INSTRUCTIONS:

- *Use this "TEMPLATE PROTOCOL (HRP-503)" to prepare a study protocol outlining your research plan.*
- *Depending on the nature of your study, some major sections might not be applicable to your research. If so, simply mark as "N/A." For example, a simple survey might have many sections with "N/A." For subsections (e.g., 1.x or 8.x) you can mark as "N/A"if you are certain that the subsection is not applicable.*
- *Once the IRB/HRPP approves your submission, your latest approved version of the protocol will be stored in the IRB Protocol Management online system.*
- *If your research plan changes and you need to modify the protocol, please submit an amendment to Protocol Management with the requested modifications. Download your current protocol from Protocol Management and indicate the changes/revisions using the track changes feature in order to make review of the modifications easier to follow. If you are unable to use track changes, please create a new paragraph wherever you need to make a change, and indicate "Amendment: Date" before making a change to any section. Protocol management will store the older versions of your protocol if the IRB or HRPP staff need to compare them during the review.*

PROTOCOL TITLE:

Include the full protocol title.

Episodic Thinking and Alcohol Use

PROTOCOL NUMBER:

Include the number assigned in Protocol Management (verify this has been added before submitting protocol to HRPP).

IRB 22-358

PRINCIPAL INVESTIGATOR:

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FUNDING:

Sponsor(s): NIAAA
Funded already or in the proposal phase?: Funded.
Is Virginia Tech the primary awardee or the coordinating center of this grant or contract? If not, list the primary institution: Yes.

VERSION NUMBER/DATE:

Include the version number and date of this protocol. Versions should start at 1.0.

Version 11.0 - 10/15/2024

REVISION HISTORY:

Use this table to keep track of changes. Add more rows as needed.

Revision #	Version Date	Brief Summary of Changes (i.e., the different sections)	Consent Change?
1	08/04/2022	Added fMRI to S5; changed compensation to match time estimates	Yes
2	09/13/2022	Changed baseline monitoring drinking days to 4; changed language to may be pilots Consent: clarified time for S5 to match compensation and removed BACtrack calibration from precautions	Yes
3	10/3/2022	Updated RAM app description; updated compensation	Yes
4	11/30/2022	Updated inclusion criteria (ln(k) > -4.3	No
5	2/22/2023	Updated inclusion criteria to remove ln(k); moved the in lab screening assessments to post consent	No
6	4/24/2023	Updated recruitment methods; Changes in the consent to modify an inconsistency	Yes
7	7/19/2023	Updated recruitment methods to include Build Clinical; Changes to daily texting procedures; Updated compensation	Yes
8	9/26/2023	Changed language for exclusion criteria	No
9	2/26/2024	Changed eligibility criteria to lower the AUDIT requirement	
10	10/15/2024	Updated PI	No

Table of Contents

1.0 Study Summary

Study Title	Episodic Thinking and Alcohol Use
Study Design	Participants will be enrolled in the study, complete two sessions and undergo a one week baseline monitoring phase where they provide breath samples to assess for recent alcohol use and report their drinks per day. Following this baseline period, participants will complete and fMRI then be randomized to either the EFT or Control group. Participants will then complete two weeks of monitoring, where they provide a breath sample three times a day and report the number of drinks they consumed. Participants will then come back to the lab to generate new EFT/CET cues, then complete two more weeks of monitoring. After conclusion of the second intervention period, participants will complete a post intervention session, including an fMRI, and then a one month follow up one month after study completion.
Primary Objective	The primary outcome measures of this study are the extent to which EFT increases an individual's temporal window and decreases their alcohol valuation, compared to baseline and/or the CET condition.
Secondary Objective(s)	N/A
Study Population	Individuals with Alcohol Use Disorder
Sample Size	200
Research Intervention(s)/ Investigational Agent(s)	In the EFT intervention, participants will generate positive future events they are looking forward to at 7 time points in the future (1 day, 1 week, 1 month, 3 months, 1 year, 5 years, and 25 years). Participants will be reminded of these events using cues throughout the study and instructed to think about these cues as they make their decisions. In contrast, in the CET intervention, participants will generate positive recent past events that have happened to them at 7 time points from the recent past (last night from 7pm-10pm, yesterday between 4pm-7pm, yesterday between 1pm-4pm, yesterday from 10am-12pm, yesterday between 7am-10am, the night before last between 7pm-10pm, and evening before last between 4pm-7pm). Participants will be reminded of these events using cues throughout the study and instructed to think about these cues as they make their decisions.
Study Duration for Individual Participants	The total study is expected to take up to approximately 15 weeks.
Acronyms and Definitions	AUD = Alcohol Use Disorder

	CET = Control Episodic Thinking EFT = Episodic Future Thinking

2.0 Objectives

2.1 Describe the purpose, specific aims, or objectives of this study:

Test reinforcer pathology via manipulation of the temporal window in the real world.

2.2 State the hypotheses to be tested:

We hypothesize that an intervention involving episodic future thinking (EFT) will increase the temporal window and dynamically decrease alcohol valuation (i.e., consumption of alcohol in the real world, demand, and craving).

3.0 Background

3.1 Summarize the relevant prior research on this topic and gaps in current knowledge within the field of study:

Episodic future thinking (EFT) is based on the new science of prospection, which was first identified in a Science publication in 2007 and refers to pre-experiencing the future by simulation. Considerable evidence suggests that prospection is important for understanding human cognition, affect, motivation, and action. Individuals with damaged frontal areas, as well as individuals with alcohol use disorder (AUD), show deficits in planning prospectively. One systematic method to engender prospection is via EFT. EFT, as applied in our prior studies and in this proposal consists of having participants develop positive plausible future events that correspond to several future time frames (e.g., 2 weeks, 1 month, 3 months etc.). For each of these timeframes participants are asked to concretize the events (e.g., What are you doing? Who will be there? What will you see, hear, smell, and feel?).

3.2 Describe any relevant preliminary data:

We and others have used EFT to decrease delay discounting (DD) in individuals with AUD and smokers, as well as normal weight, overweight, and obese populations when

compared to the control condition, control episodic thinking (CET). Consistent with reinforcer pathology, EFT also reduces alcohol valuation in the purchase task among individuals with AUD and decreases alcohol consumption when EFT cues are texted to participants during a normal day over the course of 2 weeks.

3.3 Based on the existing literature, provide the scientific or scholarly rationale for and significance of your research and how will it add to existing knowledge:

In this study, we propose to test an intervention, EFT, which we hypothesize will decrease reinforcer pathology measures in the real world over a longer time frame than has been done previously; that is, EFT will decrease delay discounting, as well as alcohol consumption in the real world, demand, and craving compared to a control episodic thinking (CET) condition. Moreover, we hypothesize EFT will enhance activation in brain regions associated with prospection (e.g., hippocampus and amygdala) and the executive decision system (e.g., DLPFC). Not only will results from these analyses help demonstrate the mechanisms by which EFT operates, but also contribute to the understanding of EFT as a potential therapeutic behavioral intervention.

4.0 Study Endpoints

*4.1 Describe the primary and secondary **study** endpoints. See links below for discussion of study endpoints and how they may differ from study objectives. These are most common in clinical trials but are sometimes applicable to other types of biomedical research, as well as social, behavioral, or educational research. See link below for a discussion.*

https://docs.google.com/document/d/1Wocz7K7a0hCQJPPO_khh5l1SQQjhGDDGHzcOPRHR5Tw/edit?usp=sharing

Delay discounting: Change in discounting rates will be compared within-subjects between pre intervention and post intervention. In addition, differences in discount rates will be compared between groups (EFT and CET).

Alcoholic Drinks: Change in drinks per day and number of positive breath alcohol samples (BrAC) will be compared within-subjects between pre intervention and post intervention. In addition, differences in drinks per day and number of positive BrAC samples will be compared between groups (EFT and CET).

Alcohol Demand: Change in demand for alcohol will be compared within-subjects between pre intervention and post intervention. In addition, differences in alcohol demand will be compared between groups (EFT and CET).

Alcohol Craving: Change in alcohol craving will be compared within-subjects between pre intervention and post intervention In addition, differences in alcohol craving will be compared between groups (EFT and CET).

*4.2 Describe any primary or secondary **safety** endpoints. These should be included for all studies that are greater than minimal risk. (Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*:

This study's procedures are not more than minimal risk.

5.0 Study Design and Statistical Analysis Plan

5.1 Describe the basic study design/approach (e.g., qualitative study using five focus groups of first year students to describe assimilation into the university community; randomized controlled trial of a behavioral change intervention to increase dietary intake of whole grains; pre- post-test evaluation of new pedagogical techniques to improve adult literacy):

Participants will be randomly assigned to experimental or control groups, stratified by demographic characteristics (e.g., drinks per day and baseline delay discounting rates). Based on our 8 years of experience recruiting this population, we expect approximately 66% retention among eligible participants. Therefore, we will enroll approximately 200 participants in order to conclude with 76 completers. We plan to enroll more than our average attrition rate because of the increased screening procedures and the time demands of the study. Randomization will be stratified on demographic characteristics (e.g., drinks per day and baseline delay discounting rate). As a result, any differences observed in our primary hypotheses will not be confounded by these variables.

EFT group participants will be asked to think about and describe the most positive event that could realistically happen at a number of delays in the future (e.g., 1 day, 2 weeks, 1 month, 1 year, 5 years, 25 years). In contrast, participants randomized to the CET condition, will be asked to think about and describe the most positive event that occurred at a number of time points from the recent past (e.g., last night from 7pm-10pm, yesterday between 4pm-7pm, yesterday between 1pm-4pm, yesterday from 10am-12pm, yesterday between 7am-10am, the night before last between 7pm-10pm, and evening before last between 4pm-7pm).

5.2 Describe corresponding data analysis plan/approach (e.g., content analysis of focus group transcripts; descriptive analysis followed by linear regression modeling; nonparametric analysis of pre- and post-test measures):

Primary hypotheses: Our primary measure of temporal window is delay discounting (DD). Our primary measure of alcohol consumption is self-reported drinks per day. Participants are asked to report how many standard drinks they had for the previous 24 hours on each day of the 7 day baseline and 28 day intervention period. Our secondary measure of alcohol consumption is breath alcohol samples from the remote breathalyzer. Participants will provide three breath samples daily for the 7 day baseline and 28 day intervention period. Our primary measures of demand are alpha and Q0. Alpha and Q0 are two derived outcomes from a hypothetical alcohol purchase task. Participants are asked to report the number of standard drinks they might hypothetically purchase at increasing price points. Q0 is a measure of how many drinks a participant might purchase when drinks are free (price = $0). Alpha is a measure of the participants sensitivity to increasing prices (i.e., how quickly they decide to stop purchasing at higher prices). Our measure of craving is the Alcohol Urges Questionnaire (AUQ). Our measure of neural activity is BOLD response. We hypothesize that baseline BOLD response will be predictive of the efficacy of the intervention. We will model our primary outcome measures using a mixed-effects hierarchical model that includes day, time (pre/post intervention), and intervention group. A random effect will be included for each participant. We will include baseline BOLD response as a fixed-effect covariate in our analysis.

6.0 Setting

6.1 Describe the sites or locations where your research team will conduct the research. Consider each of the items listed below:

- *Identify where your research team will identify and recruit potential subjects.*
- *Identify where the team will perform the research procedures.*
- *Describe the composition and involvement of any community advisory board(s).*
- *For research conducted in other locations, describe:*
  - *Site-specific regulations or customs affecting the research at those locations.*
  - *Local scientific and ethical review structure at those locations. Examples include work in other cultures or ethnic groups (within or outside of the U.S.) and work with churches. The HRPP will provide additional guidance for international research.*

Location of Recruitment:

Participants will be recruited from the Roanoke-Blacksburg community via posted flyers, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). To the extent possible, we will attempt to minimize obstacles to participation. For example, travel barriers will be addressed by providing transportation or parking costs to participants, and scheduling barriers will be minimized by offering a flexible session schedule.

In addition, we will partner with BuildClinical to accelerate enrollment. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They have worked with IRBs in the US to ensure adherence to all the appropriate guidelines and procedures. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information is HIPPA compliant and keeps potential participant information private.

Location of study:

All methods and measures will be conducted using standard operating procedures in the Addiction Recovery Research Center and LaConte Laboratory at the Fralin Biomedical Research Institute at VTC. All staff (including recruitment staff) will be provided with cultural sensitivity training. We have a history of successful recruitment of drug and alcohol users. All participants will enroll on a voluntary basis and sign an IRB-approved consent form prior to study participation.

7.0 Study Intervention(s)/Investigational Agent(s)

7.1 Describe the study interventions (including behavioral interventions) and/or investigational agents (e.g., drugs or devices) to be used in this study. Consider each of the items listed below:

- *Drug/Device Handling: If the research involves drugs or devices, describe your plans to store, handle, and administer the drugs or devices so that they will be used only on subjects, and only by authorized investigators.*

- *Describe whether any of the following will be used: microwaves, X-rays, DEXA scans, general anesthesia, or sedation*
- *If control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference the SOP in this section.*

Episodic Future Thinking: Participants will generate positive future events they are looking forward to at a number of time points in the future (e.g., 1 day, 2 weeks, 1 month, 3 months, 1 year, 5 years, and 25 years) at S3 and S4. Participants will be reminded of these events using cues throughout the session and instructed to think about these cues as they make their decisions. These cues will be the cues texted to them over the monitoring phase. Questions about the cues (e.g., "How vivid is this cue to you, on a scale from 1-5", "How real does this cue feel to you, on a scale from 1-5", etc.) will be also texted to the participants together with the cues. This procedure is to ensure the participants are actually reading their cues when texted to them. A list of question examples is attached in the supporting documents.

Control Episodic Thinking: Participants will generate positive recent past events that have happened to them at a number of time points (last night from 7pm-10pm, yesterday between 4pm-7pm, yesterday between 1pm-4pm, yesterday from 10am-12pm, yesterday between 7am-10am, the night before last between 7pm-10pm, and evening before last between 4pm-7pm) at S3 and S4. Participants will be reminded of these events using cues throughout the session and instructed to think about these cues as they make their decisions. These cues will be the cues texted to them over the monitoring phase. Questions about the cues (e.g., "How vivid is this cue to you, on a scale from 1-5", "How real does this cue feel to you, on a scale from 1-5", etc.) will be also texted to the participants together with the cues. This procedure is to ensure the participants are actually reading their cues when texted to them. A list of question examples is attached in the supporting documents.

7.2 List the name of all drugs (including any vitamins, supplements, herbs, or nicotine) to be used in the study. Indicate whether they have FDA approval, and list any limitations for their use:

N/A

7.3 List all devices, how they will be used, their purpose in the study, and if they will be used in a manner consistent with their approved uses. If they

will be used in ways that are not yet FDA approved, indicate whether they need an IDE or a determination that they are exempt from the IDE Determination. If a determination of significant risk or non-significant risk is needed for any of the devices, include the researcher's recommendation for each of those devices:

We are using a device (BACtrack Mobile breathalyzer) that is under the purview of the FDA, but we have not and we believe we are not required to obtain an IDE from the FDA for the use of this device because it meets the requirements for IDE exempt in 21 CFR §812.2(c)(3).

These requirements are as follows:

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Our use of this device is noninvasive, does not require an invasive sampling procedure that presents sufficient risk, does not by design or intention introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another procedure. Regarding point (iv) specifically, the only diagnosis under consideration in our study is alcohol use disorder, but we are not using the device to diagnose this disorder. We are using other established questionnaires and assessments as uploaded to the IRB to assess whether someone has the symptoms of alcohol use disorder, and the breathalyzer device is only being used to monitor ongoing alcohol use. Ongoing alcohol use by itself is not sufficient to diagnose alcohol use disorder and we are not using it for this purpose. Instead, we are periodically readministering behavioral diagnostic surveys to determine if incidence of alcohol use disorder symptoms change throughout the study.

The BACtrack Mobile breathalyzer is FDA cleared but confidential, which is why it does not appear in a search. The 510(k) number is regulated confidentially, but the listing number is D085312 and the premarket submission number is K090067. Additionally, the

BACtrack Mobile is not approved to treat or diagnose a disease, but we do not intend to use it for this purpose. The use of the BACtrack Mobile is non-diagnostic in this study but accurate enough to measure BAC remotely.

The team will be using the BACtrack Mobile for this protocol. The 510(k) number (i.e., K090067) is the same as the other model and this information is confidential. Our contact at BACtrack confirmed that the device is FDA cleared and also provided the below and attached information.

Attached you will find a review from Counterpoint Journal, which compares BACtrack Mobile to police and industrial/DOT handheld units: https://www.counterpoint-journal.com/

Additionally, here's a link to an abstract from researchers at the Perelman School of Medicine at the University of Pennsylvania. While BACtrack performed best relative to a police-grade breathalyzer (the Intoxilyzer 240), we've also been informed BACtrack outperformed the Intoxilyzer 240 when comparing BAC results to a blood test. http://injuryprevention.bmj.com/content/23/Suppl_1/A15.1

Additionally, here are media reviews of BACtrack Mobile compared to police units: https://well.blogs.nytimes.com/2015/12/21/turning-your-smartphone-into-a-breathalyzer/ https://www.nbclosangeles.com/investigations/Do-It-Yourself-Breathalyzers-368687801.html

Functional magnetic resonance imaging (fMRI) is a technique that noninvasively measures correlates of neural activity (Ogawa et al., 1992) and allows the identification of cerebral substrates associated with processes that shape human awareness and perception, such as visual, auditory, emotional, somatosensory. Unlike positron emission tomography (PET), fMRI does not require the injection of intravenous tracers or exposure of the subject to any ionizing radiation. Another advantage of fMRI is that multiple scans can be obtained in a single (or multiple) imaging session(s), which allows for acquisition of 1000 scans over a few minutes, while a PET study is limited to 16 scans over 2 hours (Friston et al., 1995; Buckner et al., 1996). Thus, fMRI allows us to capitalize on increased temporal resolution and repetition of conditions capabilities in an effort to study brain function.

The MRI scanner we will use has a magnetic field of approximately 3.0T. Scanners with a 3.0T field strength have been approved for clinical use by the FDA and are currently available for routine clinical applications.

The MRI imaging experiments will be performed on a Siemens 3T scanner, and we will only use structural and functional sequences that conform to FDA guidelines for specific absorption rate (SAR) of radio frequency energy. SAR is limited by both hardware and

software checks on the MRI scanners. A standard head coil will be used to collect the MR data.

The hCG Urine Pregnancy Test Cassettes is a test kit for the determination of hCG (Human Chorionic Gonadotropin) in urine specimens. This test kit is used to obtain a visual qualitative result for early detection of pregnancy. These tests are Standardized with WHO International Reference Standard and FDA Cleared & CLIA Waived.

The QuickTox 5-panel drug test dip card delivers results within 5 minutes. The QuickTox is FDA-approved and CLIA-Waived. The 5-panel test detects benzodiazepines, marijuana, opiates, meth, and cocaine.

7.4 If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

- *Identify the holder of the IND/IDE/abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

N/A

8.0 Procedures Involved

8.1 Describe and explain the study design:

Participants will be enrolled into the study and undergo the informed consent process (including signing of the informed consent) during Session 1. Session 2 will be baseline assessments, this may be on the same day as Session 1; the baseline monitoring phase will follow Session 2. During the baseline monitoring phase, participants will provide breath samples to assess for recent alcohol use and report their drinks per day and report their alcohol withdrawal symptoms per day. Following the baseline period, participants will return for Session 3, where they will undergo fMRI procedures and then be randomized to either the EFT or control group (Control Episodic Thinking, CET). Participants will complete 2 weeks of monitoring (Monitoring Phase 1) where they will provide three breath samples per day and report the number of drinks they consumed per day. Participants will then come back to the lab to generate new EFT/CET cues at Session 4, and then complete Monitoring Phase 2 for two more weeks. After conclusion of the second monitoring phase, participants will complete Session 5 which is composed of assessments and an fMRI scan. A one month follow up will be conducted as Session 6.

8.2 Provide a description of:

- *All research procedures being performed*
- *If the study has more than one procedure, session, and/or subject population, describe each procedure, session, and/or study population separately. For complex studies, you are encouraged to include a figure or chart.*

Participants will be recruited from the community via posted flyers, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). Participants will be contacted if they have given prior permission (through previous informed consent form) or by completion of a confidential pre-screening questionnaire.

Participants will be initially pre-screened for eligibility using our RedCap online/phone survey.

Following informed consent (Session 1), participants will complete a second session (Session 2). Sessions 1 and 2 may be on the same day. Following this session, participants will be asked to provide daily self-report assessments of previous-day drinking remotely (see below) and 3 breathalyzer samples per day for 7 days with no other study intervention taking place and their alcohol withdrawal symptoms per day. The purpose for this baseline period is to quantify baseline drinking patterns and ensure that the participant reliably responds to and conveys study information remotely. At the end of this baseline period, participants who indicated adequate patterns of drinking on at least 4 of the 7 days and successfully reported their level of drinking as requested on 5 of the 7 baseline days will be invited to continue in the study.

Following the baseline period, participants will return to the laboratory for Session 3. During Session 3, participants will complete an fMRI. Participants will be

counterbalanced to either the active or control group based on alcohol use (e.g., average drinks per day) and their baseline delay discounting rate. Both groups will be exposed to the same procedures. That is, participants in both groups will generate positive cues at either future timepoints (active, Episodic Future Thinking, EFT) or recent timepoints (control, Control Episodic Thinking, CET). Following this Session 3, participants will begin the first intervention period (Monitoring Part 1). The intervention period will last approximately 14 consecutive days, with three breathalyzer screens per day. During this 14-day period, participants will also self-report their previous-day alcohol use daily remotely and their alcohol withdrawal symptoms per day. Following Monitoring Part 1, participants will return to the laboratory for Session 4, where they will generate new cues and complete assessments. Following Session 4, participants will begin the second intervention period (Monitoring Part 2). The intervention period will last approximately 14 days, with three breathalyzer screens per day. During this second 14-day period, participants will self-report their previous-day alcohol use remotely. Session 5 will be conducted in the laboratory after the conclusion of Monitoring Part 2. Participants will also complete Session 6 (1-month follow-up) one month after the conclusion of the intervention. Participants may be provided a cell phone (if necessary) at the beginning of the study and a BACtrack breathalyzer at the beginning of the baseline period. Participants may receive a $100 study completion bonus at the end of the study provided they complete all six sessions (and return the cell phone if applicable). Please note: if participants are unable to complete the entire 28-day intervention period, post-intervention data will be collected regardless of the number of intervention days completed.

Cellular phone communication. All participants will either be allowed to use their own personal cell phone for study communications or receive a cell phone with service through a nationwide cell phone service provider. If a participant chooses to use their personal cell phone for study communications and pays for text messages and/or phone calls on a per unit basis, we may reimburse the participant for the cost of those messages and calls made for this study. We have used study-provided cell phones to facilitate study communication previously (Athamneh et al., 2021, Koffarnus et al., 2011).

BACtrack breathalyzer monitoring. The BACtrack breathalyzer (https://www.bactrack.com) contains a number of technological advances that make it ideally suited for remote breath samplings of alcohol use. To complete scheduled breathalyzer assessments, participants will log into the Remote Monitoring app on their smartphone, developed by the University of Kentucky. Participants will select to submit a breath sample and participants will simply blow into the device for a few seconds. The breathalyzer will be provided to the participants for the study. Participants will be able to keep their breathalyzer following completion of the study. If the breathalyzer is lost/stolen/damaged, the participant will be able to receive a new breathalyzer from the study team.

All participants will be asked to complete breathalyzer screens 3 times per day for approximately 35 days (approximately 7 days baseline, and approximately 28 days intervention). A period of approximately 28 days of the intervention was chosen to

determine if this procedure could result in alcoholic drink reduction using the EFT intervention. The breathalyzer screens will be spaced throughout the day, through the participants usual bedtime. The first sample of the following day will not be collected until 9 hours have passed from their usual bedtime. Throughout the intervention phase of the experiment, participants will be required to submit three daily breathalyzer assessments at predetermined times. They may be reminded via text message when a sample is to be collected. Samples will be accepted 90 minutes after the scheduled time. Both groups will receive a $1 payment for each breathalyzer result submitted within the allowed submission period, regardless of the result of that test. This payment is to encourage participants to complete screens, even if they had consumed alcohol that day. Breathalyzer schedules will be similarly arranged for both groups.

Participants will be assigned to either the active Episodic Future Thinking (EFT) condition or the control Control Episodic Thinking (CET) condition. EFT participants will generate positive future events they are looking forward to and that could happen at different future time points (e.g., in 2 weeks, 1 month, 6 months, 1 year) and participants in the CET condition will list positive recent events (events that have already happened) that they enjoyed that occurred at different past time points (e.g., 12 hours ago, 24 hours ago,1 week ago). Participants will be instructed to use and think about their episodic cues as they make decisions. All participants will be provided with a copy of their episodic cues to take home with them and will receive periodic text messages from research staff to remind them of their cues. Questions about the cues (e.g., "How vivid is this cue to you, on a scale from 1-5", "How real does this cue feel to you, on a scale from 1-5", etc.) will be also texted to the participants together with the cues. This procedure is to ensure the participants are actually reading their cues when texted to them. To incentivize responses to the cue, participants will be paid $1 for each response. Research staff will be available throughout business hours and periodically during evening and weekend hours to deliver text messages and payments. Participants will have immediate access to these payments as soon as they are deposited by research staff (see below).

Remote delivery of payments. To allow for payments that are both convenient and rapidly available, we will pay participants with reloadable prepaid cards through Greenphire ClinCard (www.greenphire.com), an FDIC-insured payment provider that specializes in clinical trial stipend payments that comply with IRB privacy regulations and considerations. At intake, each participant will receive a prepaid MasterCard debit card that can be used anywhere that accepts MasterCard. As payments are earned in the course of the study, additional funds will be added to the account for that participant. Funds are immediately available when added and participants can check their balance as desired. This system will allow frequent, immediately available payments without the burden of frequent laboratory visits that would negate some of the advantages of remote monitoring.

Daily alcohol use self-reports. Each day, participants will be asked to report how many alcoholic drinks they consumed the previous day (from the time they awoke to the time they fell asleep). We will ask them about the previous day's alcohol use instead of the

current day to best capture all drinks consumed each day without inconsistent response times complicating the measurement. Participants will be allowed to report this information at any time throughout the day, but will be encouraged through prompts to do so in the morning to increase the likelihood of accurate recall of previous day use. Participants will be allowed to report this information via the Remote Monitoring app. Participants may receive a reminder to report their previous-day drinking with text messages, followed by a phone call if they haven't contacted us appropriately. For completing this daily self-report, participants will receive $1 in compensation.

Daily alcohol withdrawal symptoms. Each day, participants will be asked to report their alcohol withdrawal symptoms. Specifically, participants are instructed to report the maximum severity of alcohol withdrawal symptoms experienced "today" on a scale of 0 (no symptoms) to 9 (severe symptoms). Participants are instructed to contact the study team immediately if they have concerns about their withdrawal symptoms. Participants are provided with common alcohol withdrawal symptoms, including: anxiety, headache, insomnia, irritability; and severe symptoms including: convulsions and delirium tremors. Participants will be allowed to report this information via the Remote Monitoring app.

Assessment sessions (sessions 2, 3, 4, 5 and 6). Participants will complete a battery of questionnaires and tasks grouped into three general categories: measures of substance use (including a urine test for drug and alcohol metabolites and a breath sample to test for recent alcohol use), clinically relevant measures including treatment acceptability, and measures of alcohol value and sensitivity. At the end of Session 6, participants will be provided alcohol treatment resources.

fMRI Scan. Investigators of the study will review safety issues related to MRI scanner with the participant and answer any questions immediately prior to entering the MRI scanner (see attached preMRI screening form). The subjects will lie still in the MRI scanner for approximately one hour. During the first several minutes acquisition of the structural scans will take place (e.g., localizer, T1-, T2-, and/or DTI-weighted), which will be followed by acquisition of the functional images. While the participant is inside the scanner, an investigator will be in constant visual observation of the participant and in between scans will use voice-communication via an intercom to assure the participant remains comfortable. The participant will also have a hand-held squeeze bulb to signal the investigators at any point in the experiment. In the event the participant wishes to be withdrawn, the investigator will take the participant out of the scanner immediately.

The fMRI session will consist of resting state scan(s).

Urine samples to assess pregnancy and recent substance use will be collected at the Addiction Recovery Research Center in restrooms designated for participant use that have built in stainless steel sample pass-throughs. Trained research personnel will provide specimen cups labeled only with study ID and will be responsible for testing the samples in a designated laboratory space using laboratory procedures to ensure validity and safety. To test the urine, specifically, we will utilize the hCG Urine Pregnancy Test Cassettes, which is a test kit for the determination of hCG (Human Chorionic

Gonadotropin) in urine specimens. This test kit is used to obtain a visual qualitative result for early detection of pregnancy. These tests are Standardized with WHO International Reference Standard and FDA Cleared & CLIA Waived. We will also use the QuickTox 5-panel drug test dip card which delivers results within 5 minutes. The QuickTox is FDA-approved and CLIA-Waived. The 5-panel test detects benzodiazepines, marijuana, opiates, meth, and cocaine.

8.3 Describe:

- *Procedures or safeguards intended to reduce the probability and magnitude of risks. (For example: Reducing the risk of injury in a virtual reality study either by having the subjects sit during the study or by providing an obstacle-free space for walking.)*
- *Be sure to describe all drugs and devices used in the research, when they will be administered or used, and their purpose.*
- *Methods used to collect data about subjects. Please upload all data collection forms to Protocol Management. Some common examples are:*
  - *Screening questionnaires*
  - *Survey(s), including online surveys*
  - *Demographic questionnaire(s)*
  - *Interview guide(s), e.g., questions or pool of questions for semi-structured interviews*
  - *Focus group guide(s)*
  - *Other documents used to collect data*

Affect Circumplex Measure: Measures positive and negative affect.

Alcohol Purchase Task: Assesses alcohol demand, where participants report the quantity of standard alcoholic drinks they would consume across various prices.

Alcohol Relative Reinforcement Schedule: Measures substance-related and substance-free reinforcement.

Alcohol Urges Questionnaire: Assesses alcohol craving.

Alcohol Withdrawal Symptoms: Assesses alcohol withdrawal.

Beck Anxiety Inventory: Assesses symptoms of anxiety

Beck Depression Inventory: Assesses symptoms of depression.

Breath Alcohol Concentration (BrAC): Assesses BrAC prior to and during laboratory sessions.

Brief Assessment of Alcohol Demand (BAAD): Assesses alcohol demand indices independent of alcohol purchase task.

Contemplation Ladder: Assesses readiness to change alcohol use.

Corsi Block Tapping Test: This task measures working memory capacity.

Delay Discounting (DD): DD tasks (a measure of the temporal window) examine the devaluation of monetary or alcohol rewards as a function of delay to their receipt. These computerized assessments present hypothetical choices between smaller, sooner and larger, later rewards available at a range of delays.

Height: Self report height

Penn Alcohol Craving Scale: Assesses alcohol craving.

Reward Responsiveness Scale: Measures responsiveness to reward through a single component measure

Timeline FollowBack Interview (TLFB): Assesses the number of alcoholic drinks and other substances daily for the past 30 days, or since the previous assessment, whichever is fewer.

Urinalysis: Assesses substance use and/or pregnancy.

Weight: Self report weight

8.4 What data will you collect during the study and how you will obtain them? Please include descriptions of electronic data collection, database matching, and app-based data collection:

All of the survey and questionnaire data will be collected using Qualtrics, online survey platforms used to develop, administer, and collect participant data in a secure password protected database. Only study personnel will have access to the survey and collected data.

The fMRI tasks will be administered using python-coded tasks, wherein the participant data will be securely collected on a password protected shared-drive hosted by FBRI.

fMRI analyses. GLM-based analysis will be performed using AFNI. We will perform slice timing correction, motion correction, and spatial smoothing (Gaussian kernel with full-width-at-half-maximum of 2.0 Å~ the voxel size). Linear regression coefficients (beta-weights) and t-statistic maps will be calculated. Since fMRI relies on neurovascular coupling, which changes due to the vasoactive properties of alcohol, nicotine, and caffeine (short term) and for vascular damage (long term for AUD individuals), we will model our data with a finite impulse response basis set rather than a "standard" HRF model.

The RAM (Remote Alcohol Monitoring) app was designed and custom built by Co-Investigator Koffarnus. This application is being used in other funded and approved studies, and will be used in this protocol to collect and track breath sample results (BAC) and number of drinks per day securely. Participants are provided a username and password to login to the app that will be on their phone (or the study provided phone) with study personnel help as needed. Participants will open the BAC Measurement activity within the app, hold down the button on their BACtrack to turn it on. The device will automatically connect, and a status message in the app will inform the participant if the device connected successfully. When they are ready, participants will press the "Measure" button on the screen and follow on-screen instructions to complete the measurement submission. To report drinks, participants will have access to a running counter you can use to keep track of the number of drinks they have consumed throughout the day and they will also be asked to confirm the number of drinks from the previous day. This confirmation will meet the requirements for your daily submission of drinks per day. To report alcohol withdrawal symptoms, participants will report the maximum severity of alcohol withdrawal symptoms that they experienced in the day. They are instructed to contact the study team immediately if they are concerned about their withdrawal symptoms.

8.5 Who will transcribe or code audio and/or video recordings?:

N/A

8.6 Include a description of any deception to be used in the study. Include justification for the use of deception (why the deception is necessary), describe the debriefing process, and describe how the study meets <u>all</u> the

following criteria for alteration of consent (deception is considered an alteration of informed consent):

- *The research involves no more than minimal risk to the subjects*
- *The alteration will not adversely affect the rights and welfare of the subjects*
- *The research could not practicably be carried out without the alteration/deception*
- *(Optional but encouraged in most cases) Subjects will be provided with additional pertinent information after participation (i.e., debriefing for studies involving deception)*

N/A

8.7 If the study involves long-term follow-up (once all research related procedures are complete), describe what data will be collected during the follow up period and when it will occur:

N/A

9.0 Data and Specimen Long Term Storage and Use

9.1 If you will store data or specimens for future use, describe where you will store the data or specimens, how long they will be stored, and how and by whom the data or specimens will be accessed:

All participant data, including electronic data, will be stored in secure places to protect confidential participant information. Secured places will include locked filing cabinets, locked rooms accessible only to study personnel, and/or password-protected databases. Moreover, all data will be quality controlled in preparation for data analyses. All discrepancies in data entry will be checked against the raw data source, and the correct data entry will be used. All data entered into spreadsheets and databases will be coded by participant ID number and not by name (i.e., first and last name), stored in a master ID log. The master ID log will be stored in REDCap, which is HIPAA compliant. Additionally, all entered data will be backed up on secure password-protected servers. Computers used in the studies will also be password protected, accessible only by study

personnel. Computers and password-protected servers used for this study are Virginia Tech secured and managed. We will provide certification of IRB approvals of the study protocol to NIAAA prior to screening study participants. VT IRB regulations will be strictly adhered to in the conduct of the proposed research. Specifically, prior to implementation of any protocol changes, amendments will be submitted to the IRB for approval. Data will be stored for three years following publication in accordance with NIH policy. Individuals on the IRB approved protocol will have access to data in long term storage.

9.2 For specimens, list the data to be stored or associated with each specimen:

N/A

9.3 Describe the procedures to release data or specimens outside of the research team, including the process to request a release, approvals required for release, who can obtain data or specimens, and what data will be provided with specimens:

Investigators will adhere to all NIH requirements regarding data sharing. Participant data collected in this project will be de-identified and made available if requested. We will also share the analysis results. As part of this process, all investigators will be required to agree to the following conditions: 1) will adhere to the reporting responsibilities; 2) will not redistribute the data beyond the requesting individual and named collaborators; 3) will give appropriate acknowledgement; 4) will not use the data for commercial purposes; and 5) will obtain appropriate ethical approvals.

Results from research conducted will be shared and disseminated, including: regular project meetings, annual meetings, symposia, workshops, and/or conferences for related groups. Manuscripts will be written and submitted for publication in peer-reviewed journals/conferences, following the NIH Public Access Policy guidelines. All necessary ethical approvals will be obtained.

Raw data will be made available upon request after dissemination of results.

Access Criteria:

Data requests will be reviewed by the principal investigator and data will be shared with the expectation of acknowledgment of funding source and primary study team.

9.4 Describe the identifiers to be included with stored data or specimens, as well as any key or code that could be used to make them identifiable. Describe where the code will be stored, who will have access to it, and when it will be destroyed:

All screened participants are assigned study IDs that are thereafter associated with all collected data, whether paper or electronic. The electronic de-identified data is stored on the Bickel shared server which is password protected and only accessible to members of the research team on the VT IRB approved protocol. Non-electronic data that is collected is stored in participant specific binders identified only by study ID. These binders are stored in a locked file room inside a locked office within ARRC, accessible to only members of the research team on the VT IRB approved protocol.

Study ID and full name are available together electronically only in REDCap (Harris et al. 2009), a widely used secure web-based application that enables us to build and maintain a participant database. Specifically, we use REDCap to collect demographic and other screening criteria for eligibility for study enrollment. This service is password protected and has been approved by Virginia Tech IRB. Personnel with access to REDCap will be approved on the IRB protocol and will be limited to personnel directly involved in recruitment, enrollment, and eligibility verification. We use a REDCap pre-screening survey to determine appropriateness for enrollment of ongoing studies within our lab. REDCap assigns a number to each survey completer and we use this ID for study data. If participants agree to be contacted about future research opportunities, we retain their information in the secure REDCap database separate from any study data.

9.5 Please select the identifiers you will obtain (whether directly from participants or from another source), including but not limited to:

☒	*Name*
☒	*Geographical subdivisions smaller than a state, including street address, city, county, precinct, zip code, and equivalent geocodes (note, the initial three digits of a zip code are not considered identifiable)*
☒	*Elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death, and single year of age over 89 and all elements of dates (including year) indicative of such age (note, such ages and elements may be aggregated into a single category of age 90+)*
☒	*Phone numbers*
☐	*Fax numbers*
☒	*Electronic mail addresses (e-mail)*
☒	*Social Security numbers*
☐	*Medical record numbers*

☐	*Health plan beneficiary numbers*
☐	*Account numbers*
☐	*Certificate/license numbers*
☐	*Vehicle identifiers and serial numbers, including license plate numbers*
☐	*Device identifiers and serial numbers*
☐	*Web Universal Resource Locators (URLs)*
☐	*Internet protocol (IP) address numbers*
☐	*Biometric identifiers, including finger and voice prints (audio recording)*
☐	*Full face photographic images and any comparable images (including video recording)*
☐	*Student record number or identification number*
☐	*User name for online or computer accounts*
☐	*Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)***:** Click here to explain.

10.0 Sharing of Results with Subjects

10.1 Describe whether you will share results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) with subjects or others (e.g., the subject's primary care physician). If so, describe how you will share the results and include this information as part of the consent document. Upload materials you will use to explain the results to subjects:

We will not share any results with the study participants. In the event of incidental findings, we will follow the established protocol highlighted in the NIAAA Data and Safety Monitoring Plan (DSMP) for the R01 associated with this project. As an example, we will review our current procedure for handling incidental neuroimaging findings below:
Specific to incidental neuroimaging findings: The Human Neuroimaging Lab at Virginia Tech has a standardized approach to incidental findings across approximately 60 currently active protocols (including scanning over 150 individuals with AUD). Moreover, our process is consistent with the best practices recommendations of the NIMH "MRI Research Safety and Ethics: Points to Consider" whitepaper (https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/mri-research-safety-ethics_33826.pdf). Furthermore, our procedures conform with those reported in the literature as appropriate for our research setting. During the consenting process, participants are informed that the scans that will be performed in the study are not the same as those that would be used in a clinical setting, and thus have limited diagnostic value. Further, some of the scans require subsequent data analysis and would never be read by a neuroradiologist. As is common and acceptable in many academic institutions, we do not have a neuroradiologist on staff to read every scan. Our policy (which is communicated to all participants verbally and written in the consent document):

"This is not a study to diagnose these structures. Your brain images will not be read by a doctor who specializes in reading brain images. If something abnormal is observed by chance, we will tell you. You will then be counseled as to what clinical referral would be appropriate. We are not qualified to make any diagnosis, nor is this fMRI of diagnostic quality for medical purposes. In the event of an incidental positive pregnancy test finding, the study personnel will share the results with you. They will counsel you as to what clinical referral might be appropriate."
We also communicate, however, that we will err on the side of caution in communicating with them if we do observe a possible abnormality. The DSMB will review these procedures, and their adequacy of protection against risk, at each semi-annual DSMB meeting.

11.0 Study Timelines

11.1 Describe:

- *The duration of an individual subject's participation in the study (for example, 1 hour, 2-4 weeks, 3-5 years).*
- *The amount of time expected to enroll all study subjects (weeks, months, years, etc.)*
- *The amount of time expected for the investigators to complete this study including primary data analyses.*

The total study is expected to take up to approximately 15 weeks. The study team has projected this study to take approximately 2 years to complete enrollment and data analysis.

<table>
<tr><th>Time</th><th>Session 1</th><th>Session 2</th><th>Baseline Monitoring</th><th colspan="2">Session 3 - fMRI then Group Assignment</th><th>Monitoring Part 1</th><th>Session 4</th><th>Monitoring Part 2</th><th>Session 5 (fMRI)</th><th>Session 6 - 1 month follow up</th></tr>
<tr><td>All Participants</td><td>✓</td><td>✓</td><td rowspan="2">~ 7 days</td><td>fMRI</td><td>→ EFT</td><td rowspan="2">~ 14 days</td><td>✓</td><td rowspan="2">~ 14 days</td><td>✓</td><td>✓</td></tr>
<tr><td></td><td></td><td></td><td>fMRI</td><td>↘ CET</td><td>✓</td><td>✓</td><td>✓</td></tr>
</table>

12.0 Inclusion and Exclusion Criteria

12.1 Describe how you will screen individuals for eligibility. When will screening occur and what procedures will you use? Upload any screening scripts or surveys to Protocol Management:

We have developed and are currently using a separate pre-screening survey (online/phone pre-screen), which occurs prior to enrolling participants into our intervention protocols.

This pre-screening ensures that participants are likely to meet all inclusion/exclusion criteria (e.g., MRI scanner eligibility) prior to enrolling into any randomized study. This initial pre-screening (online/phone) may be completed online or over the phone. Information is stored in REDCap, which is HIPAA compliant and password protected. If participants seem eligible from the online/phone screen, they will be scheduled for the in-lab screen in the laboratory to further determine eligibility and appropriateness for this specific intervention-based study.

12.2 Describe the eligibility criteria that define who will be included and who will be excluded from enrollment for each procedure of your study. Include any geographic criteria (e.g., Virginia Tech undergraduate students, a national sample of adults with engineering degrees, minors aged 8-12 in the New River Valley, university faculty in Virginia and Paris, France):

Inclusion criteria for signing consent will require that participants: (1) demonstrate high-risk or harmful drinking (AUDIT>15; i.e., 16 or higher), (2) be between 21-65 years old, and (3) have a desire to quit or cut down on their drinking, but do not have proximate plans to enroll in treatment for AUD during the study period.

Exclusion criteria include: (1) meeting moderate to severe DSM-5 criteria for substance-use disorders other than alcohol, nicotine, or marijuana, (2) having a current diagnosis of any psychotic disorder, (3) having a history of seizure disorders or traumatic brain injury they have not fully recovered from, (4) having any contraindication for participation in the fMRI session, or (5) reporting current pregnancy or lactation.

12.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate them in the description of your subject population.)

- *Minors, as defined by state law where the study is performed (infants, children, teenagers)*
- *Pregnant women (can be included in minimal risk studies by mentioning in section 13.1)*
- *Prisoners (including all incarcerated individuals)*
- *Adults not capable to consent on their own behalf*

This project will focus on individuals with alcohol use disorder, aged 21 to 65. We will not include individuals under the age of 21 in compliance with Virginia state law.

Vulnerable subjects, such as individuals with cognitive impairments, minors, prisoners, and pregnant women will be excluded.

13.0 Vulnerable Populations

13.1 If the research involves individuals who are vulnerable to coercion or undue influence, please describe additional safeguards you will include to protect their rights and welfare. Consider the applicable items listed below:

- *If the research involves Virginia Tech students, indicate whether these are students of any of the investigators. If so, describe whether the activities will take place during class time as part of the curriculum and the steps you will take to reduce the possibility that students feel obliged to participate in order to improve their course grade. The HRPP can provide further guidance as needed. Describe whether you will request access to student records (e.g., SAT, GPA, GRE scores).*
- *If the research involves employees of Virginia Tech or the research sponsor, describe steps you will take to ensure that the employees are freely participating and describe how their data will be protected from inspection by their supervisors.*
- *If the research involves Virginia Tech NCAA athletes, you must obtain approval from the athletic department.*
- *For research involving Montgomery County Public Schools, you must obtain county approval (after obtaining contingent Virginia Tech approval). Other locales have different requirements; please check on these and describe here. Approval is typically granted by the superintendent, principal, and classroom teacher (in that order). Approval by an individual teacher is insufficient. School approval, in the form of a letter or a memorandum should be uploaded as a supporting document.*
- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information in this protocol.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information in this protocol.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research (minors), review the "CHECKLIST: Minors (HRP-416)" to ensure that you have provided sufficient information in this protocol.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information in this protocol.*

This research study will not include any vulnerable populations.

14.0 Number of Subjects

14.1 Indicate the total number of subjects to be enrolled and how this number was determined (e.g., sample size calculation [show], number of available subjects in a finite pool, number of tests funding award would allow):

Although we have observed large effect sizes of EFT on DD in AUD participants in our preliminary studies (pre-post d=1.6; post-only d = 0.68), we used a more conservative medium effect size (f= 0.25) to inform sample sizes to increase power to detect effect on the broader range of measures proposed here (e.g., intensity of demand). Using the method proposed by Borm, Fransen, and Lemmens, and a pre- and post-measurement correlation of 0.70218, 76 total participants would be needed to complete this study (38 participants per group), assuming a type 1 error rate of 0.01 and 95% statistical power, based on an ANCOVA comparing the intervention while using the baseline measure as a fixed-effect covariate in the analysis.

We have been successfully recruiting individuals with AUD in our community for the past 8 years. Based on these 8 years of experience recruiting alcohol users into studies of comparable length and complexity, we anticipate that over 80% of consented participants will be eligible (i.e., randomized) and about 65% of those eligible individuals will complete this study. Thus, to achieve a final sample size of 76, we anticipate consenting 200 participants. We plan to enroll more than our average attrition rate because of the increased procedures and the time demands of the study.

14.2 If this is a multi-site study, indicate the number of subjects to be enrolled at this site and the total to be enrolled from all sites:

N/A

14.3 If applicable, indicate the number of potential subjects you expect to screen for enrollment, and the number of subjects you will need to complete the research procedures:

We have developed and are currently using a separate pre-screening protocol, which occurs prior to enrolling participants into our intervention protocols, in order to effectively decrease attrition in our studies by ensuring that participants meet most inclusion/exclusion criteria (e.g., MRI scanner eligibility) prior to enrolling into the randomized study. Given that this separate screening protocol is used for all currently on-going studies in the lab, we cannot accurately estimate the total number of potential participants we expect to screen. However, as described above, we anticipate enrolling 200 participants in order to complete a total of 76 participants. We plan to enroll more than our average attrition rate because of the increased screening procedures and the time demands of the study. Additionally the first few participants enrolled into the study may be pilots.

14.4 If the study has more than one procedure, indicate the total number of subjects to undergo each procedure separately:

All participants will undergo all sessions unless they withdraw from the study.

15.0 Recruitment Methods

15.1 Describe when, where, and how you will recruit potential subjects:

Participants will be recruited from the community via posted or mailed flyers/postcard, word of mouth, and electronic advertisements (e.g., Craigslist, Facebook). Participants will be contacted if they have given prior permission (through previous informed consent form) or by completion of a confidential pre-screening questionnaire. Services from mailing list companies may be used.

Group posting rules will be checked and followed when posting to community pages. If posting requires approval, or if it is unclear if our post meets group rules, the research staff will send the following message to a group administrator along with the picture/post to be shared: “Hello! My name is ____ and I work for the ____ lab(s) at the Fralin Biomedical Research Institute at Virginia Tech Carilion. We are currently recruiting for an Institutional Review Board approved study which investigates decision-making in individuals who drink alcohol. Would it be alright if I posted the attached ad to this group for those who might be interested in participating?” All posted materials, including captions and images, will be submitted to and approved by the VT IRB prior to reaching out to community pages. In situations where the post would violate group rules or is rejected by a page administrator, it will not be shared on that page. If an administrator reaches out to the study staff following posting and requests the post be taken down, it will be taken down.

In addition, we will partner with BuildClinical to accelerate enrollment. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They have worked with IRBs in the US to ensure adherence to all the appropriate guidelines and procedures. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information is HIPPA compliant and keeps potential participant information private.

15.2 Describe the source of subjects (for example, clinic patients with specific conditions, students in the library, community members at a gathering, or members of a local gym):

Participants will be recruited from the community via posted or mailed flyers/postcards, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). Participants will be contacted if they have given prior permission (through previous informed consent form) or by completion of a confidential pre-screening questionnaire. Services from mailing list companies may be used.

In addition, we will partner with BuildClinical to accelerate enrollment. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They have worked with IRBs in the US to ensure adherence to all the appropriate guidelines and procedures. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information is HIPPA compliant and keeps potential participant information private.

15.3 Describe the methods that you will use to identify potential subjects:

Participants will be recruited from the community via posted or mailed flyers/postcards, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). Participants may contact the lab directly via email, facebook, phone, walk-in, face-to-face at tabling events, or completing the online pre-screening questionnaire. Participants will also be contacted directly if they have given prior permission (through previous informed

consent form) or by completion of a confidential pre-screening questionnaire. Services from mailing list companies may be used.

In addition, we will partner with BuildClinical to accelerate enrollment. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They have worked with IRBs in the US to ensure adherence to all the appropriate guidelines and procedures. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information is HIPPA compliant and keeps potential participant information private.

15.4 Describe materials that you will be use to recruit subjects. Attach copies of these documents with this protocol in Protocol Management and be sure to include the IRB protocol number on each document.

- *For flyers, attach the final copy of printed flyers.*
- *For Virginia Tech News, Facebook postings and ads, newspaper ads, websites, MTurk/SONA/online survey systems, etc., attach the final wording and graphics to be used.*
- *For email recruitments, please include the subject line.*
- *For advertisements meant for audio broadcast, please submit the wording of the advertisement prior to taping (to avoid having to re-record with approved language) and submit the final recorded version for IRB review before use.*
- *Describe any compensation to subjects. Separate compensation into appropriate categories, such as: reimbursement for expenses, time and effort, and additional incentives for study participation. For each category, specify the amount (including any pro-rated amount), schedule, and method of payment.*

Flyers to be used in community and online posting are attached.

Compensation. The compensation for this study is based an hourly rate of approximately $20/hr. Compensation also includes incentives for participant performance and attendance.

Compensation will follow the following schedule:

Session 1 = $15

Session 2 = $25

Baseline Monitoring = $1 for daily self-reports and $1 per BAC sample submission (x3). During baseline monitoring, participants who submit all required reports in a given day will receive a $1 bonus for that day. Thus they can receive $1 per information submitted or $5 for submitting all required information.

= up to $35 (for 7 days; total amount will be more/less depending on the exact number of baseline monitoring days completed by participant)

Session 3

MRI = $15**

Session = $30

Monitoring Part 1 = $1 for daily self-reports and $1 per BAC sample submission (x3), and $1 per reply to cue text (x2). Participants who submit all required reports in a given day will receive a $4 bonus for that day. Thus they can receive $1 per information submitted or $10 for submitting all required information.

= up to $140 (for 14 days; total amount will be more/less depending on the exact number of monitoring days completed by participant)

Session 4

Session = $30

Monitoring Part 2 = $1 for daily self-reports and $1 per BAC sample submission submission (x3), and $1 per reply to cue text (x2). Participants who submit all required reports in a given day will receive a $4 bonus for that day. Thus they can receive $1 per information submitted or $10 for submitting all required information.

= up to $140 (for 14 days; total amount will be more/less depending on the exact number of monitoring days completed by participant)

Session 5

MRI = $15**

Session = $30

Session 6 = $50

Study Completion Bonus***: $150

***Participants receive if they complete all six sessions

As an incentive for session attendance, participants may participate in a fishbowl drawing contingent upon arriving on time for the sessions. Some fishbowl drawings may result in receipt of either a small, medium, or large prize and some may result in verbal positive reinforcement. The prizes may be in the form of $1.00, $5.00, and $10.00 rewards. The odds of receiving a prize will be: “Good Job” (odds 13/50), $1 (odds 25/50), $5 (odds 10/50), $10 (odds 2/50).

Additionally, participants will be eligible for a $10 Scan bonus** per MRI. Participants will receive this bonus if they remain still and awake for the fMRI scan.

Total Compensation: approximately $700 for completion of all sessions and remote reports, plus bonuses.

We note that compensation will be prorated proportional to the amount of sessions or duration of session completed.

In addition, scheduling barriers will be minimized by offering participants a flexible session schedule and travel compensation, if necessary, etc.

Participants may be compensated for travel expenses (i.e., travel time) if traveling from outside of Roanoke to Roanoke for study sessions. For example, traveling from Blacksburg to Roanoke for a study session. In these cases, participants will receive additional compensation consistent with minimum wage (e.g., approximately $10 per hour) for their round trip travel. Currently there are no costs for parking at the FBRI, where the study sessions occur.

To allow for payments that are both convenient and rapidly available, we may pay participants with reloadable prepaid cards through Greenphire ClinCard (www.greenphire.com), an FDIC-insured payment provider that specializes in clinical trial stipend payments that comply with IRB privacy regulations and considerations. At the beginning of the study, the participant will receive a prepaid MasterCard debit card that can be used anywhere that accepts MasterCard. As payments are earned in the course of the study, additional funds will be added to the account for that participant. Payments will be added to the participant's ClinCard within 24 hours of the session completion. Funds are immediately available when added and participants can check their balance as desired. This system will allow frequent, immediately available payments. Payments may also be made via check or cash; however remote debit card payments and checks will be used most often.

16.0 Withdrawal of Subjects

16.1 Describe circumstances under which you anticipate subjects could be withdrawn from the research without their consent:

Participants may be withdrawn from the research without their consent if they become ineligible based on inclusion/exclusion criteria or learning of a contraindication for continuing, they demonstrate inconsistent delay discounting rates at the baseline session, there is an emergency, and/or they are not adherent with ARRC policies.

16.2 If applicable, describe any procedures for orderly termination (e.g., discontinuation of a study drug or debriefing after a behavioral intervention):

If a participant is withdrawn from the study, he or she will be informed that we have collected all the data required from their participation. If a participant is withdrawn or voluntarily discontinue, their compensation for the study will be pro-rated accordingly.

16.3 Describe procedures that you will follow when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection (e.g., participant declines to continue with regular blood draws, but continues with periodic behavioral questionnaires):

If a participant is withdrawn or discontinued, they will be withdrawn from the entire study.

17.0 Risks to Subjects

17.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include for the IRB's consideration a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, privacy, and economic risks. Do not indicate "No risk" or "N/A." Instead, for studies with very low risk (e.g., anonymous online questionnaire on a mundane topic) indicate "The investigators are not aware of any risks from participation in this study." or "No more than risks than are found in everyday life." The example consent form presents a tabular method for risk information, which you can also use here. Common risk types include:

- *Physical (e.g., potential for pain, discomfort, infection)*
- *Psychological (e.g., potential for stress, discomfort, and/or embarrassment)*
- *Social (e.g., potential for discrimination or stigmatization and disruption of personal and family relationships)*
- *Legal (e.g., potential for disclosure of illegal activity, negligence)*
- *Privacy (e.g., potential for personal information being accessed, used, or disclosed without the subjects' knowledge or consent, breach of confidentiality/security)*
- *Economic (e.g., potential for individuals to lose access to economic services, employment, insurability)*

There are minimal risks involved in participation, including:

1. Adverse emotional reactions: These reactions may be related to changes in drinking, or to some of the research tasks. Participants may also feel uncomfortable disclosing personal information such as drug use history.

2. Alcohol withdrawal: At sessions not including alcohol, participants may experience alcohol withdrawal symptoms such as shaking, sweating, or chills.

3. Loss of confidentiality: The research team will employ every effort to maintain participant confidentiality, however the loss of confidentiality is a potential risk, specifically associated with the collection, storage, and transmission of data via an app.

4. Incidental findings: Incidental findings including positive pregnancy tests and possible neuroimaging abnormalities may occur.

17.2 Indicate the measures you will use to minimize risks and monitor subjects for safety. (e.g., asking a subject at regular intervals to rate how they are feeling from 1 to 10, or to slowly crouch in order to check their balance.)

Informed Consent. All consenting methods will be conducted using standard operating procedures, and all staff (including recruitment staff) will be provided with human subjects protection training as well as cultural sensitivity training. All participants will enroll on a voluntary basis and sign an IRB-approved consent form prior to study participation.

Participants will be provided with a copy of the consent form following phone or online screening by email or mail when possible. To accommodate "walk-in" study screens and/or participants unable to receive email or physical mail (e.g., "homeless" without physical address, email address, or access to a computer), we will provide a hard copy of

the consent form to review. In all cases, participants will be given as much time as needed to review the consent and ask any questions. Participants will also be informed that they may choose to take the consent with them and return at a later date to enroll into the study. During the consent process, participants will be given adequate time in a quiet room to read (or further review) the written consent form.

Research staff will review each element of the written consent form with the potential participant. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. Staff will reiterate that the potential participant can choose to decline participation in the study at that time or at any time thereafter without consequence. The potential participant and person obtaining consent will sign the consent form after the potential participant verbally states that they understand the conditions of the study, have no more questions, and chooses to participate. In addition, an Evaluation to Consent will be administered to ensure participants have a good understanding of the study. Participants unable to provide informed consent for themselves will not be eligible.

Participants will be informed that the breathalyzer provided to them in this study should not be used as a tool to determine whether research participants should operate a motor vehicle or other equipment, or perform any other dangerous act. The participants will be informed, verbally and in the informed consent document, that the results of any study breath samples using the study provided breathalyzer cannot be used in court.

Protections Against Risk:

Participants will be screened, using medical history and structured interviews, for a history of medical contraindications (e.g., recent myocardial infarction, current pregnancy), current unstable medical illness, and psychiatric disorders (including other substance use disorders). The studies will be conducted at FBRI. Participants will be free to withdraw from the study at any time, and their refusal to continue will not affect other medical care. In addition, if participants develop medical problems during the course of the study, assessments to determine whether participants should continue will be conducted by the Study Physician and necessary referrals will be provided. The risks enumerated above will be addressed by the following protections against risk, and reviewed by the Data and Safety Monitoring Board:

1. Adverse emotional reactions: Dr. Kablinger will monitor participants' adverse emotional reactions.

2. Alcohol withdrawal: In addition, participants who are not drinking alcohol may experience alcohol withdrawal symptoms during any of the laboratory sessions or if they are drinking less than they normally do during the proof-of-concept field study portion of this study. At each laboratory session, participants will complete the Alcohol Withdrawal Symptom Checklist (AWSC), a validated 17-item checklist of symptoms in which the

participant rates their experience from 0 (“Not at all”) to 4 (“Extreme”). A score of >23 on this checklist requires medical oversight for alcohol withdrawal and will trigger the research staff to contact Dr. Kablinger. Dr. Kablinger will speak with the participant to determine appropriateness and safety to continue in the study and to provide medical consultation and/or a referral to a clinic/primary care physician. If the participant produces a score of >23 on the checklist, Dr. Kablinger will be contacted to assess the participant’s risk and refer as necessary. We have successfully implemented these procedures with Dr. Kablinger in our previous and ongoing studies.

3. Loss of confidentiality: The use of ID numbers for participants, and keeping all data in a locked cabinet in locked offices, will protect confidentiality. Password protected computer databases will have coded identifiers, and a Certificate of Confidentiality will be obtained. Master files linking subject names to study ID numbers will be kept separate from the data. These screening, monitoring, and confidentiality procedures have been in effect for decades and for thousands of participants across the various protocols employed by our group across various institutions. Although there is a potential risk to confidentiality, there are actions taken to reduce the risk to confidentiality via collection of data through an app. First, all transmissions from the breathalyzer to the phone and from the phone to University of Kentucky are encrypted and secured. The RAM app is HIPAA compliant. Additionally, servers are password protected and located behind firewalls to minimize the risk to confidentiality.

4. Incidental findings: In the event of an incidental positive pregnancy test finding, the study personnel will share the results with the participant, and will counsel the participant as to what clinical referral might be appropriate. . Incidental findings are an important factor in the risk/benefit analysis of neuroimaging studies. The Human Neuroimaging Lab at Virginia Tech has a standardized approach to incidental findings across approximately 60 currently active protocols (including scanning over 150 individuals with AUD) approved by two separate IRBs (Virginia Tech and Carilion Clinic). Moreover, our process is consistent with the best practices recommendations of the NIMH “MRI Research Safety and Ethics: Points to Consider” whitepaper (https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/mriresearch-safety-ethics_33826.pdf). Furthermore, our procedures conform with those reported in the literature as appropriate for our research setting. During the consenting process, participants are informed that the scans that will be performed in the study are not the same as those that would be used in a clinical setting, and thus have limited diagnostic value. Further, some of the scans require subsequent data analysis and would never be read by a neuroradiologist. As is common and acceptable in many academic institutions, we do not have a neuroradiologist on staff to read every scan. Our policy (which is communicated to all participants verbally and written in the consent document):

"This is not a study to diagnose these structures. Your brain images will not be read by a doctor who specializes in reading brain images. If something abnormal is observed by chance, we will tell you. You will then be counseled as to what clinical referral would be appropriate. We are not qualified to make any diagnosis, nor is this fMRI of diagnostic

quality for medical purposes. In the event of an incidental positive pregnancy test finding, the study personnel will share the results with you. They will counsel you as to what clinical referral might be appropriate "

We also communicate, however, that we will err on the side of caution in communicating with them if we do observe a possible abnormality. Finally, we will institute a DSMB that includes a radiologist and will, on a semi-annual basis, review our process for recognizing and reporting incidental findings in this project.

17.3 If applicable, indicate which procedures might have risks to the subjects that are currently unforeseeable. This will be rare, and usually applicable when testing a new drug or device or a new use of an existing drug or device:

N/A

17.4 If applicable, indicate which procedures might have risks to an embryo or fetus should the subject be or become pregnant:

N/A

17.5 If applicable, describe risks to others who are not subjects (e.g., collection of sensitive health data that might affect sexual partners if disclosed, mandatory reporting of abuse, DNA testing that might affect family members or relationships):

N/A

18.0 Potential Benefits to Subjects

18.1 Describe the potential benefits that individual subjects might experience from participating in the research. Include the probability, magnitude, and duration of the potential benefits, as this will be useful to the IRB's risk:benefit analysis. Do not include benefits to society or others. Do not

list monetary or non-monetary compensation for participation, as this is not a benefit These should be included in section 2 or 3 of this document:

Participants may benefit from possible improvement in self-control from this study, plus education about research participation. The project involves minimal risk to confidentiality or other personal rights or to physical or emotional health. The results from this behavioral economic study will inform the development of new treatments for problem drinking. Thus, in general, the expected benefits outweigh the very minimal risks to participants.

18.2 If applicable, specify that there are no anticipated direct benefits for participants:

There are no anticipated direct benefits for participation in this study.

19.0 Data Management and Confidentiality

19.1 Describe procedures that you will use for quality control to ensure validity of collected data:

The Co-PIs and the IRB will oversee monitoring of the data collection procedures. These procedures will be reviewed regularly in a number of settings. For instance, issues pertaining to data validity and integrity will be addressed formally during regularly scheduled study personnel meeting in which all study personnel, including the Co-PIs, will be in attendance. Issues pertaining to participant safety also will be addressed at these meetings. Moreover, the Co-PIs and the Senior Research Associate Project Manager will meet on a regular basis to discuss these topics further.

19.2 Describe any existing data or biospecimens you will obtain as part of this study. Include:

- *Variables or samples to be obtained*
- *Source of the data or specimens*
- *Your authorization to access or receive the data or biospecimens*
- *Whether the data or biospecimens are publicly available*

- *Whether the data or specimens you receive will contain identifiers*

N/A

19.3 Describe the steps that you will take to handle and secure study data during data collection, storage, use, and transmission. Include information about training of study staff, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, separation of identifiers and data, etc.:

Access to study data will be limited to study personnel who have completed the IRB Human Subjects Tutorial and who have been delegated the responsibility of data collection, management, or analyses by the PI.

All screened participants are assigned study IDs that are thereafter associated with all collected data, whether paper or electronic. The electronic de-identified data is stored on the Bickel shared server which is password protected. Non-electronic data that is collected is stored in participant specific binders identified only by study ID. These binders are stored in a locked file room inside a locked office within ARRC. Study ID and full name are available together electronically only in REDCap (Harris et al. 2009), a widely used secure web-based application that enables us to build and maintain a participant database. Specifically, we use REDCap to collect demographic and other screening criteria for eligibility for study enrollment. This service is password protected and has been approved by Virginia Tech IRB.

A BuildClinical specific screen form will also be used to collect demographic and other screening criteria for eligibility for study enrollment. BuildClinical keeps data secured using server authentication and data encryption, and uses the same standard network security methods as healthcare institutions. They encrypt all data, whether in transit or at standstill. Data is transmitted via HTTPS, and per BuildClinical, the Transport Layer Security (TLS) 1.2 has a 2048-bit server key length with industry-leading modern browsers. Screening information stored by BuildClinical can be accessed by authorized members of the VT research team. The only individuals outside of the research team that will have access to these data is the BuildClinical internal team that needs the information to help the research team with improvements on the campaign. BuildClinical maintains the right to the information prospective participants provide at screening and will retain the data in perpetuity. The BuildClinical terms of service and privacy policy are available on the landing page when prospective participants first link to the site. All participants that screen for the study using the BuildClinical form will also be assigned study IDs that are thereafter associated with all collected data, whether paper or electronic.

In addition, as an NIH funded study, this protocol will include a certificate of confidentiality.

19.4 For multi-site studies, describe how data or specimens will be handled and secured for each site (e.g., central or disseminated data storage, data coordinating center):

N/A

19.5 Describe the plan for data disposition following the conclusion of the study (e.g., long term maintenance of data, data destruction methods).

- *What information will be included in the long term storage of data or specimens?*
- *How long will the data or specimens be stored?*
- *Where and how data or specimens will be stored?*
- *Who will have access to the data or specimens during long term storage?*
- *Who is responsible for receipt or transmission of the data or specimens?*
- *How will data or specimens be shared or transported?*
- *When and how will personal identifiers be destroyed?*

All data will be securely stored for 3 years following final publication of the study results. Data will be deleted at the designated time. Information included in the long term data storage will include eligibility information, survey responses, alcohol use data, and demographic information. In addition, informed consents will be stored separately from data labeled by study ID. This study will not involve any long term storage of specimens. Long term storage of the electronic study data will occur in password protected Virginia Tech servers and paper study data will be stored in locked rooms. All data (paper and electronic) will only be accessible by study personnel approved by the PI. The receipt or transmission of the data will be the responsibility of study personnel designated by the PI. Data that does not contain any personally identifying information may be shared with other investigators as needed for data analyses.

20.0 Provisions to Protect the Privacy Interests of Subjects

20.1 Describe the steps that you will take to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on with whom they interact or to whom they provide personal information (e.g., collecting the minimal amount of private information required to complete the study, protecting the data once it is obtained):

Original signed consent forms will be stored in a study specific binder for this protocol. This binder is stored behind a locked door in our project manager's office. Importantly, these consent forms are separate from all other study documents, identifying information, and data collection.

All screened participants are assigned study IDs that are thereafter associated with all collected data, whether paper or electronic. The electronic de-identified data is stored on the Bickel shared server which is password protected. Non-electronic data that is collected is stored in participant specific binders identified only by study ID. These binders are stored in a locked file room inside a locked office within ARRC. Study ID and full name are available together electronically only in REDCap (Harris et al. 2009), a widely used secure web-based application that enables us to build and maintain a participant database. Specifically, we use REDCap to collect demographic and other screening criteria for eligibility for study enrollment. This service is password protected and has been approved by Virginia Tech IRB.

20.2 Describe steps that you will take to make subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures (e.g., use of a same gender investigator to place sensors on the torso, a private changing area if clothing must be changed, sensitivity when discussing pregnancy testing with subjects, making it clear on surveys that participants can discontinue at any time, not asking questions about private or sensitive issues unless necessary for the research):

The Addiction Recovery Research Center (ARRC) has private offices and interview rooms, 12 individualized computer testing and/or interview rooms. In all cases in which private information is collected, the participant is in a private interview room with a trained research staff member. The lab is equipped with white-noise machines to reduce excess noise. All participants are informed that their information will be kept entirely confidential.

20.3 Describe how you plan to access existing sources of information about the subjects (e.g., medical records, grades) and how you will protect participant privacy through the data security plan:

All ARRC participants who have previously given consent to be contacted for future studies will be searchable in the RedCap database, using the report feature. Eligibility

criteria, based on demographics and current use, may be reviewed to contact potentially eligible participants for this study.

20.4 Describe any required reporting that might occur as a result of your research questions, study populations, and data collection methods. Examples for Virginia and Virginia Tech include:

- ***Any*** *suspicions (e.g., circumstantial, disclosed) of child abuse (physical, emotional, sexual) and neglect*
- *Sexual discrimination and/or sexual violence that involves a student*
- *Disclosure or signs of intention to harm oneself (i.e., suicidal ideation and/or plan)*
- *Disclosure or signs of desire to harm others (i.e., homicidal ideation and/or plan)*
- *Suspected abuse, neglect or exploitation of vulnerable adults (e.g., individuals with a disability, elderly persons)*

We will report any disclosure or signs of intention to harm oneself (i.e., suicidal ideation and/or plan). In the event of this disclosure study staff will follow ARRC's SOP related to suicidal ideation. This SOP is attached.

21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Safety monitoring is required when research involves greater than minimal risk and is sometimes appropriate for other studies.

21.1 Describe:

- *The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe (e.g., periodic reporting to the IRB, establishing a data monitoring committee, reporting data monitoring committee findings to the IRB and the sponsor).*
- *What data you will review, including safety data, unexpected events, and data that show the ability to produce the intended results.*
- *How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with subjects).*
- *The frequency of data collection, including when safety data collection starts.*
- *Who will review the safety data and with what frequency.*
- *The statistical tests for analyzing the safety data to determine whether harm is occurring.*
- *Any conditions that will trigger an immediate suspension of the research (e.g., a serious adverse event).*

See attached Data Safety and Monitoring Plan associated with the R01 AA027381.

22.0 Compensation for Research Related Injury

22.1 If the research involves more than minimal risk to subjects, describe the available compensation in the event of research-related injury, if any:

N/A

22.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury. At Virginia Tech, this is most common for sponsored research:

N/A

23.0 Economic Burden to Subjects

23.1 Describe any costs that subjects might be responsible for because of participation in the research, including any uncompensated costs for items such as transportation, missed work, and childcare:

There are no costs to participate in this research study. In some cases, additional compensation will be provided for time and travel in order to reduce barriers to participation. Participants will be provided with a copy of the consent form following phone or online screening by email or mail when possible. To accommodate "walk-in" study screens and/or participants unable to receive email or physical mail (e.g., "homeless without physical address, email address, or access to a computer), will be given a copy of the consent form to review. In all cases, participants will be given as much time as needed to review the consent and ask any questions. Participants will also be informed that they may choose to take the consent with them and return at a later date to enroll into the study. During the consent process, participants will be given adequate time in a quiet room to read (or further review) the written consent form. Research staff will review each element of the written consent form with the potential participant. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. Staff will reiterate

that the potential participant can choose to decline participation in the study at that time or at any time thereafter without consequence.

24.0 Consent Process

24.1 Indicate the process by which you will obtain consent for study participation. Please upload all consent, parental permission, and assent forms, documents, and scripts referenced in this section to Protocol Management.

Describe the following:

- *Where the consent process will take place (e.g., clinic waiting area, classroom, online)*
- *The time interval between sharing the consent information with the prospective subject and obtaining consent. For lab, interview, and focus group studies, the Virginia Tech IRB prefers that subjects have at least 24 hours to review the consent form and study information before the appointment where consent will be obtained. For simple online survey studies, you can typically present the consent information immediately before subjects begin participation.*
- *If applicable, processes to ensure ongoing consent or assent (e.g., for multiple sessions; for research in which a minor will turn 18 during the study; for longitudinal research with minors who will later be asked to provide or affirm their assent).*
- *Please review "SOP: Informed Consent Process for Research (HRP-090)" for recommended procedure. Describe your process, being sure to include:*
  - *The name and role of all study personnel who will be trained and certified by the PI to conduct the consent process*
  - *The time that will be devoted to the consent discussion*
  - *Steps that you will take to minimize the possibility of coercion or undue influence*
  - *Steps that you will take to gauge or ensure the subjects' understanding*

Participants will be provided with a copy of the consent form following phone or online screening by email or mail when possible. To accommodate "walk-in" study screens and/or participants unable to receive email or physical mail (e.g., "homeless without physical address, email address, or access to a computer), will be given a copy of the consent form to review. In all cases, participants will be given as much time as needed to review the consent and ask any questions. Participants will also be informed that they may choose to take the consent with them and return at a later date to enroll into the study. During the consent process, participants will be given adequate time in a quiet room to read (or further review) the written consent form. Research staff will review each

element of the written consent form with the potential participant. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. Staff will reiterate that the potential participant can choose to decline participation in the study at that time or at any time thereafter without consequence.

Participants will be reminded throughout their study participation that they are voluntarily participating in the study as indicated in their original consent form. Research personnel are trained to communicate this information during study visits subsequent to the initial consent session.

Non-English Speaking Subjects

- *Indicate what language(s) other than English are understood by prospective subjects or representatives.*
- *If non-English speakers will be recruited, describe the process you will use to ensure that the oral and/or written consent information provided will be in a language that they understand.*
- *If you translate consent forms and study materials, please provide a certified translation of the form as well as the certification document.*
- *Indicate the spoken language that study personnel obtaining consent will use. Describe how you will assess fluency of personnel obtaining consent to ensure that the translation is accurate.*

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- *Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations (i.e., that it meets the criteria for a waiver or alteration of the consent process).*

N/A

Subjects who are not yet adults (minors: infants, children, teenagers)

- *Describe the criteria that you will use to determine legal age for consent to treatments or procedures involved in the research under*

the applicable law of the jurisdiction in which the research will be conducted (e.g., in Virginia, individuals under the age of 18 years).

- *For research conducted in Virginia, review "SOP: Legally Authorized Representatives, Minors, and Guardians (HRP-013)" to determine which individuals in the state meet the definition of "minor."*
- *For research conducted outside of the state, please describe the legal requirements for the definition of "minor."*

- *Describe the process for obtaining parental permission.*
  - *Permission from one parent is acceptable for studies that involve no greater than minimal risk OR involve greater than minimal risk but present the prospect of direct benefit to the minor subject.*
  - *Permission from both parents is required in all other cases (unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the minor).*
- *Describe whether you will obtain permission from individuals other than parents or Legally Authorized Representatives, and if so, who will be allowed to provide permission. Describe the process you will use to determine these individuals' authority to consent to the minor's general medical care.*
- *Indicate whether you will obtain assent from all, some, or none of the minors. If you will obtain assent from some minors, indicate which minors will be required to assent. Consider chronological age and intellectual capacity when determining who will be required to provide assent (e.g., infants are unable to assent. However, teenagers are likely able to read and sign an assent form).*
- *When assent of minors is obtained, describe whether and how you will document it. Will minors sign an assent form or give verbal assent?*
- *Attach parental permission and minor assent forms or scripts in Protocol Management.*

N/A

Adults Unable to Consent

- *Describe the process you will use to determine whether an individual adult is capable of consent.*
- *List the individuals from whom you will obtain permission in order of priority (e.g., durable power of attorney for health care, court*

appointed guardian for health care decisions, spouse, and non-minor child).

- *For research conducted in the Virginia, review "SOP: Legally Authorized Representatives, Minors, and Guardians (HRP-013)" to determine which individuals in the state meet the definition of "legally authorized representative."*
- *For research conducted outside of Virginia, please describe the legal requirements for obtaining permission from a legally authorized representative in the state where the research will occur.*

- *Describe the process for assent of the subjects.*
  - *Indicate whether you will require assent from all, some, or none of the subjects. If some, indicate which subjects will be required to assent and which will not.*
  - *If you will not obtain assent from some or all subjects, please provide justification for not obtaining assent.*
  - *Describe whether and how you will document assent.*

N/A

25.0 Process to Document Consent in Writing

25.1 Consult "SOP: Written Documentation of Consent (HRP-091)" for recommended procedures, and describe whether and how consent of the subject will be documented in writing:

The potential participant and person obtaining consent will sign the consent form after the potential participant verbally states that s/he understands the conditions of the study, has no more questions, and chooses to participate.

Written consent will include printed name, signature, and date from each of the person obtaining consent (e.g., research coordinator/study staff member) and the research participant. In addition, a copy of the consent form will be provided to the study participant, if they wish.

25.2 If the research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, you can request that the IRB waive the requirement to obtain written documentation of consent (e.g., consent to participate is indicated by pressing a button for an online

questionnaire – after the consent information is presented and before the questionnaire begins):

N/A

25.3 If you will document consent in writing, attach a consent document with places for signatures. If you will obtain consent, but not document consent in writing, please attach the consent script or text. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You should use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script:

Written Consent attached.

26.0 Resources Available

26.1 Describe the resources available to conduct the research. For example, as appropriate:

- *Describe the PI's availability to supervise the research.*
- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*
- *Describe the time that you will devote to conducting and completing the research.*
- *Describe your facilities.*
- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated or unanticipated consequence of participation in the research.*
- *Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions (e.g., training plans, detailed study notebooks).*

The organizational structure of the study team involves overall leadership by Principal Investigator (PI) Drs. Stephen LaConte, who will assume full responsibility for all aspects of the project. Dr. LaConte will oversee recruitment and retention of participants with alcohol use disorder. He will also oversee and delegate to the Co-Investigators the responsibility of training study personnel, consenting of participants, and data collection.

The Research Coordinator(s) will be trained and supervised as appropriate for any delegated study procedures. Behavioral data analysis will be overseen by Dr. LaConte and conducted by the Co-Is and the Statistician. Dr. LaConte will also oversee the collection and analysis of fMRI data. Specifically, Dr. LaConte will work with the Co-Is, the Research Associate, the Graduate Student, and the MRI Technician to design and program the fMRI stimuli and analyze the neuroimaging data from this project. In addition, Dr. James MacKillop (McMaster University) will contribute to the preparation and execution of fMRI design and interpretation. Dr. Anita Kablinger (Carilion Medical Center) will monitor participant safety throughout the study. Dr. Samuel McClure (Arizona State University) will be responsible for developing a computational model of reinforcer pathology.

All staff involved in the conduct and/or monitoring of this study will have completed the VT Human Subject Protection Training and Good Clinical Practice Training. Documentation of training will be maintained. The Co-PIs and Study Physician will be responsible for continuous data and safety monitoring of all participants enrolled in this study. In terms of standard operating procedures, trained research staff members will administer all assessments. The Study Physician will be directly responsible for monitoring risk related to alcohol withdrawal.

Participants will be recruited from the community via posted flyers, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). To the extent possible, we will attempt to minimize obstacles to participation. For example, travel barriers will be addressed by providing transportation or parking costs to participants, and scheduling barriers will be minimized by offering a flexible session schedule. All methods and measures will be conducted using standard operating procedures, and all staff (including recruitment staff) will be provided with cultural sensitivity training. We have a history of successful recruitment of drug and alcohol users. All participants will enroll on a voluntary basis and sign an IRB-approved consent form prior to study participation. Note that we have been successfully recruiting individuals with AUD in our community for the past 8 years and the demographics of participants have been stable.

In regards to medical and psychological resources, study personnel have lists of psychological resources including resources for people with suicidal thoughts or other emergency mental health issues readily available that can be provided to participants immediately. In addition, we have a Study Physician, Dr. Anita Kablinger, who can communicate with participants regarding medical and psychological issues that arise throughout participation in the research.

As far as facilities, the Addiction Recovery Research Center (ARRC; Interim Co-Directors, Stephen LaConte and Kirstin Gatchalian) is part of the FBRI, located in Roanoke, Virginia. Multidisciplinary research projects include examining the effects of behavioral, pharmacological, and transcranial magnetic stimulation (TMS) interventions as potential therapies for alcohol, cocaine, and nicotine dependence as well as other

health behaviors such as obesity. ARRC also develops potential computerized therapies, applies principles from behavioral and neuro-economics to the understanding of addiction, and assesses nicotine product abuse liability.

ARRC resides on the 3rd floor of the FBRI and consists of several laboratories for clinical research. ARRC has private offices and interview rooms, 12 individualized computer testing and/or therapy rooms, a ventilated, negative air pressure smoking laboratory that is equipped with computers and five additional behavioral booths, a dedicated TMS suite, and a conference room. The research space also includes a customized alcohol self-administration "bar lab" space and adjacent male and female restrooms with one-way observation windows and connecting stainless steel specimen pass-through cabinets. Office space for Multiple PI Bickel, Co-Investigators, Project Coordinators, Postdoctoral Associates, and Research Coordinators/Assistants is provided in the FBRI. The ARRC office suite has a copy machine, fax machine, network printer, scanner, and storage space for participant files and supplies as well as comfortable waiting rooms with entertainment (e.g., magazines, television, etc.) for research participants.

The laboratory of Multiple PI LaConte is part of the FBRI located in Roanoke, VA. Dr. LaConte has a primary faculty appointment at FBRI as well as a tenure-track appointment in the Department of Biomedical Engineering and Mechanics, School of Biomedical Engineering and Sciences, in Blacksburg, VA. Projects include fMRI methodological development and analyses, including real-time fMRI in substance-dependent (including alcohol) and traumatic brain injury populations. Moreover, Dr. LaConte has been collaborating with Dr. Bickel for five years as Multiple PI's of an existing NIAAA funded grant (R01AA021529) examining executive function training in alcohol dependent participants and real time fMRI.

In addition to his independent office space, Dr. LaConte has full access to the following facilities and resources of the FBRI Human Neuroimaging Lab sited in ~10,000 square feet divided among: 10 staff offices, 40 open-area Graduate Student and Postdoctoral Associates workstations, 18 behavioral testing rooms, 2 observation rooms with video/audio recording, 4 conference rooms with 20+ person capacity and AV/video conferencing capabilities, 1 data center with 16 rack capacity, 3 fMRI scanning suites (includes one on the Virginia Tech Blacksburg campus). Dr. LaConte's laboratory includes two Graduate Students, one Medical Student, two Clinical Coordinators, and one Research Programmer. The PI also has access to one MR Research Technician, two full-time System Administrators affiliated with the FBRI for research support.

27.0 Multi-Site Research

Contact the HRPP for multi-site research (involving multiple institutions) and the details required for this section will be provided. Otherwise, indicate N/A.

N/A