PROTOCOL VERSION	4/12-18-19
FILE NAME	RAP AABM + ADP Protocol
STUDY TITLE	**ALCOHOL APPROACH BIAS MODIFICATION EFFECTS ON ALCOHOL CONSUMPTION: A PILOT HUMAN LABORATORY STUDY**
STUDY NUMBER	18-25069/NCT03898323
CLINICAL PHASE	Phase 2

1. INTRODUCTION

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines (CRF 21 Part 312), applicable government regulations and Institutional research policies and procedures.

2. BACKGROUND

2.1 Background Prevalence of Research Topic

Alcohol use disorder (AUD) remains a critical public health problem and requires more efficacious behavioral and pharmacologic treatments. Existing behavioral and pharmacologic treatments have major limitations. Currently approved medications have only modest efficacy and are therefore underutilized. They have only small to moderate effect sizes and are limited by availability, while behavioral treatments have limited access and adherence. Neither behavioral nor pharmacologic treatments by themselves are likely to provide maximal/optimal outcomes. While pharmacotherapies can be effective as long as medications are provided, they may lose effectiveness after discontinuation of treatment, whereas neurocognitive training interventions such as AABM have been shown to have more lasting effects. New treatments are needed – in particular, treatments that could lead toward combinations of behavioral interventions and pharmacotherapy.

The project will conduct a pilot human laboratory feasibility study of alcohol approach bias modification as a potential treatment in heavy-drinking individuals. The purpose of the trial is to assess and establish the feasibility of conducting controlled trials of AABM in human laboratory alcohol drinking studies. The pilot data and feasibility demonstration will allow for future funding proposals to be submitted to allow larger studies of AABM alone and combined with pharmacotherapy for AUD.

Importantly, early clinical studies by other investigators have shown that Alcohol Approach Bias Modification (AABM) training may reduce relapse to alcohol use in patients with AUD who have already stopped drinking.
One potential AUD treatment modality is to reduce automatic alcohol approach tendencies through alcohol approach bias modification (AABM) training. AABM has effects on reducing alcohol use and relapse to AUD. However, few treatment trials have been conducted with AABM and little is known about its efficacy in reducing drinking in human laboratory alcohol consumption, especially in non-treatment-seeking, heavy-drinking individuals.

2.2 Prior Experience

2.2.1 Clinical Experience

Behavioral and neural correlates of implicit alcohol-approach behavior

Patients with substance use disorders exhibit an automatic tendency to approach rather than to avoid drug cues[1,2,3-6]. The associative process central to alcohol-approach behavior can be measured with a relatively new joystick task called the Approach-Avoidance Task (AAT) developed by Rinck et al. (2007)[6]. Differences in pulling an image toward one vs. pushing it away in relation to the content (e.g., alcohol pictures) are interpreted as automatic action tendencies[7]. Responses to appetitive cues typically occur outside of awareness[8]. The alcohol AAT taps implicit automatic approach tendencies[9-11]. To assess implicit responding or unconscious bias[12], participants are asked to respond to an irrelevant feature of the picture – its format (left- or right-tilt) rather than to the alcohol or non-alcohol content of the picture (explicit responding). The first study of alcohol approach-bias using the AAT was conducted by Wiers et al., (2009)[12]. In this study, heavy drinking students exhibited an alcohol approach-bias toward alcohol but not to generally positive/negative pictures (e.g., people and animal images)[12].

Modification of implicit alcohol-approach tendency: Alcohol Approach Bias Modification

Implicit alcohol approach-bias is related to changes in the motivational system in alcohol dependence and in heavy drinkers. Implicit alcohol-approach bias represents a target for clinical intervention. Wiers et. al., (2010)[13] adapted the implicit alcohol AAT to be used as an intervention by manipulating the percentage of pictures of alcohol or soft drinks, which were to be pulled or pushed. To train participants to avoid alcohol, 90% of the alcohol pictures were presented in push-format and 90% of the soft-drink pictures were presented in pull-format. Wiers et. al., (2010)[13] demonstrated that this alteration in task resulted in reductions in alcohol approach-bias (measured with the original implicit alcohol AAT), and in reduced drinking behavior in "hazardous drinkers" (not AUD) compared to those who were trained to approach-alcohol. This was the first study to show that retraining automatic approach processes could help to regain control over addictive impulses. A training version of the implicit alcohol AAT, named Alcohol Approach Bias Modification (AABM), has been studied in a handful of RCTs targeting alcohol dependent patients in in-patient treatment settings.

RCTs of Alcohol Approach Bias Modification
The first randomized controlled trial of AABM for alcohol was completed by Wiers et. al.(2011)[14]. An inpatient cohort of 214 AUD patients (not active heavy drinkers) were assigned to one of two experimental conditions; an explicit and implicit condition in which they were trained to make avoidance movements (pushing joystick) or to one of two control conditions in which they received sham or no training. Results showed successful alcohol approach-bias modification[14]. Furthermore, clinical outcomes were obtained from 87% of the patients one year later. Patients in the experimental condition showed better treatment outcomes; only 46% of the experimental group relapsed (resumed drinking >2 days) vs 59% of the control group[14]. Eberl et al,[15] extended the AABM work to determine the optimal amount of training needed to maximize the change in alcohol approach bias. Based on these responses, the recommended number of training sessions is 6, 9, or 12, dependent on resources[15]. We will provide 6 sessions over 2 weeks.

The Role of Pilot Feasibility Studies
The term 'pilot study' is widespread in clinical and translational research[16.] UCSF biostatistician Kraemer[17], asserts that pilot studies should be conducted to assess feasibility, rather than attempt to establish the sample size for a future larger study. "Pilot studies are important in the preparation of proposals for hypothesis-testing studies," because they can "check on the availability of … subjects using the recruitment methods proposed, "test the feasibility of the treatment and measurement protocols, train researchers, and to set up data… capabilities". The present proposal is designed to do so.

3. RATIONAL SIGNIFICANCE

3.1 Problem Statement
We will combine AABM with a human laboratory methodology of assessing alcohol consumption – the Yale Alcohol Drinking paradigm (ADP) – to assess the feasibility of these combined methods for use in future studies to test AABM efficacy in alcohol use reduction and abstinence initiation in actively drinking individuals with AUD -- not only for relapse prevention in already abstinent individuals (as previous trials have done) -- and not just to rely on self-reports of drinking/relapse behavior, but to obtain actual measures of alcohol use.

3.2 Purpose of Study/Potential Impact
We will conduct the first pilot trial of AABM effects on alcohol consumption in the human laboratory in non-treatment-seeking, heavy-drinking individuals and the first trial of AABM effects on the Yale Alcohol Drinking Paradigm - a method of rapidly assessing the potential efficacy of putative pharmacologic and possibly behavioral treatments for AUD. Participants will be 12 non-treatment-seeking heavy-drinking male volunteers. After baseline assessment, participants will undergo Human Lab session 1, in which we will administer the Alcohol Approach-Avoidance Task (AAT) (not AABM training) to measure baseline (pre-treatment) alcohol approach bias tendency, and then conduct the ADP to measure baseline alcohol consumption. After Human Lab/ADP Session 1, participants get 2 weeks of a total of 6 sessions of training; they will have been randomly assigned to undergo AABM or a sham training condition. Outcomes will be various measures of feasibility, including recruitment, retention, safety, and adverse effects and assessment of measurement burden, and the tolerability of ADP and AABM interventions

3.3 Potential Risks and Benefits

3.3.1 Potential Benefits
There is no direct benefit to these participants besides referral to treatment, which will be provided at the end of the study. They will be able to withdraw from the study at any time. The direct benefit is not great for participants, but given the potential benefit to developing effective treatments for alcoholism, the risk-benefit ratio appears favorable.

Participants may benefit somewhat from the extra physical examination, laboratory tests, and attention. In the informed consent form, participants are instructed: "Taking part in this study may not make your health better. If you are in this study, you may benefit from the physical examinations, blood tests, and review of your symptoms. Others may benefit from the overall conclusions drawn from the results of this study."

AUD is major public health problem that contributes prominently to the global burden of disease [58]. While there are several approved medications for the treatment of AUD, the available pharmacotherapies are hampered by small effect sizes, adverse effects, and limited adoption into practice. Currently available FDA-approved pharmacological agents have major limitations and there is a critical need to identify novel medication strategies for AUD treatment. Despite the large numbers of patients who suffer from AUD, medications are greatly underutilized and only a small minority of adults in the

United States who have AUD are treated with medications. *This low utilization is thought to be in part due to a perception of AUD medication ineffectiveness*. The potential knowledge to be gained in this study is judged to be highly significant. This research seeks to expand the knowledge base regarding the treatment of alcohol use disorder. Because of the known low to moderate risk profile of the study medications and the close monitoring afforded by the study design, the level of risk for prospective participants is judged to be modest, and therefore, is considered to be reasonable, in comparison with the potential knowledge to be gained.

The results of this laboratory-based drinking paradigm will provide an important initial signal regarding the potential efficacy of Alcohol Approach Bias Modification in reducing alcohol drinking. There is a great need for the development of new methods to treat alcohol use disorder. This laboratory paradigm will also provide information regarding the mechanism of action of this novel method and thus significantly contribute to the literature**.**

3.3.2 Potential Risks and Procedures to Minimize Risks

The major potential risks in this study are related to administration of alcohol, blood drawing during the physical exam and the alcohol drinking period, and risks to privacy.

Alcohol

A number of medical conditions could potentially be worsened by acute alcohol administration (e.g., liver disease, cardiac abnormality, pancreatitis, diabetes, neurological problems, diabetes, and gastrointestinal disorders). During screening, the study physician will conduct a medical history and physical exam and review laboratory findings. As a result, participants with medical problems that are judged by the study physician/PI (Dr. Batki) will be excluded from the study.

Alcohol may also cause nausea in high doses; however, nausea is not expected at the dose being used in this sample of heavy drinkers. Participants will not be drinking to levels more than they typically consume in their own drinking context, and, with the exception of the priming dose, they determine the amount of alcohol consumed.

Another area of potential risk to participants under the influence of alcohol involves their safety during the experimental procedures. Although impairment of gross motor coordination in heavy drinkers is rare at the alcohol dose used in this study, all participants will be under the supervision of the experimenters to prevent possible accidents such as falls. Participants will not leave the laboratory during the self-administration procedure,

Alcohol is a reinforcing agent, which may cause changes in behavior including repetitive or excessive alcohol consumption. Because of this, the administration of alcohol to alcoholics in treatment could potentially impede the progress of their recovery. In addition, the administration of alcohol to sober alcoholics living in the community presents a possible risk of relapse. As a result, we will be recruiting non-abstinent non-treatment-seeking alcoholics in keeping with the National Advisory Council on Alcohol Abuse and Alcoholism's recent update of its 1989[41] recommended guidelines on ethyl alcohol administration. At completion of the study, we will make a serious and concerted effort to link the participant with treatment for their alcohol problems. This will be done by giving the participant objective feedback about the fact that their drinking exceeds standards for avoiding hazardous drinking, providing a brief one-session motivational intervention for their drinking, and by arranging for alcohol treatment services if they are interested. In our previous and ongoing work, several participants quit drinking and many others reduced their drinking in the three months following this intervention.

****Protection against risks of alcohol challenges****

The alcohol challenges will be conducted by Dr. Batki and research staff, using methodology adopted from the Yale group, and trained by our Yale colleague, Dr. Suchitra Krishnan-Sarin.

We provide a number of safeguards to reduce the risk of physical injury by supervising all sessions and having participants stay in the CRC until they are alert and do not show signs of psychomotor impairment. We also exclude participants for whom physical or psychological problems contraindicate alcohol consumption. By selecting non-treatment-seeking participants who are currently drinking heavily on a regular basis, we are not exposing participants to alcohol consumption levels that differ from their normal drinking context. Although this has not happened in the Yale group's experience, should a participant insist on leaving the research setting prematurely, we will provide transportation back to their residence. This contingency will be explicitly addressed in the consent form.

Clearly, participants are free to discontinue the experiment at any time, although we would strongly encourage them to remain in the research setting until their blood alcohol level is below .02 and alertness and psychomotor status are judged to be safe.

Because participants are not in treatment, participation in an alcohol challenge study will not interfere with efforts to achieve abstinence. At the end of the study, however, a potential benefit is that participants will be provided with a professional evaluation and treatment will be arranged if they express interest.

****Protection against the risk of heavier alcohol use, suicidality, or other medical or psychiatric problems that may arise over the course of the study****
To protect against this risk, we will do the following:
-We will closely monitor alcohol use at each visit.
-Participants will be withdrawn from the study if, in the opinion of the PI or the DSMB, there is: sustained clinically significant increase in alcohol use between ADP sessions 1 and 2, suicidal ideation consisting of suicidal intent or plan, unacceptable adverse events judged by the study physician (the PI, Dr. Batki) to be related to study interventions, or any other clinically significant medical, psychiatric, or substance use related poor outcome that makes continued study participation unsafe.

Blood and Urine Collections
Screening blood and urine collections are performed primarily as safeguards to participants and should add no risks other than those normally associated with these procedures. Participants will have approximately 8 mL or 2 tsp of blood drawn at the intake appointment to determine liver and kidney functioning, and during the self-administration portions of the study we will draw approximately 3 mL or ½ tsp of blood at each of the 2 visits. Therefore, the total amount of blood drawn during the study (17 ml or 3.5 tsp) poses minimal risk in healthy participants. We will advise participants against donating blood for six weeks following study participation.

Blood Drawing (Venipuncture) Risks
Participation in the study requires participants to have their blood drawn 3 different times over the course of study (screening and human laboratory ADP sessions 1 and 2). Having blood drawn may cause pain (common), fainting/passing out (not very often), a bruise where the needle goes in (not very often), and infection at the same place (rare).

****Protection against blood drawing (venipuncture) risks****
To protect against this risk, we will do the following:
1) Professionally trained phlebotomists at the CTSI Clinical laboratory will perform all phlebotomies.

Risk of Privacy/Confidentiality
Participation in the study presents a risk to the participant of loss of privacy and confidentiality regarding research material, particularly with respect to potentially embarrassing or harmful personal health information, particularly related to mental health and alcohol and substance use. This includes detailed and sensitive information regarding alcohol and drug use, and psychiatric symptoms. For example, urine drug testing will be conducted. Potential release of information regarding drug use, in particular, could have serious implications if made known, for example legal ramifications, jeopardizing insurability or employability.

In order to ensure the safety of the participant and others, information may be shared between research staff and the clinical team only under the following circumstances: 1) If in the judgment of the study physician, the participant has a psychiatric or medical condition that requires urgent attention to protect the safety of the participant or others; and 2) If a participant has missed several study appointments, and research staff needs to verify the participant's whereabouts and/or verify the participant's safety. These above circumstances will be clearly outlined in the informed consent form, and be discussed and clarified with prospective participants at the start of the study.

****Protection against risks to privacy/confidentiality****
To protect against this risk, we will do the following:
- In the informed consent form, participants are instructed: "Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. If you do not already have a medical record at the VA Medical Center, San Francisco, one will be created because of your participation in this study."
- *HIPAA regulations will be followed throughout this study.* Several methods will be used to decrease the risk *of loss* of confidentiality to participants.
  - First, all study forms will be labeled with a unique, identifying code number, and maintained in a locked cabinet. Those

that contain the names of participants or other identifying information will be stored in a locked cabinet, separate from other study forms.

- Second, research material will not be shared between the research team and clinical staff - with the exception of information to be shared only to ensure the safety of the participant and others.
- Third, no names will be used in any published reports about this study.
- Fourth, most of the questionnaire data will be collected using an online survey instrument called Qualtrics:

All collected research data will be referenced by unique study identification codes only, stored in an electronic database (SQL server) on a password-protected secure VA server behind a secure VA firewall at SFVAMC available to study staff only. After receiving CHR and R&D approval, we will be collecting most of our questionnaire measures in digital format, so that this questionnaire data can be collected using an online survey instrument called Qualtrics, which meets strict IRB and HIPAA data security requirements. Data will be entered into SQL Server tables using MS Access as a front-end or batch load from an external file. At a point of entry, form values are subjected to consistency edit checks (e.g. range and type verification, missing data). Scoring algorithms are applied where appropriate. Once data is entered into the database, edit checks are run for accuracy.

Unknown Risks

Participants may experience side effects that are not known yet.

****Protection against unknown risks****

To protect against this risk, we will do the following:

-During the informed consent process, participants will be notified about the possibility of unknown risks associated with taking lacosamide or their combination with alcohol.

-During the informed consent process, the possibility of unknown risks are explained and that researchers will let participants know if new information about risks and side effects becomes available over the course of the study.

-Adverse effects will be carefully monitored during each ADP lab session.

4. STUDY OBJECTIVES

4.1 Hypothesis

Include a clearly defined hypothesis, if relevant, and list the key questions the study is expected to answer. Be detailed, clear and as specific as possible.

4.2 Primary Objective

As this is a small pilot study, the Primary Aims are *process*- rather than *outcome*-oriented:

1. To establish the feasibility and safety of giving alcohol to human participants in a laboratory alcohol self-administration procedure;

2. To establish the feasibility and safety of administering AABM training sessions; and

2. To allow our research team to gain experience with these procedures and fine-tune them.

4.3 Secondary Objectives

The Secondary Aim is to obtain a preliminary assessment of the effects of Alcohol Approach Bias Modification training on alcohol consumption and related behaviors in individuals with AUD.

5. STUDY DESIGN

5.1 General Design

We will conduct the first pilot trial of AABM effects on alcohol consumption in the human laboratory in individuals with AUD and the first trial of AABM effects on the Yale Alcohol Drinking Paradigm - a method of rapidly assessing the potential efficacy of putative pharmacologic and possibly behavioral treatments for AUD. Participants will be 12 non-treatment-seeking heavy-drinking male volunteers. After baseline assessment, participants will undergo Human Lab session 1, in which we will administer the Alcohol Approach-Avoidance Task (AAT) (not AABM training) to measure baseline (pre-treatment) alcohol approach bias tendency, and then conduct the ADP to measure baseline alcohol consumption. After Human Lab/ADP Session 1, participants get 2 weeks of a total of 6 sessions of training. Outcomes will

be various measures of feasibility, including recruitment, retention, safety, and adverse effects and assessment of measurement burden, and the tolerability of ADP and AABM interventions.

5.1.1 Study Duration

The study begins with a screening visit that is expected to last approximately 4 hours. If it is deemed safe for the participant to enroll in the study and they meet all eligibility criteria, then the participant will be scheduled for 2 human lab sessions, each 12 hours long. The human lab sessions will take place on Week 2 (1st human lab session) and Week 5 (2nd human lab session). After each human lab session, a study coordinator will conduct a phone visit which is estimated to take 10 minutes. In addition to the human lab sessions, participants will come to the Ft. Miley campus 3 times per week for 3 weeks to complete Alcohol Approach Bias Modification (AABM) training sessions. These computerized training sessions last 20-30 minutes and will occur during Weeks 3 and 4 of the study. A follow-up visit will be scheduled 7 days after the 2rd and final human lab session. In total, participants can expect to spend about 32 hours over the course of 6 weeks.

5.2 Outcome Variables

This section describes the primary and secondary outcome variables, which are the endpoints that will be used to assess the study.

5.2.1 Primary Outcome Variables

The primary outcome variables are measures of feasibility:

1. Time needed to recruit, screen, and run the study procedures for 12 participants.
2. Retention rates at the various in the study process (screening, Human Lab ADP session 1 + 2, AABM training sessions 1 – 6, and follow-up).

5.2.2 Secondary Outcome Variables

Secondary outcomes:

1. Alcohol craving
2. Alcohol consumption during each of the 2 Human Lab ADP sessions.

5.3 Study Population

A total of 12 male non-treatment seeking healthy community volunteers will be enrolled.

5.3.1 Number of Participants

The study will enroll 12 men participants. We anticipate needing to start up to 15 participants to get 12 to complete 2 human lab sessions and the majority of the 6 AABM training sessions.

5.3.2 Eligibility Criteria

Inclusion Criteria:

1. Men, ages 21-50;
2. Able to read English and to complete study evaluations;
3. Heavy (also known as risky, high-risk, or hazardous) alcohol use, defined as 15-70 standard drinks per week on average over the past 30 days;
4. No more than 3 days/week of alcohol abstinence in the past 30 days, to maximize likelihood that participants will choose to drink during the laboratory sessions.
5. At least 1 heavy drinking day ($\geq$ 5 drinks/day) per week on average during the 30 days prior to screening.

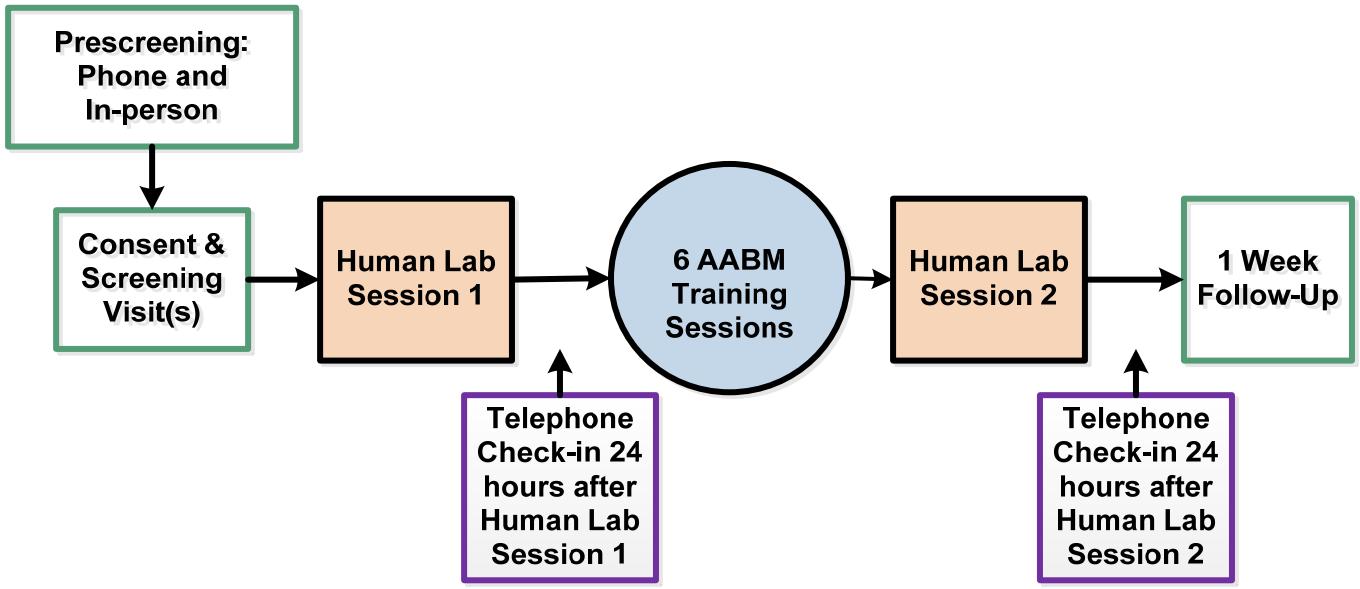
Exclusion Criteria:

1. Individuals who are seeking AUD treatment or have been in treatment within the past 6 months;
2. Current DSM-V non-alcohol substance use disorder other than tobacco and marijuana;
3. Positive urine drug test results at more than one baseline appointment for opioids, cocaine, benzodiazepines, or barbiturates;
4. Regular use of psychoactive drugs including antipsychotics, anxiolytics and antidepressants during the 30 days prior to entry, as well as anticonvulsants, beta blockers, central nervous system stimulants or depressants, or other drugs that cause excessive sedation;
5. Psychosis or any other serious mental illness as judged by MINI and study physician assessment;

6. Medical conditions that in the judgment of the study physician contraindicate the consumption of alcohol or would make study participation hazardous;
7. History of serious alcohol withdrawal (e.g. seizures, DTs, hospitalization) or a Clinical Institute Withdrawal Assessment Scale (CIWA-AD) score $\geq$ 8;
8. Participants who report disliking beer will be excluded because beer will be provided during the alcohol self-administration periods.

6. METHODS

The study will consist of the following steps, replicating the Yale ADP methods:
(1) Recruitment;
(2) Pre-screening: Brief telephone or in-person to determine eligibility for full screening beginning with establishing non-treatment seeking status;
(3) Full Screening/baseline visit: 1-3 in-person visits to obtain consent and to evaluate eligibility (e.g. to reject participants with medical conditions): participants who meet *heavy drinking criteria*, and by confirming that the individual is *non-treatment seeking*. If these criteria are met, physical examination and laboratory testing will be conducted. Eligible participants then proceed to the main part of the study, which includes participation in 2 human lab sessions and 6 AABM training sessions.
(4) Human Lab ADP Sessions 1 and 2: There will be two sessions, Human Lab/ADP Session 1 (Pre-training), and Human Lab/ADP Session 2 (post-training). Alcohol Drinking Paradigm (ADP): After the alcohol cue-induced craving, subjects will be given the opportunity to self-administer alcohol using the ADP. (**Table 1**) Subjects are first given a moderate Priming Drink of alcohol at 11 AM, designed to raise blood alcohol to ~0.03 mg%, and are instructed to drink it within 5 minutes. At 1 PM, and again at 2 PM, subjects undergo two 1-hour long alcohol Self-Administration (SA) periods. For each SA period, a tray of 4 beer drinks (each containing an amount of alcohol calculated to increase blood alcohol concentration by 0.015 mg%) will be brought into the Lab room along with a "tab" sheet worth $12. Participants are told that these 4 drinks will be available for the next 60 minutes, and they can choose to drink or keep the money; each drink will cost $3. The money will be given by check at the end Human Lab Sessions. This monetary cost for each drink was determined to reliably reflect the trade-off between desire to drink and cost[20,21]. **The main measure is the number of drinks consumed over the course of two 1-hour-long SA periods.** Dr. Krishnan-Sarin at Yale University helped to develop the ADP, and it has been adopted by other prominent research groups[22-33].
(5) Phone Visits 1 and 2: After each Human Lab ADP session, a study coordinator will call the participant to check in by phone.
(6) Alcohol Approach Bias Modification (AABM) training: Immediately following completion of Human lab Session 1, patients will be randomly assigned to receive 6 sessions of AABM training over 2 weeks beginning 2-7 days after Human Lab/ADP Session 1. We will use a training version of the Alcohol Approach-Avoidance Task: patients are asked to respond to the format of presented pictures using a joystick (push right-tilted pictures, pull left-tilted pictures), irrespective of the pictures' content. Pushing a picture away decreases picture size; pulling a picture closer increases size (zoom effect). There are 2 categories of pictures; 20 different alcoholic and 20 different non-alcoholic beverages. Training effect is achieved by presenting alcohol pictures in push format only and non-alcoholic drinks in pull format only. 200 trials are presented per session (~20 minutes) with a short break halfway through.
(7) Participants then undergo a Follow-up visit 1 week after the last ADP session, where adverse events and alcohol use will be assessed and a research clinician will provide a motivational enhancement session to encourage these non-treatment seeking participants to consider treatment and provided with referral materials.



6.1 Treatment – Computerized Training

6.1.1 Identity of Investigational Treatment
The Alcohol AAT is a joystick-task that measures automatic approach tendency toward alcohol. The proposed Alcohol AAT was developed based on the previous work of Wiers et. al., (2009) [10,12] and Rink et al., (2007)[50].

6.1.2 Dosage, Administration Schedule
Patients are instructed to respond to the format of presented pictures using a joystick (push right-tilted pictures, pull left-tilted pictures), irrespective of the pictures' content. Pushing the picture away decreases picture size, while pulling a picture closer increases size (zoom effect). There are 2 categories of pictures; 20 different alcoholic and 20 different non-alcoholic beverages (soft drinks). Patients are instructed to either push or pull for left-tilted images and to perform the alternative response for right-tilted images. All images are presented in both formats. The difference in reaction times (RT) between push and pull is the approach bias. The task starts with 10 practice trials showing neutral objects (containers), followed by 80 test trials. A standardized d-score is calculated which represents differences in reaction time for pushing vs. pulling[75]. Negative values indicate less alcohol-approach bias[75].

6.1.3 Method of Assignment/Randomization
All participants will receive the active AABM training intervention.

6.1.4 Blinding and Procedures for Unblinding
Not applicable

6.1.5 Packaging/Labelling
Not applicable

6.1.6 Concomitant Therapy
Participants will be informed that they cannot use psychoactive drugs including antipsychotics, anxiolytics and antidepressants during the 30 days prior to entry, as well as anticonvulsants, beta blockers, central nervous system stimulants or depressants, or other drugs that cause excessive sedation in the judgment of the study physician/PI. Additionally, if participants engage in treatment for alcohol use disorder while enrolled in the study, then they will be withdrawn as they are no longer considered eligible.

6.1.7 Restrictions
As per Exclusion Criteria, above.

6.2 Assessments
Please see the list of study measures below, Sec. 6.3.5

6.2.1 Efficacy
This is a pilot feasibility study, not an efficacy study. The primary outcome variables are measures of feasibility:

1. Time needed to recruit, screen, and run the study procedures for 12 participants.
2. Retention rates at the various in the study process (screening, Human Lab ADP session 1 + 2, AABM/sham training sessions 1-6, and follow-up).

6.2.2 Safety
Please see the study procedures, below, Sec. 6.3.5, and steps to minimize risks, above, in Sec.3.3.5.

6.2.2.1 Adverse Events Definition and Reporting

Adverse Events
During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any adverse events. Important clinical information that comes to light during study participation will be communicated by research coordinators to the study physician in real time.

The study physician (either the PI, Dr. Batki) will review each participant's safety at each study visit.
-Lab results will be reviewed on the same day that the results are received.
-Adverse effects reported by participants will be reviewed on the same day as they are reported by the study participant.
-Adverse effect assessment will be done by the research coordinators and discussed with the study physician on a daily basis, immediately after these adverse effects are reported by the participant to the study coordinator.

As with our current, CHR-approved clinical trials, the study physician, if not immediately present at the time of adverse effect data collection, will be contacted in real time by the study coordinator by phone, pager, or text message, so that adverse effects can be discussed with the study physician. The study physician, based on examination of the participant and/or review of the participant's data, will make a clinical judgment at each visit regarding whether it is safe to proceed with study medications.

The PI will report to the IRB, DSMB and study sponsor his assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug via the CRF. For each adverse event recorded on the Adverse Event CRF, the PI will make an assessment of seriousness, severity, and causality.

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug. If a participant's dosage is reduced or treatment is discontinued as a result of an AE, the PI will report to the study sponsor via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Events leading to the clinical outcome of death from progressive disease will not be recorded as adverse events unless the PI believes that the event may have been caused by the study drug.

Serious adverse event (SAE) collection begins after the participant has signed informed consent and has received study drug. If a participant experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the PI feels the event may have been caused by a protocol procedure.

The PI will alert the study sponsor of any SAE within 24 hours of the PI's awareness of the event. Alerts issued via telephone will be immediately followed with official notification on study-specific SAE forms.

An SAE is any adverse event from this study that results in one of the following outcomes:

- death (excluding death due to progression of study disease, unless related to study drug);
- initial or prolonged inpatient hospitalization;
- a life-threatening experience (that is, immediate risk of dying);
- persistent or significant disability/incapacity;
- congenital anomaly/birth defect;
- considered significant by the PI for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events (SAEs) occurring after a participant has taken the last dose of study drug will be collected for 7 days after the last dose of study drug, regardless of the PI's opinion of causation. Thereafter, SAEs will not be reported unless the PI feels the events were related to either study drug, or drug delivery system, or a protocol procedure. Any SAE occurring prior to enrollment that the PI believes may have been caused by a protocol procedure will be reported to the study sponsor within 24 hours of the PI's awareness of the event and recorded on the CRF.

Study-specific clinical outcomes of death from progressive disease will be reported as SAEs only if the PI deems them related to use of the study drug.

Immediate Reporting Requirements From

PI to Sponsor:
Certain events will be immediately reported to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The PI will report such events to the Sponsor immediately; under no circumstances will be reporting take place more than 24 hours after the PI learns of the event. The following is a list of events that the PI will report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study providers:
Serious adverse events
Non-serious adverse events of special interest
Pregnancies

The PI will report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis;
- Significant new diagnostic test results;
- Change in causality based on new information;
- Change in the event's outcome, including recovery;
- Additional narrative information on the clinical course of the event.

Emergency Medical Contracts

Medical Monitor Contact Information:
Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the PI to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an CRF within 24 hours.

The following is the contact information that will be utilized by the PI:
MEDICAL MONITOR
Anne Richards, MD, MPH
SFVAMC/UCSF
4150 Clement Street
San Francisco, CA 94121
Telephone:415/221-4810 x 23312
Email: anne.richards@va.gov

Follow-up of Participants after Adverse Events

PI Follow-Up:
The PI will follow all unresolved treatment-related adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the PI, new therapy is initiated, the participant is lost to follow-up, or the participant withdraws consent.

Every effort will be made to follow all serious adverse events considered to be related to study procedures until a final outcome can be reported. During the study period, resolution of adverse events (with dates) will be documented on the Adverse Event CRF and in the participant's medical record to facilitate source data verification (SDV). If, after follow- up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event CRF.

Data Review - For Phase II or III Sponsor Studies
PIs will conduct continuous review of data regarding participant safety at weekly study group meetings where the results of each participant's treatment are discussed, as is currently done for the PI's other UCSF CHR approved clinical trials. The discussion will include the number of participants, significant toxicities as described in the protocol, doses adjustments, and observed responses.

6.3 Study Procedures

6.3.1 Study Schedule

WEEK	STUDY VISIT	TIME PER VISIT^
Week 1	Screening visits	2.5 hours
Week 2	ADP Session # 1	12 hours
	Phone visit #1	10 minutes
Week 3	AABM training session #1 + #2	1.5 hours
	AABM training session #3 + #4	1 hour
	AABM training session #5 + #6	1.5 hours
Week 4	ADP Session #2	12 hours
	Phone visit #2	10 minutes
Week 5	Follow-up visit	30 minutes
TOTAL	12 study visits	approximately 31-32 hours

^The amount of time is an approximation

6.3.2 Informed Consent
The process of informed consent will minimize undue influence or coercion and offer sufficient time for review. Typically study coordinators will receive thorough training on the correct way to conduct informed consent. On a rare occasion, a study physician or project manager will conduct informed consent. All staff conducting informed consents have at least a Bachelor of Arts or Science in a health-related field and/or have 2 years of research-related experience. Training for the administration of informed consent teaches study staff how to move through the consent, assessing participant's comprehension along the way. A staff member in training will (1) shadow a trained staff member conducting informed consent 2 times, then (2) practices informed consent with other lab members, and finally (3) conducts informed consent with a participant while another trained lab member watches. Once the staff member-in-training satisfactorily conducts informed consent under the supervision of another trained staff member, the staff-in-training becomes authorized to conduct informed consent.

6.3.3 Screening
After consent, participants will be scheduled for screening assessments. The screening phase is accomplished over a total of 1 to 3 visits.

6.3.4 Enrollment
Once a participant has completed all screening/baseline measures and procedures and it has been determined that the participant is eligible and it is safe to participate, then they will be enrolled in the study.

6.3.5 On study visits

Baseline/screening visit 4 hours	Informed consent + HIPAA
	Participant Locator form
	Demographics
	Eligibility form
	Medical History
	Physical Exam
	Lab tests
	Height/weight
	Concomitant Medications
	Columbian Suicide Severity Rating Scale
	AE Spontaneous
	Breath alcohol test
	Structured Clinical Interview for DSM-5 (SCID)
	Timeline Followback (TLFB)
	Clinical Institute Withdrawal Assessment (CIWA-AD)
	Urine Drug Screen (UDS)
	Barratt Impulsiveness Scale (BIS-11)
	Alcohol Use Disorders Identification Test (AUDIT)
	Alcohol Purchase Task (APT)
	Obsessive Compulsive Drinking Scale (OCDS)
	Vitals
	Balloon Analogue Risk Task (BART)
	Delay Discounting (DD)
	Iowa Gambling Task (IGT)
	Salience Task
Phone Visits 1 and 2 10 minutes each	AE Spontaneous
	Timeline Followback (TLFB)
Human Lab Sessions 1 and 2 12 hours each human lab	Weight
	AE Spontaneous
	Concomitant Medications
	Breath alcohol test
	Timeline Followback (TLFB)
	Clinical Institute Withdrawal Assessment (CIWA-AD)
	Urine Drug Screen (UDS)
	Blood alcohol level (BAL)
	Vitals
	Alcohol Urge Questionnaire (AUQ)
	Biphasic Alcohol Effects Scale (BAES)
	Balloon Analogue Risk Task (BART)
	Delay Discounting (DD)
	Ratings of Drinking Behavior During the Alcohol Self-Administration Period
AABM/Sham Training Sessions 1-6 30 minutes each visit	Concomitant medications
	AE Spontaneous
	Breath alcohol test
	TLFB (Sessions 2, 5, and 8 only)
	CIWA-AD
	AABM/Sham training
AABM/Sham Training Sessions 1 and 6 an additional 1.5 hours	Obsessive Compulsive Drinking Scale (OCDS)
	Alcohol Purchase Task (APT)
	Iowa Gambling Task (IGT)
	Delay Discounting (DD)
	Balloon Analogue Risk Task (BART)

	Barratt Impulsiveness Scale (BIS-11)
	Stop Signal Task (SST)
Follow-up Visit 1 hour	Breath alcohol test
	Timeline Followback (TLFB)
	Concomitant medications
	AE Spontaneous
	Medical Management (MM)
	Participant End of Study Questionnaire

Assessments at Study Entry and During and After Human Lab Sessions

At Entry:
These are adapted from previous/ current clinical studies at the UCSF/SFVAMC Addiction Research Program.
▪ Demographic data, will be assessed with data on age, race, socioeconomic status, marital status, educational and occupational levels, and significant medical history.
►A number of safety evaluations are included: Medical history and physical examination; Suicide Risk Assessment: The Columbia Suicide Severity Rating Scale [101]. It is a standard, thorough, frequently used method to screen for suicidal ideation, used by our group in alcohol use disorder clinical trials;
▪ Clinical Laboratory Tests for Health/Safety Monitoring: Blood samples will be collected for chemistry, liver panel, renal panel and complete blood count (CBC); urine will be collected for urinalysis.
▪ Structured Clinical Interview for DSM5, (SCID) [96]**:** the SCID will be used to determine DSM-V diagnosis of current (current year) Alcohol Use Disorder, and the DSM-V current psychiatric diagnoses for anxiety, mood, psychotic, and non-alcohol substance use disorders in order to determine study eligibility.
▪ Study Physician Review: All health measures, medical history/exams and labs will be reviewed by a study physician to ensure that the subject meets all the eligibility criteria and are ready for randomization
▪ Alcohol Approach Task (AAT): A way to measure pre-treatment alcohol approach bias tendency. Salience Task: A survey that measures the salience of each stimulus image for participant.

At Entry and at various times throughout the study:
▪ Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD): at entry and before each Human Lab Session and at each Follow-up;
▪ Urine Drug Screen: For opioids, benzodiazepines, cocaine, amphetamines, cannabis, barbiturates: at entry and before each Human Lab Session.
▪ Breath alcohol concentration (BrAC); at entry and before each Human Lab Session; and during each Human lab Session
▪ Vital Signs**:** Temperature, heart rate, and blood pressure will be measured at study entry and multiple times during each Human Lab Session.
▪ Concomitant Medications Review: at entry and before each Human Lab session: thorough review of all concomitant medications (prescription or over-the-counter) in the past 30 days, as well as those started during the study.
▪ Concomitant Treatment Log: At Entry and A way to track any type of alcohol treatment at baseline/screening and throughout the study.
▪ Adverse Effects: Spontaneous: At Entry and at Human Lab Session 1 and 2; Phone visits 1 and 2; AABM Sessions 1-6; 1-wk FU. This form is designed to collect information about adverse health events. We will ask about emergent AEs, follow-up with AEs reported at previous study visits, and ask if there has been a hospital admission since the last study visit.
▪ Timeline Followback (TLFB): at study entry, then Human Lab Session 1 and Human Lab Session 2. TLFB will be used to calculate standard drinks consumed per week in the past 30 days prior to consent and at the two Human Lab Sessions, and the 1-week follow-up. The TLFB will be used to determine whether subjects meet minimum alcohol consumption criteria at entry. Other substance use will also be collected by TLFB.
▪ Barratt Impulsiveness Scale (version 11) (BIS-11) [98]: This provides a trait measure of impulsiveness and will be used to characterize the study cohort at study entry.

At AABM Training Sessions:
▪ Alcohol Use Disorders Identification Test (AUDIT): The AUDIT [97] is valid and reliable self-report measure of alcohol-related problem severity.
▪ Obsessive Compulsive Drinking Scale (OCDS): At AABM sessions 1 and 6. A questionnaire that measures cognitive aspects of alcohol craving.

▪ Alcohol Purchase Task (APT): At AABM sessions 1 and 6. A questionnaire uses hypothetical choices regarding alcohol purchases at varying prices to generate several indices of alcohol-related reinforcement.

At Follow-up visit:

▪ Motivational Enhancement Therapy: at the follow-up visit, research clinician will provide a motivational enhancement session to encourage the non-treatment seeking participants to consider treatment.

Measures of Alcohol Effects:

▪ Breath alcohol concentration (BrAlc) [99] *at each visit, and multiple times in ADP Sessions 1 and 2*. BrAlc will be measured at each session to detect recent alcohol use with the *Intoximeters Alco-Sensor IV* instrument.

▪ Blood Alcohol Levels**:** Human Lab Sessions 1 and 2 (Table 1)**:** Blood samples will be drawn to measure plasma levels of blood alcohol (BAC) during the priming dose and during the alcohol self-administration paradigm. Blood samples will be stored at -4°C and will be analyzed at the San Francisco VA.

- Time-line Follow-back (TLFB): To collect alcohol and drug use in the 90 days prior to entry and all days included in the 11 weeks of the study. TLFB will be used to calculate standard alcohol containing drinks consumed per week in the past 90 days prior to consent and then throughout the 11 weeks of the study. Cigarette and substance use will also be collected by the TLFB.

▪ Biphasic Alcohol Effects Scale (BAES) [81]: Human Lab Sessions 1 and 2 (Table 1). This 14-item self-report rating scale measures alcohol stimulant/ sedative effects and is used regularly in the Yale ADP.

▪ Alcohol Urge Questionnaire (AUQ): At study entry; multiple times in Human Lab Sessions 1 and 2 (Table 1); 1-wk FU; 1-mo FU: The AUQ is an 8-item questionnaire assessing *desire, expectation of positive effect,* and *inability to avoid drinking if alcohol is available.* The AUQ is a reliable and valid scale for the measurement of self-reported alcohol urges. Its brevity and time frame for ratings (i.e. right now) makes it suitable for the ADP.

▪ Yale Craving Scale (YCS): multiple times during ADP Sessions 1 and 2. A measure of craving for alcohol.

▪ Ratings of Drinking Behavior During the Alcohol Self-Administration Period: multiple times in in Human Lab Sessions 1 and 2. Subjects will be videotaped during the alcohol self-administration portion of ADP 1 and ADP 2. Videotapes will be rated by two independent for the onset and offset of each sip of alcohol. Dependent measures will be constructed including time until the first sip and average time to consume each drink.

▪ Vital Signs: Human Lab Sessions 1 and 2 (Table 1). These will include heart rate, blood pressure, and skin. The blood pressure cuff will be on subject's dominant arm while the probe of will be attached to the middle finger of the subject's non-dominant arm. These data will be further used to examine the safety of using the study medications during alcohol self-administration.

Neurocognitive Assessments:

The battery was developed to assess performance in cognitive domains commonly affected by heavy alcohol use and contains standardized instruments with good-to-excellent norms administered (~1.5 hours) at AABM sessions 1 and 9. Raw scores will be converted to z-scores. Domain-specific summary scores will be calculated by averaging z-scores of the individual constituent measures. When feasible, alternate forms will be used for repeated administrations.

Domains and constituent measures:

a) *Risk Taking, Decision-making, and Motor/Choice Impulsivity:* Balloon Analogue Risk Task[86]; Iowa Gambling Task[87]; Stop-signal[88], Delayed Discounting[89];

Cognitive Training – Alcohol Approach Bias Modification (AABM) Training:

Immediately following ADP Session 1, heavy drinking participants will begin to receive 6 sessions of AABM training taking place over 3 weeks. We will use a training version of the Alcohol Approach-Avoidance Task: patients are asked to respond to the format of presented pictures using a joystick (push right-tilted pictures, pull left-tilted pictures), irrespective of the pictures' content. Pushing picture away decreases picture size; pulling a picture closer increases size (zoom effect). There are 2 categories of pictures; 20 different alcoholic and 20 different non-alcoholic beverages (soft drinks). Training effect is achieved by presenting alcohol pictures in push format only and non-alcoholic drinks in pull format only. Two hundred training trials are presented per session (~20 minutes) with a short break halfway through.

Participant Incentives

WEEK	ATTEND STUDY VISIT	TOTAL PER VISIT
Screening	$55*	$55
ADP Session #1 Phone visit #1	$200 (+ $24 for tab)**	$224
AABM 1 + 2	$50	$50
AABM 3 + 4	$40	$40
AABM 5 + 6	$50	$50
ADP Session #2 Phone visit #2	$200 (+ $24 for tab)**	$224
Follow-up @ 1 Week	$40 (+ $50 bonus if attended all study visits)***	$90
TOTAL		$733

*At the screening/baseline visit, participants are paid per task they complete. At the end of screening, they will earn $55.

**Participants will receive $200 for each ADP Lab Session they complete. They could earn an additional $24 per ADP Lab Session, depending on how many drinks they consume per session. At each session, participants are offered 8 drinks, each worth $3. They will receive $3 per drink for every drink that is not consumed.

6.3.6 Removal of participants

Stopping Rules

Discontinuation of participants:
Participants for whom there has been at least 2 weeks without participant contact will be discontinued from the study. Exceptions may be made after discussions with the PIs, approval by the Medical Monitor, and consistency with the regulations of the Institutional Review Board/Ethics Committee (IRB/EC).

Discontinuation of study:
The study will be stopped if, in the judgment of the DSMB or the PI, there are sufficient safety concerns that arise during the conduct of the study that would indicate that participants are being harmed by the study interventions. Examples of such safety concerns would be:
-Other events that pose unacceptable risks to participants, e.g., multiple SAEs that are judged to be related to study interventions.

Withdrawal Rules

Discontinuation of Participants:
If a participant who does not meet enrollment criteria is enrolled, the study sponsor will be contacted. In such cases, the PI will provide information on the participant´s anticipated benefit or current benefit from being enrolled in the study or continuing to receive study drug respectively. In addition, the PI will discontinue participants from the study drug or the study or both in the following circumstances:

- Participant has evidence of progressive disease.
- The participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.
- The PI decides that the participant should be withdrawn from the study. If a SAE or a clinically significant laboratory value is the basis for this decision, the PI will discontinue the study therapy and take appropriate measures. The PI will immediately notify the study sponsor or its designee.
- The participant or attending physician requests withdrawal of the participant from the study.
- The investigator or the study sponsor stops the study or stops the participant's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

- The study therapies have shown unacceptable side effects.
- The participant is noncompliant with study procedures.
- In the clinical judgment of the investigator, the participant requires acute detoxification from the alcohol.

When a participant withdraws before completing the study, the reason for withdrawal will be documented in the CRF and in the source document.

6.4 Statistical Method
Descriptive statistics will be used to summarize the data set. Measures of central tendency and measures of variability will be reported for the chief variables of interest as noted below in 6.4.3.

6.4.1 Statistical Design
As this is a pilot feasibility study, no inferential statistics will be used.

6.4.2 Sample Size Considerations
Not applicable.

6.4.3 Planned Analyses
Descriptive statistics will be used to describe the data set. Measures of central tendency and measures of variability will be reported. Chief variables of interest are listed below in 6.4.3.1, 6.4.3.2, and 6.4.3.3.

6.4.3.1 Primary Analyses
Primary analyses will consist of descriptive statistics. These measures of feasibility are:
1. Time needed to recruit, screen, and run the study procedures for 4 participants
2. Retention rates at the various timepoints in the study process (screening, Human Lab ADP session 1,2,3, and follow-up).

6.4.3.2 Secondary Objectives Analyses
Descriptive statistics will be used to summarize the data set. The variables analyzed will include:
1. Alcohol craving
2. Alcohol consumption during each of the 2 Human Lab ADP sessions.
3. Alcohol – medication interaction effects on BAES and computer tasks (AAT, BART, and DD)

6.4.3.3 Safety
Descriptive statistics will be used to summarize the data. The SAFTEE will be used to assess adverse effects. Descriptive statistics will be used.

7. TRIAL ADMINISTRATION

7.1 Institutional Review Board (IRB) Review
The Human Research Protection Program (HRPP) reviews and monitors research involving human participants at UCSF and affiliate institutions to ensure the ethical and equitable treatment of the research participants. Within the HRPP, the Institutional Review Board (IRB) reviews all research that involves human participants performed by UCSF faculty.

7.2 Unanticipated Problems
[Explain how unanticipated problems that may occur during the study will be handled, communicated to the IRB, sponsor, and FDA, if applicable.]

7.3 Study Monitoring
Study monitoring will be conducted by the DSMB.

7.4 Data Safety Monitoring Plan

Plan to monitor study progress and safety: The Data and Safety Monitoring Plan (DSMB)
The DSMP for this project consists of:
- a Data and Safety Monitoring Board (DSMB)
- a schedule of DSMB meetings to review study data and events

- a list of study data and event items to be reviewed by the DSMB
- procedures for communicating DSMB findings to the CHR, the study sponsor (Department of Defense) and other appropriate entities
- a plan for conducting and reporting interim analysis
- stopping rules
- rules for withdrawing study participants from the study interventions

These elements of the DSMP are described below:

The Data and Safety Monitoring Board (DSMB)
The Data and Safety Monitoring Board (DSMB) is a group of 3 physicians who are not study investigators and who are experts in the area of clinical research and substance use disorders. The current composition of the PI's DSMB is: William Wolfe, M.D., a clinical investigator and Medical Director, PTSD Clinic, SFVAMC; Anne Richards, M.D. [medical Monitor], an experienced human clinical investigator, Assistant Professor of Psychiatry at University of California, San Francisco and Steven Lieske, M.D., Ph.D., an experienced basic neuroscience investigator and attending psychiatrist, SFVAMC.

The DSMB will meet biannually to review data reports prepared by the PI regarding the progress of the study and will monitor patient enrollment, retention, outcomes, adverse events, and other issues related to patient safety. The DSMB will make recommendations to the PI as to whether the study should continue or be modified or terminated. The DSMB can consider patient safety or other circumstances as grounds for early termination. Any member of the DSMB can ask for a meeting of the group if he/she feels that it is necessary, based upon the data.

During the course of the study, reports will be prepared and distributed to the Data and Safety Monitoring Board on a biannual basis. In order for the Data and Safety Monitoring Board to discharge their duties for overseeing the study and the rights of the patients, they will receive analyses of the primary outcome measures and the important secondary measures on a quarterly basis. The DSMB will receive reports of serious adverse events (SAEs) within 72 hours of their occurrence.

DSMB Minutes will be prepared by the Study Coordinator within 5 working days after each biannual DSMB meeting.

Medical Monitor
Anne Richards, M.D., Medical Director of the PTSD Clinic at San Francisco VA Medical Center will serve as the Medical Monitor. As Medical Monitor, Dr. Richards will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor will comment on the outcomes of the event of problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The Medical Monitor will also indicate whether she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the IRB and other governing authorities.

7.5 Study Discontinuation
If a serious adverse effect occurs and is considered by the PI and DSMB to be study-related, the study will be stopped until study procedures can be reassessed and modified as needed, with concurrence by the DSMB.

7.6 Study Completion
We will conduct the following procedures to close-out the study:
Submit a close-out report to the UCSF CHR
Submit a notification to the Biosafety Committee to close-out the Biological Use Authorization (BUA).
Submit notification to the SF VA R&D Committee to close-out the project.
Once all close-out reports have been processed, we will submit a notification to the study sponsor (UCSF RAP) with all other close-out reports.

7.7 Funding Source
The study is funded by the University of California, San Francisco (UCSF) Resource Allocation Program (RAP).

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Department of Veterans Affairs	INFORMED CONSENT FORM
Subject Name:	**Date:**
Title of Study: **ALCOHOL APPROACH BIAS MODIFICATION EFFECTS ON ALCOHOL CONSUMPTION: A PILOT HUMAN LABORATORY STUDY**	
Principal Investigator: **Steven L. Batki, M.D.**	**San Francisco VAMC**

CONSENT TO PARTICIPATE IN RESEARCH

This is a research study investigating the benefits of a "cognitive training program" – a training program to improve your thinking – designed to help you to reduce your alcohol use. The principal investigator, Steven L. Batki, M.D. or Co-investigators and Dr. David Pennington, Ph.D. from the San Francisco VA Medical Center and UCSF Department of Psychiatry, or a designated research staff associate, supervised by Dr. Batki, will explain the study to you.

Research studies include only people who choose to take part. The purpose of this form is to give you the information you will need to help you decide if you want to be in this study. Read this form carefully and ask questions about anything you do not understand. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. When all your questions have been answered, you can decide if you want to be in this study. If you do decide to be in the study, you will get a copy of this signed and dated form to keep for your records.

1. Why is this study being done?

The purpose of this study is to discover if a "cognitive training program" called "alcohol approach bias modification (AABM)" can help reduce alcohol use and improve your thinking.

AABM is a computer training program that has been well-studied and shown to reduce alcohol use.

This study is funded by the University of California, San Francisco (UCSF).

2. How many people will take part in this study?

About 12 men will be enrolled in this study.

3. Are there some people who should not be in this study?

The study doctor or a member of the study staff will talk with you about the requirements to participate in this study. It is important that you are truthful with them about your history. You should not be in this study if you do not meet all the qualifications.

You should not be in this study if:

- You are younger than 21 years of age or older than 50 years of age.
- You are seeking treatment for alcoholism, or if you would like to receive treatment to help reduce alcohol use.
- You are currently receiving treatment for alcoholism, or have received treatment for alcoholism in the past 6 months.
- You are currently receiving medication for alcoholism, including disulfiram (Antabuse), naltrexone (Depade, Revia or Vivitrol) or acamprosate (Campral).
- You are already in another alcohol treatment study or study involving medication as a treatment for alcoholism.
- You have liver disease, heart disease, pancreas problems, diabetes, neurological problems, or if you have gastrointestinal problems that are worsened by drinking alcohol.
- You regularly used opioids, cocaine, benzodiazepines or barbiturates in the past 30 days.

- You regularly used medications that can affect your brain and nervous system in the past 30 days, such as medicines used to treat psychiatric conditions like psychosis, anxiety, depression or medications to treat epilepsy (seizures).

4. How long will I be in the study?
In total, you will be asked to commit approximately 35 hours of your time over the course of 6 weeks.

5. What will happen if I take part in this study?
All study procedures will take place at the San Francisco VA Medical Center. The study can be divided into 4 parts:

a. Screening: 1-3 visits over approximately 1 week.

b. Main – ADP sessions: 2 all-day Alcohol Drinking Paradigm (ADP) sessions.

The 2 all-day ADP sessions will be at the San Francisco VA Medical Center. At each of these 2 all-day study visits, you will participate in an alcohol drinking session under observed conditions. We refer to each of these all-day alcohol drinking sessions as the "Alcohol Drinking Paradigm (ADP)".

c. Main – AABM sessions: 6 sessions over 2 weeks of Alcohol Approach Bias Modification (AABM) computer training.

The AABM is a computerized training session during which you will interact with a computer by pushing and pulling a joystick. During the task you will be asked to respond to the format of a presented picture, irrespective of the pictures' content. Pushing a presented picture away will decrease picture size, whereas pulling a picture closer will increase size (zoom effect). The duration of the training is approximately 20 minutes, and you will be given the option of a break halfway through the task.

d. Follow-up: 1 visit 1 week after the last ADP session.

5a. Procedures for the Screening:
To see if you are eligible to participate in the study, we will ask that you take part in the following exams, tests and procedures. Any information that we collect will be kept confidential (as detailed later in this Consent Form).

Breath alcohol test + informed consent:
The study will be discussed with you, and you will be asked to sign this consent form after you blow a 0.00 on your breath alcohol test. If you have ANY alcohol on your breath, as measured by the breathalyzer, you will be asked to wait until you have no alcohol on your breath or to complete your visit at another time.

- You can also ask to be referred to other treatment if you wish.
- If you are legally intoxicated, you will be offered transportation home.

Contact information:
You will be asked to provide the names and phone numbers of people we may contact in case you miss a study appointment. Research staff will confirm your personal contact information, as well as that of your alternate contact, before you can continue in the study.

Medical history and physical exam:
The study doctor will take your medical history and review the medication you use. You will also have a brief physical examination. The history and physical exam are similar to those done for regular medical care.

Vital signs:
A study staff member will measure your blood pressure, heart rate, height and weight.

Concomitant medication:
A study doctor will review all the other medications you are currently taking to make sure it is safe for you to participate in the study.

Blood drawing (venipuncture):
You will be asked to give a blood sample for routine laboratory tests to check your health. Approximately 2 teaspoons of blood (8 ml) will be drawn by inserting a needle into a vein in your arm for these tests. Blood will be taken for routine medical tests.

Urine sample:
You will be asked to give a urine sample to test for drug use, including recreational and illegal drugs and alcohol.

Medical and psychiatric diagnoses:
You will be evaluated for current and previous diagnoses.

Substance use assessments: You will be asked to report your use of alcohol and other substances (cigarettes, marijuana, cocaine, etc.) and possible alcohol withdrawal symptoms.

Questionnaires: You will be asked to complete questionnaires about your education, work, and other aspects of life. Some of the questionnaires ask that you answer detailed questions about your alcohol use, alcohol craving and family history of alcohol use.

Cognitive testing:
You will be asked to complete tests of your thinking ability that measure your thinking and decision-making. Some of these tests are paper and pencil tests and some are completed on the computer. We will repeat these tests at the end of the study so that we can try to understand how alcohol and the AABM (computerized training) affects your use of alcohol, your craving for alcohol, and your thinking.

5b. Procedures for the main phase – ADP Sessions:
After the Screening tests have been reviewed by a study doctor, and if you continue to meet the eligibility requirements, you will begin the main part of the study.

Overview:
You will be asked to attend 2 all-day study visits at the San Francisco VA Medical Center for the main part of the study. At each of these 2 all-day study visits, you will participate in an alcohol drinking session under observed conditions. We refer to each of these all-day sessions as an Alcohol Drinking Paradigm (ADP).

At each of these 2 ADP sessions, you will be offered alcoholic beverages and allowed to drink them within a certain period of time, under observed conditions. Study staff will be measuring how much alcohol you drink at each of these 2 ADP sessions. Each ADP session starts at 8 AM and finishes around 8 PM, for a total of 12 hours.

Details:
We ask that you not consume alcohol after 5 pm on the evening prior to each ADP session. When you arrive at the San Francisco VA Medical Center (SFVAMC), we will check your breath alcohol level by asking you to blow into the breathalyzer. If you arrive with a positive breath alcohol level and your breath alcohol level is above 0.00 and/or is increasing, indicating recent alcohol use, then the session will have to be rescheduled. If your breath alcohol level is above 0.05 and the session has to be rescheduled, we will have to keep you at the SFVAMC and advise you not to drive until it comes down to 0.02. Alternatively, we could provide you with transportation.

We will also collect a urine sample to screen for the use of drugs (e.g. cocaine, opiates, marijuana, benzodiazepines).

Then we will measure your height and weight, your heart rate and blood pressure, and ask you to complete some assessments and computer tasks. You will be given a light breakfast around 9:00 am, and a late lunch/early dinner around 3:30pm. If you are a smoker, you will be provided with 2 “smoke-breaks” during which you will be escorted out and allowed to smoke up to 2 cigarettes. Non-smokers will also be given the option of taking ‘breaks’ at certain intervals. When you are not completing assessments, you will be able to relax, read a book or be on your cell phone.

Later that same day, you will participate in the ADP. A video camera will be recording this session to monitor your drinking behavior. Prior to the start of this session, you will be asked to complete some questionnaires and rating scales. We will test your breath alcohol level over the course of the ADP and we will test your blood alcohol level once during the ADP. To test your blood alcohol level, about a half-teaspoon of blood (3 ml) will be drawn by placing a needle into a vein in your arm.

At 12 noon, you will be given your first alcohol drink. The amount of alcohol in this drink will vary depending on how much you weigh and will be the same as a typical mixed drink. You will be asked to drink it in 5 minutes. You must consume this drink in order to remain in the study. If you do not wish to consume the drink, you will be discharged from the study. You will then be monitored for the next 55 minutes and asked to complete some measurements.

At 1:00 pm you will be given a tray with 4 drinks, each worth $3, for a total of $12. During the next 50 minutes, you can either choose to drink or keep the money value of the drinks ($3 per each drink that you do not drink). If you choose the money, it will be given to you after the session is completed.

At 1:50 pm, the old drinks will be removed.

At 2:00 pm you will be given a tray with 4 fresh, new drinks, each worth $3. These will be available to you for the next 50 minutes. Again, you can choose to drink them or keep the money. The drinks will be removed at 2:50 pm at which time the alcohol drinking part of the session is over. Your breath alcohol level, blood pressure and heart rate will be checked until your breath alcohol level returns to 0.02 or less. You will also be asked to complete various measurements during the rest of your stay.

It is important to note that during the ADP sessions phone use, watching TV, and sleep will be restricted as follows:

TIME	PHONE USE	TV	SLEEP
8:30 AM – 9:30 AM	NO	NO	NO
9:30 AM – 10:00 AM	YES	NO	NO
10:00 AM – 11:00 AM	NO	NO	NO
11:00 AM – 11:30 AM	YES	NO	NO
11:30 AM – 3:00 PM	NO	NO	NO
3:00 PM – 8:00 PM	YES	YES	NO

At 8:00 pm you will be discharged and paid in return for your time and effort. If your breath alcohol level is above 0.02 at 8:00 pm, then a study doctor will conduct a brief examination to make sure it is safe for you to go home. If in the judgment of the study physician you are too intoxicated to safely go home, you will be taken to SF VA Emergency Department by the study physician for further evaluation and treatment, if needed.

You will repeat the ADP session 1 more time, for a total of 2 ADP sessions. There will be 2 weeks between the 1st and 2nd ADP session. Both ADP sessions are identical in nature. The day after each ADP session, a member of the study team will call you to conduct a 10-minute study visit by phone. During the conversation, you will be asked how you feel and if you are experiencing any side effects.

5c. Procedures for the main phase – AABM training:
After you complete your first ADP session, you will be receive AABM training.

At each of the 6 AABM training sessions, the following will take place:

Breath alcohol test
A breath alcohol test ("breathalyzer") test will be performed and you must have a blood alcohol concentration of 0.00%. If you have ANY alcohol on your breath, as measured by the breathalyzer, you will be asked to wait until you have no alcohol on your breath or to complete your visit at another time.

Substance use assessments: You will be asked to report your use of alcohol and other substances (cigarettes, marijuana, cocaine, etc.) and any alcohol withdrawal symptoms you may have.

Medications:
You will be asked if you have started taking any new medications since your last visit.

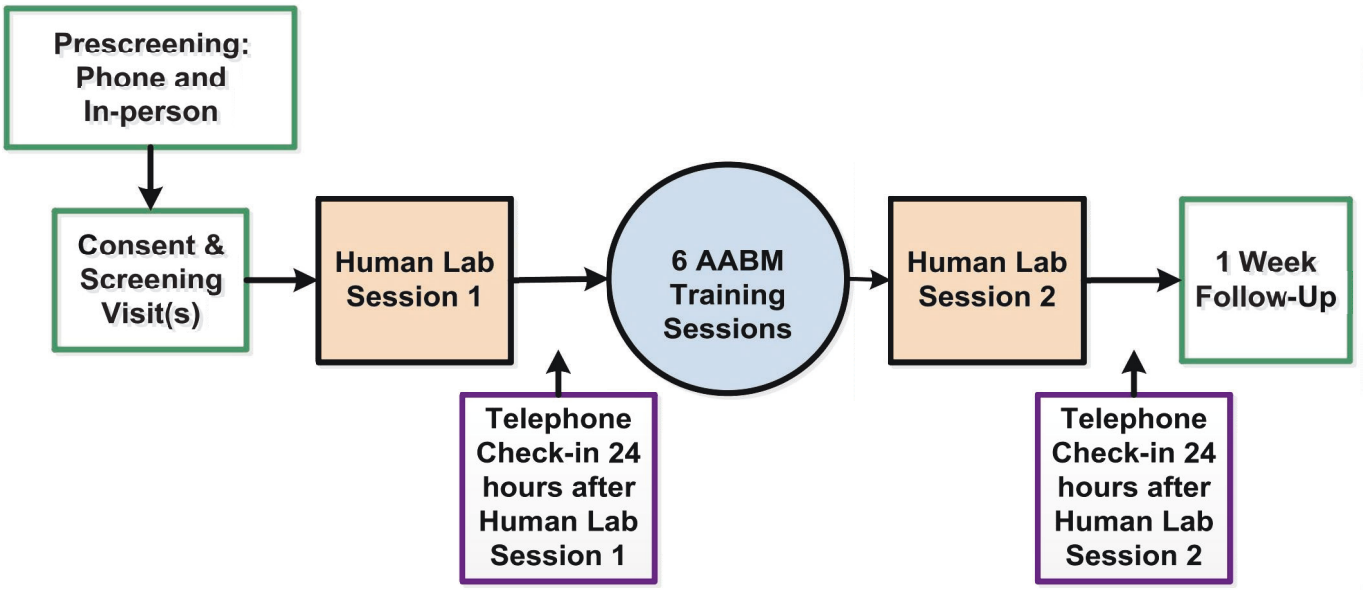
AABM training:
You will complete 6 sessions of an AABM training over the course of 2 weeks. Each session takes about 20 minutes to complete. You will be asked to complete 2 sessions of the AABM training per AABM study visit for a total of 3 AABM study visits. During this task you will work with a computer by pushing and pulling a joystick. During the training sessions you will be asked to respond to the shape of a picture, regardless of the picture's content, by pushing or pulling on a joystick. Pushing a picture away will make it smaller, while pulling a picture closer will make it bigger. Each training is about 20 minutes, and you will have a chance to take a break halfway through the session.

During AABM Session 1 and AABM Session 6:
To measure the effects of the AABM training, we will ask you to complete several extra questionnaires and tests of your thinking at your first (Session 1) and last (Session 6) AABM sessions.

5d. Procedures for the follow-up visit:
There is one follow-up visit – 1 week after your 2nd and final ADP session.

Follow-up visit:
You will be asked to describe any side effects you may have had since the last study visit. You will be asked questions about substance use and possible alcohol withdrawal symptoms since the last visit. You will also be asked to complete questionnaires that you took at the beginning of the study, as well as undergo the same tests of your thinking. A psychiatrist or psychologist will talk to you about your alcohol use, and if you are interested, will provide you with treatment referrals. This appointment will be conducted with all participants, even those who do not complete the entire study, and will take approximately 1 hour.

5e. Study Plan:
Another way to find out what is being asked of you if you decide to participate in the study is to read the chart below. Start reading on the left side of the paper, and follow the lines and arrows.



6. How long will I be in the study?
After you complete the screening visits, the study is 6 weeks total. There are 7 visits over the course of 5 weeks. Please refer to the Study Visit Schedule below.

Study Visit Schedule

WEEK	STUDY VISIT	TIME PER VISIT^
Week 1	Screening visits	2.5 hours
Week 2	ADP Session # 1	12 hours
	Phone visit #1	10 minutes
Week 3	AABM training session #1 + #2	1.5 hours
	AABM training session #3 + #4	1 hour
	AABM training session #5 + #6	1.5 hours
Week 4	ADP Session #2	12 hours
	Phone visit #2	10 minutes
Week 5	Follow-up visit	30 minutes
TOTAL	12 study visits	approximately 31-32 hours

^The amount of time is an approximation

7. Can I stop being in the study?
Yes, you can decide to stop at any time. It is important to tell the study research staff if you are thinking about stopping. Also, the study PI or co-investigators may stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

8. What side effects or other risks can I expect from being in the study?
The study visits and procedures are designed to limit risks to your health and limit your discomfort as much as possible. These procedures closely monitor your safety throughout the study.

You may have side effects while in the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. You should talk to your study doctor about any side effects you experience while taking part in the study.

Risks associated with alcohol:
A number of medical conditions could potentially be worsened by acute alcohol administration, such as liver disease, heart disease, pancreas problems, diabetes, nervous system problems, or stomach and intestine problems. If you have any of these medical problems, you should not participate in this study. Alcohol may also cause nausea in high doses; however, nausea is not expected at the dose being used in this study. In order to ensure that you do not fall and hurt yourself after consuming alcohol, we will ask you to stay at the SF VA Medical Center until your breath alcohol level returns to 0.02 or less. Alcohol can be addictive. We do not recommend that you continue drinking alcohol in the quantities that will be used in this research study.

Risks associated with alcohol withdrawal:
We are not going to ask you to change your drinking behavior while you are participating in this study. However, you should know that some individuals who suddenly reduce or stop their drinking can experience alcohol withdrawal symptoms such as nervousness, shaking, loss of appetite, difficulty sleeping or more severe symptoms like extreme restlessness, confusion, hallucinations (hearing and seeing things that are not there) and seizures -- but these are extremely rare. We will monitor you very closely for withdrawal symptoms during your daily visits to our clinic. If you experience worsening of withdrawal symptoms, you may have to be hospitalized and will be given the standard medications that are used to treat and manage withdrawal.

Risks of tests of your thinking, and AABM training:
Risks related to answering questions about your medical/psychiatric history, reporting of drug use, taking part in tests of your thinking, or taking part in AABM training may include fatigue and distress. You are free to decline to answer any questions or to stop the assessments/training at any time. Tests of your thinking, interview sessions, and computer training will include breaks. In the event that you appear to be under undue strain, the session will be immediately discontinued.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, infection and fainting. We expect to draw 17 mL amount of blood (about 3.5 teaspoons) over the course of the study.

STUDY VISIT	AMOUNT OF BLOOD
Screening	8 mL or 2 tsp
1st ADP session	3 mL or ½ tsp
2nd ADP session	3 mL or ½ tsp
TOTAL	14 mL or 3.5 tsp

Risk of distress/fatigue due to psychiatric and other assessments:
Risks related to answering questions about your medical/psychiatric history, reporting of drug use, taking part in assessments of your thinking may include fatigue and distress. You are free to decline to answer any questions or to stop assessments at any time. Assessments and interviews will include breaks. If you are uncomfortable, let us know and the session will be immediately discontinued.

Risks of loss of privacy:
Other risks of being a study participant include a loss of privacy. In this study, you will be asked about drug use and other possibly illegal activities. The researchers will keep information about participants as confidential as possible, but complete confidentiality cannot be guaranteed. All information we obtain about you will be de-identified, meaning your name will not be used in any reports or publications resulting from this study and your name will not be recorded on any test materials or other research-related records. An identification number will be used instead of personally identifiable information. Your identification number will be kept in a secured database. Other sites associated with this study, and other University of California institutions may review or receive information about you. De-identified data, that is data that has been stripped of any information that could be used to identify you, will be shared with collaborating investigators.

Unknown risks:
The study intervention may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

9. Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. If you are in this study, you may benefit from the psychological assessments and review of your symptoms. You may respond favorably to the training and reduce your drinking, but there is no guarantee that this will happen.

10. What other choices do I have if I do not take part in this study?
You do not have to be in this study.

You may choose to seek treatment services.

You can obtain FDA-approved medications for alcoholism through your general medical care provider. You are free to seek treatment through your general care providers.

You may also choose not to seek treatment for your use of alcohol.

11. Will my information about me be kept private?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Because you are a volunteer from the community, a medical record will be created for you at the San Francisco VA Medical Center. A note about your participation in the study, along with the results from your urine drug screen and blood alcohol level tests, will be added to the medical record.

The information that will be collected includes demographic information (for example: name, address, age, date of birth, social security number) and health information (psychiatric information, alcohol and drug use, and medical information).

If you begin the screening period but are found to be ineligible, the research team will keep the information collected, as required by VA rules and regulations. This information will be kept in a locked room, in a locked storage unit or on a password-protected computer, depending on how the information was collected. This data will be saved for the entirety of the study and will not expire.

Every effort will be made to protect the confidential nature of your identifying information by assigning you a unique identification code during the study. All information and data collected by the study staff during this study will contain this identification code instead of any identifying personal information. This identification code will be stored in an electronic database on a password-protected, secure web server managed through the SFVAMC. The data manager will download study data from the server that will be needed for analysis and store it in a password-protected database, stored on a VA server behind a secure VA firewall at the SFAVMC. The written log that connects your identification code to the demographic information you give us will be kept in a file separate from the collected data. This log will have restricted access and will be stored in locked cabinets when not in use. Any data sent via email messages or delivery service will be encrypted and password-protected.

Video recordings will be stored on a password-protected, secure web server managed through the SFVAMC and will not be deleted in accordance with VA research rules.

To ensure your safety and the safety of others, information may be shared between research staff and your clinical team only under the following circumstances: 1) If in the judgment of the study physician, you have a psychiatric or medical condition that requires urgent attention to protect your safety and that of others; and 2) If you have missed several study appointments, and research staff needs to verify your whereabouts and/or verify your safety.

Progress notes related to your participation in this study indicate that you have been in enrolled in a research study, and the name and contact information for the investigator conducting the study. Details like urine drug test results, any mention of alcohol, the study name or number will not be included in the progress notes.

Except for the results of your urine drug screen and blood alcohol level test, study tests that are performed by non-VA research labs and information gathered directly from you by the study staff will be part of your research study records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Authorized representatives from the following organizations may review your research data for the purpose of monitoring or managing the conduct of this study:

- Representatives of the Sponsor (University of California, San Francisco)
- Representatives of the University of California
- Representatives of the Veterans Affairs
- Members of the study's Data and Safety and Monitoring Board

In this study, you will be asked questions about illegal drug use and your urine will be tested for illegal drugs. The researchers will keep information about you as confidential as possible, but complete confidentiality cannot be guaranteed. On rare occasions, research records have been subpoenaed by a court.

12. Are there any costs to me for taking part in this study?

No. The sponsor has agreed to pay for all items associated with this research study; you or your insurer will not be billed.

13. Will I be paid for taking part in this study?

You will be compensated in return for your time and effort to attend study visits. Payment is also intended to cover, or partially cover, the cost of public transportation/gas/parking. You will not be paid for any missed visits. If you complete all study visits and procedures, you will be paid as follows:

WEEK	ATTEND STUDY VISIT	TOTAL PER VISIT
Screening	$55*	$55
ADP Session #1	$200 (+ $24 for tab)**	$224
Phone visit #1		
AABM 1 + 2	$50	$50
AABM 3 + 4	$40	$40
AABM 5 + 6	$50	$50
ADP Session #2	$200 (+ $24 for tab)**	$224
Phone visit #2		
Follow-up @ 1 Week	$40 (+ $50 bonus if attended all study visits)***	$90
TOTAL		$733

*Payment for screening visits depends on the completion of tasks at each visit. You will earn up to $55 total if you complete all screening measures.

**Please note that you could earn up to $24 per ADP session depending on how many drinks you consume per session. At each session, you will be offered 8 drinks, each worth $3. You will receive $3 per drink for any drinks that you do not consume.

***If you attend all possible study visits, then you will receive an extra $50 at the last study visit.

Payments will be made in check or cash upon the completion of each visit.

Check reimbursement
For ADP sessions you have the potential to earn up to $224 per visit. You will be paid $200 by check for each of the completed ADP sessions. The check will be issued by UCSF, mailed to the address you provide, and should be received within 2 weeks after your visit.

Cash reimbursement
You will receive cash for attending the AABM training sessions, the phone visits, the follow-up visit and an additional bonus payment if you attend all study visits. The cash reimbursements will be dispersed at the end of the corresponding study visits.

Depending on how many drinks you consume per ADP session, you could receive up to $24 in cash. This cash payment will be issued at the end of each drinking session.

Because this study offers participants total payments equal or greater than $600 in a calendar year period, then the payments are considered tax reportable income. This means that we will share your home address and Social Security Number with the Accounts Payable Manager, using a secured file via email. You will also be asked to fill out a W-9 form.

14. What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Steven L. Batki, MD, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him at 415-221-4810 x 23671.

Treatment and Compensation for Injury: If you are experiencing a medical emergency, please call 9-1-1. If you incur an injury or illness as a result of being in this study, the Department of Veterans Affairs (VA) will ensure that treatment is made available at a VA medical facility or non-VA facility, as appropriate. If you were following study instructions, the costs of such treatment will be covered by the VA or the study sponsor (if applicable). If you were NOT following study instructions, the costs of such treatment may be covered by the VA or the study sponsor (if applicable), or may be billed to you or your insurer just like any other medical costs, depending on a number of factors. The VA and a study sponsor do not normally provide any other form of compensation for injury or illness. For further information about this, call the study team at the number(s) provided.

15. What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

16. What are my responsibilities as a study participant?

- As a participant in this study, your responsibilities are as follows:
  Following the instructions given to you by the study staff and study doctor.
- Attending all study visits as scheduled.
- Communicating with study staff if you will not be able to attend a study visit as scheduled.
- Reporting any side effects, injuries, or other changes in your health to the study doctor.

- Reporting all medicines, vitamins, recreational drugs, herbal products, supplements, or over-the-counter products you use during the study.
- Speaking with the study doctor if you would like to stop participation in the study.

IMPORTANT: We request that you abstain from driving to the VA Medical Center for study visits if you have been drinking. If you do drive and your breath alcohol level is above a 0.08, then a clinician will assess your safety before you will be allowed to leave. This is a VA protocol established to ensure your safety.

17. Clinical Trial Registry Data Bank

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

18. Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. At the San Francisco VA, please contact you study doctor, Steven L. Batki, M.D. at 415-221-4810 x 23671 or page him at 415-313-6537.

For questions about your rights while taking part in this study, call the office of UCSF's Institutional Review Board (a group of people who review the research to protect your rights) at 415-476-1814.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

Optional Procedures: Please indicate if you agree to participate in the following optional procedures by placing your initials on the lines below:

_____ I *agree* to be contacted after this study is done or to be asked to be in other studies.

_____ I *do not agree* to be contacted after this study is done or to be asked to be in other studies.

If you wish to participate in this study, you should sign below.

_____

Signature of Participant Date

_____

Printed Name of Participant