsible for ensuring the quality of data collected. As needed, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the study staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the any measures or study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic database (RedCAP) will be consistent with the data recorded on the source documents. The RedCAP data system in which information is entered and securely stored includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Per NIH policies, study records will be retained records for a period of at least three years from the date of final Federal Financial Report (FFR) submission.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations will be addressed in study source documents, reported to the NIH program official. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB).

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Data Sharing Policy and Policy and as such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AAS	Adherence and Acceptability Scale
ACC	Anterior Cingulate Cortex

ACQ-SF	Alcohol Craving Questionnaire Short Form
AE	Adverse Events
AMP-A	Affective Modulation of Positivity for Alcohol Use Disorder
CBT	Cognitive-Behavioral Therapies
CDDR	Customary Drinking and Drug Use Record
CFR	Code of Federal Regulations
CM	Contingency Management
CNS	Central nervous system
COPES	Community Outreach Psychiatric Emergency Services
DAST	Drug Abuse Screening Test
DCR	Alcohol Cue Reactivity
DEVS	Distress/Endorsement Validation Scale
dlPFC	Dorsolateral prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
EPI	Echo-planar imaging
FFR	Federal Financial Report
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GAD	Generalized Anxiety Disorder
HIPAA	Health Insurance Portability and Accountability Act of 1996
HITECH	Health Information Technology for Economic and Clinical Health Act
IAPS	International Affective Picture System
ICH GCP	International Council on Harmonisation Good Clinical Practice
IRB	Institutional Review Board
ISO	International Organization for Standardization
KSS	Karolinska Sleepiness Scale
LIBR	Laureate Institute for Brain Research
MASQ	Mood and Anxiety Symptom Questionnaire-Short Form
MDD	Major Depressive Disorder
MI	Motivational interviewing
MID	Monetary Incentive Delay Task
MINI	Mini International Neuropsychiatric Inventory
MP-RAGE	Magnetization prepared rapid gradient-echo
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NAPS	Normative Appetitive Picture System
NCT	National Clinical Trial
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
OASIS	Overall Anxiety Severity and Impairment Scale
OCD	Obsessive-Compulsive Disorder
OFC	Orbitofrontal Cortex
OHRP	Office for Human Research Protections
PACS	Picture archiving and communication systems
PANAS	Positive and Negative Affective Schedule
PCL	Posttraumatic Stress Disorder Checklist

PD	Panic Disorder
PHQ-9	Patient Health Questionnaire
PI	Primary Investigator
PII	Personally identifiable information
PLUS	Participant Last Use Summary
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	Posttraumatic stress disorder
QC	Quality control
QIDS	Quick Inventory of Depressive Symptomatology
REDCap	Research Electronic Data Capture
SAD	Social Anxiety Disorder
SAE	Serious adverse events
SCS-R	Social Connectedness Scale - Revised
SDS	Sheehan Disability Scale
SHAPS	Snaith-Hamilton Pleasure Scale
SoA	Schedule of Activities
SP	Special publication
SPSRQ	Sensitivity to Punishment and Sensitivity to Reward Questionnaire
SUD	Substance Use Disorder
TENS	Transcutaneous electrical nerve stimulation
TEQ	Traumatic Events Questionnaire
UP	Unanticipated problems
US	United States
USB	Universal serial bus
VPN	Virtual private network
WIR	Women in recovery
WIRB	Western Institutional Review Board

11 REFERENCES

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