Effects of a Cognitive Interference Task on Alcohol Craving and Consumption Among Women

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Effects of a Cognitive Interference Task on Alcohol Craving and Consumption among Women (Christine Hahn, PhD, Assistant Professor, Dept. of Psychiatry)

Despite the prevalence and serious consequences of alcohol use disorder (AUD) among women, only 5.4% receive treatment.[1] Brief mobile interventions are a promising way to delivery accessible, evidence-based interventions to women who would not otherwise seek help. The primary objective of the proposed study is to test the effects of a brief, cognitive interference task (Tetris) in reducing alcohol craving and consumption among women with at-risk drinking according to NIAAA guidelines.[3] Elaboration Intrusion Theory (EIT) proposes that visual working memory processes are central to craving, and that imagined experiences of engaging in substance use increases motivation to engage in the actual behavior.[4] In laboratory and real-world settings, participants report decreased craving for food and substances after completing Tetris, a visuospatial task that increases the demands of working memory processes.[5-6] Based on previous research, the current study will collect ecological momentary assessment (EMA) data for a 1-week baseline period, followed by a 2-week intervention phase in which participants will be randomly assigned to the experimental condition (Tetris) or a control condition (assessment only). During the intervention phase, participants will receive a combination of event- and signal-contingent EMA assessments, and the experimental condition will also receive daily prompts to complete Tetris in-between assessments. EMA will be used to assess alcohol craving and consumption during the baseline and intervention phase and deliver the intervention in real-time.

Specific Aim 1: Evaluate the effects of a brief cognitive interference task on alcohol craving among women who report at risk drinking. Hypothesis: Participants in the experimental group, relative to controls, will evidence significantly lower craving 1) immediately after completing the task, and 2) during the 2-week intervention phase.

Specific Aim 2: Evaluate the effects of a brief cognitive interference task on alcohol consumption, as measured by self-report among women who report at risk drinking. Hypothesis: Participants in the experimental group, relative to controls, will demonstrate significantly lower consumption of alcohol (fewer standard drink units) during the 2-week intervention phase and at 1-month follow-up.

Approach

Participants: Forty women who report at risk drinking will be recruited nationally from online campaigns, the community, and locally from the Women's Health Clinic at the Medical University of South Carolina (MUSC). Many women use obstetricians and gynecologists (OB/GYN) as their primary resource for behavioral health care making OB/GYN health care settings an ideal place to provide accessible interventions for AUD to women.[2] The inclusion criteria for alcohol consumption will be having a positive score on the AUDIT-C (i.e., a score of 3 or greater) at the time of screening. Additional inclusion criteria include: 1) female, any race or ethnicity; 2) ages 21-65; 3) able to comprehend English to provide informed consent and complete the assessments. Exclusion criteria include: 1) currently engaged in treatment for AUD; 2) current clinically significant bipolar affective disorder, schizophrenia, or psychotic disorder; 3) pregnant; 4) imminently suicidal or homicidal; 5) participants taking medications known to affect alcohol craving or consumption and 6) a score of 10 or higher on the Clinical Institute of Alcohol Withdrawal Revised (CIWA-R).[24]

Study Procedures

Initial Screening. Potential participants will complete a brief screener over the phone or via REDCap to determine initial eligibility. The brief screener will ask yes/no and multiple choice questions focused on inclusion/exclusion criteria.

Upon enrollment, participants will be given a full description of study procedures and asked to sign an electronic IRB-approved consent form before any additional study procedures or assessments, aside from the initial screener, are conducted. E-consent will be completed on REDCap. Participants will be sent a link to review the e-consent. Research staff will review the consent form over the phone or teleconferencing and answer any questions. Participants will be given as much time as needed to review the consent form. Participants and staff will sign the form electronically. A PDF of the completed consent form will be emailed securely to participants. Participants will complete a baseline assessment, followed by an EMA assessment period, and a post-experiment visit. To decrease risk regarding COVID-19 and increase feasibility, all study procedures will be

conducted with via telemedicine. Vidyo or doxy.me video conferencing will be used. Participants will complete study measures via a REDcap link.

Baseline Visit: The baseline visit will include interview measures that will be completed on doxy.me or vidyo, and self-report surveys completed on REDcap. Self-report measures include items from the DIAMOND[18] screener, the Alcohol Use Disorder Identification Test (AUDIT),[8] the patient health questionnaire (PHQ-9)[19] and Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES),[9] Life Experiences Questionnaire[20], Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5)[21], Drinking Motives Questionnaire[22], the Obsessive Compulsive Drinking Scale (OCD)[12], four items assessing COVID-19 related stress, and Short UPPS-P[23]. Interview measures include the Time Line Follow Back (TLFB),[7] substance use modules of the DIAMOND, Treatment Services Review[25], and for participants who screen positive for mood disorders, psychotic disorders, or suicidality will receive the corresponding modules of the DIAMOND. Eligible participants will be instructed on how to complete ecological momentary assessments (EMAs), including instructions on how to measure a standard drink and report craving. Participants will be randomized to the experimental or control condition stratified by self-report craving and depression scores. Participants assigned to the experimental condition will be instructed on how to complete the Tetris task.

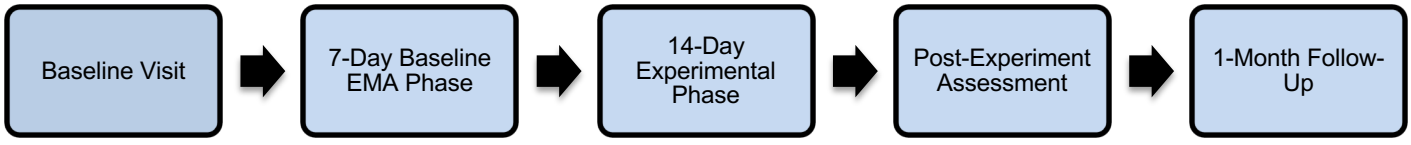
EMA Assessment Period: The current study will employ a 1-week baseline EMA period followed by a 2-week experimental EMA protocol that uses a combination of event- and signal-contingent assessments. Based on previous EMA research, participants will be instructed to initiate a morning assessment each day to assess behaviors that may not have been captured during the in-vivo assessments the previous evening *("How may alcohol drinks did you consume yesterday?; How many alcohol drinks do you plan to consume today?"*)[10]. They will be provided with examples of standard drinks to help accurately assess their drinking. In addition, participants will complete the imagery subscale from the Craving Experience Questionnaire (CEQ)[11] to retrospectively measure their strongest episode of craving during the previous day. Participants will also be prompted once per day to complete a Cue Reactivity Ecological Momentary Assessment (CREMA). CREMA provides real-time responses to alcohol-related stimuli presented in participant's natural environment. Participants will be randomly prompted between 2:00-9:00 PM to begin a CREMA session. Participants will have 60 minutes to respond to the prompt. Participants will complete baseline measure of craving, stress and mood, and then view a photograph of an alcoholic beverage. Each item will be presented for 30 seconds. Different photographs will be presented at each study trial. After viewing the photograph, participants will be complete post ratings of their craving, stress and mood.

Between the hours of 2:00 p.m. and 9:00 p.m., participants will receive up to three random text message prompts to complete in-vivo assessments assessing craving and mood including: "How many standard drinks have you consumed since your last assessment?"; "Are you drinking alcohol right now?"; "How is your mood right now?"; "How stressed do you feel right now."' "How strong is your craving for alcohol right now…" An automated text message system will be used with at least 1-hour between assessments and will de-activate after an hour has expired. Participants who responded to at least 80% of the morning assessments will be invited to continue participation in the experimental portion of the study.

During, the experimental phase, the same assessments will be administered. In addition, any occasion in which a positive response to current craving is reported, an automated prompt will be displayed to re-rate cravings four minutes later. Participants in the experimental condition will receive an automated prompted to complete the Tetris task in-between the ratings. After four minutes the application will upload a screen shot of the Tetris game into RedCAP. The Tetris task involves manipulating basic shapes to form rows that then disappear. Participants in the experimental condition will be asked to play Tetris after CREMA sessions and after any of the three random craving assessment that participants report experiencing craving. Participants in the control condition will just be asked to re-rate craving four minutes later and report what activities they completed during the three-minute break.

Post-Experiment Assessment: Participants will complete self-report questionnaires via REDCap. In addition, participants will complete the TLFB over a video call at a 1-month follow-up. Figure 1 below illustrates the study design.

Figure 1. Study design



Statistical Analyses

To establish feasibility, descriptive analyses will be used to measure the proportion of prompts participants respond to, and the response time to complete prompts. An intent-to-treat analysis will be conducted with mixed-effects regression to test between-group differences in urge to drink after completing the task, nested within individuals. We will use a random-effects mixed modeling approach using maximum likelihood estimation to test differences in mean craving and drinking outcomes (i.e., alcohol consumption) between baseline and post-experiment. We will test differences in alcohol consumption between baseline and one-month follow-up. Participants will be modeled as random factors and the group allocation will be a fixed factor. Maximum likelihood estimation will provide unbiases estimates assuming missingness at random.[13]

Impediments and Future Directions: While we have chosen a reasonable starting point for alcohol consumption to be eligible for participation, this pilot study will allow us to ascertain this range for alcohol consumption and, if necessary, change the drinking inclusion criterion to more closely match the population motivation and health needs. Future studies can build on this pilot data to further focus the intervention more clearly on the patients of greatest need and who might benefit most from this cognitive interference technique. Also, data collected in this study will provide information on the sustainability of the effect and whether longer intervention periods are necessary or perhaps whether repeat "bolus" interventions might be required. Irrespective of outcome, conducting this research is novel and could lead to stronger collaborations that will ultimately improve the health of women by providing mechanisms to detect and assist in reducing harmful alcohol consumption.

HUMAN SUBJECTS RESEARCH

The proposed research meets criteria for an NIH clinical trial. A Detailed Data and Safety Monitoring Plan is provided. This plan includes continuous, close monitoring by the study investigators and prompt reporting procedures. All procedures and materials will be reviewed and approved by the Institutional Review Board (IRB) at the Medical University of South Carolina (MUSC) before any study procedures occur.

1. RISKS TO SUBJECTS

Dr. Hahn and co-investigators on this project have completed the Miami Collaborative IRB Training Initiative (CITI) online training. The candidate is a licensed clinical psychologist (South Carolina #1570). The investigators on the research team includes a licensed clinical psychologist (Dr. Back) and board-certified psychiatrists (Drs. Brady and Guille) with extensive clinical research experience in alcohol use disorder (AUD), randomized clinical trials, and women's health. All research activity, informed consents and continuing reviews will be reviewed by the MUSC IRB in compliance with 45CFR46 before the research is initiated. Continuing review will occur annually.

Human Subjects Involvement, Characteristics, and Design: A total of 40 women between the ages of 21 and 65 who report at risk drinking will be enrolled over a 1-year period. Participants will be randomly assigned (1:1) to the experimental group or an assessment-only group using a computer-generated randomization scheme (N=20) in the experimental condition; N=20 in the assessment-only condition). Ecological momentary assessments (EMA) will be used to collect baseline data on craving and alcohol consumption during a 1-week baseline phase. Participants will complete a morning assessment and receive random prompts four times per day during the hours of 2 PM – 9 PM. One of the prompts will be to complete a Cue Reactivity Ecological Momentary Assessment (CREMA). During the 2-week experimental phase, participants will continue to receive EMA prompts. In addition, when participants report alcohol cravings, they will be prompted to re-rate their cravings four minutes later. The experimental group will receive prompts to complete a Tetris task during the four-minute period. Post assessments will be completed via self-report questionnaires, followed by a 1-month follow-up assessment conducted by telephone or video conferencing.

Participants will be recruited nationally from online campaigns and from primary care, and Women's Health at the Medical University of South Carolina using flyers and physician referral (see

Letter of Support from Dr. Soper). IRB approved research staff (e.g., Anna Foster, Sara Del Mas, Christine Hahn) will also meet with interested patients in a private room within Women's Health to inform them about the research study. Research staff will only meet with potential participants who indicate to someone directly involved in their clinical care (e.g., nursing staff) that they agree to talk with research staff about the study. Research staff will provide a brief overview of the study and those who are interested in learning more will be provided with a link to the online screener.

In addition, patients will be identified through EPIC to contact about interest in the study. Potential participants in EPIC will be women aged 21-65 who were seen in the past year in primary care/Women's Health and have not opted out of research. In addition, potential participants in EPIC will be identified by a diagnosis of ETOH use disorder, depression, and/or a positive screen for depression in their charts. We are using positive screen for depression as a way to identify potential participants because of the co-occurrence of alcohol misuse and depression. Potential participants identified through EPIC will be called, emailed, and mailed letters providing initial information about the study. Interested participants will complete a screener. Eligible participants will be asked to read and sign an electronic IRB-approved consent form before any study procedures are conducted. E-consent will be completed on REDCap. Participants will be sent a link to review the e-consent. Research staff will review the consent form over the phone or teleconferencing and answer any questions. Participants will be given as much time as needed to review the consent form. Participants and staff will sign the form electronically. A PDF of the completed consent form will be emailed me to participants from a secure MUSC email address. Participants will be informed that the project is completely voluntary and that they can withdraw at any time. Participants will be informed that the study is confidential and the limitations to confidentiality with be reviewed (e.g., in the case of harm to self or others). Participants will be informed that their participation will not affect their regular medical care at the clinic in any way. Participant recruitment will begin at the start of Year 1 and will continue until the targeted enrollment number has been reached (*N*=40). The inclusion/exclusion criteria are as follows:

Inclusion Criteria:

1. Female, any race or ethnicity, age 21 to 65 years old.
2. Able to comprehend English.
3. Positive AUDIT-C score (i.e., score of 3 or greater)

Exclusion Criteria:

1. Currently engaged in treatment for AUD.
2. Current clinically significant bipolar affective disorder, schizophrenia, or psychotic disorder.
3. Pregnant.
4. Imminently suicidal or homicidal.
5. Participants taking psychoactive medications that may affect alcohol craving or consumption.
6. A score of 10 or higher on the Clinical Institute of Alcohol Withdrawal Revised (CIWA-R).[24]

No special classes of subjects, such as, pregnant women, prisoners, institutional individuals, or others will be recruited for this study.

Study Procedures, Materials, and Potential Risks

Study Procedures: Upon enrollment, participants will be given a full description of study procedures and asked to sign an electronic IRB-approved consent form before any study procedures or assessments are conducted. Participants will complete screening and a baseline visit via video conferencing on doxy.me or vidyo. Participants who meet eligibility criteria will be enrolled in the 1-week EMA assessment period, followed by a 2-week EMA experimental phase. Participants will complete post-experiment assessments via REDCap survey, and will be contacted via phone or video conferencing to complete a 1-month follow-up assessment.

All forms and consent procedures will be approved by the Institutional Review Board (IRB) at MUSC. The principal investigator, and co-investigators (Drs. Back, Brady, Guille) have been very successful in recruiting patients with AUD to participate in research. Participants will be mailed a

pregnancy test. They will be asked to complete the test in privacy and show the results of the test strip on the screen to the researcher.

Sources of Materials: Data will be in the form of structured clinical interviews, self-reported questionnaires, obtained specifically for research purposes. Access to research records will be limited, as they will be maintained in a locked cabinet in the PI's locked office. All files will be code-linked (a random number will be used to link participants to their data and only the researchers will have access to the password protected file that links the participant to their code) to protect participants' privacy and anonymity. Only researchers working on this project will have access to the subjects' data. The materials will be specifically obtained for research purposes. Trained study personnel under the direct supervision of Dr. Hahn will collect data. Subjects will be permitted to ask questions (at this or any other time during the study), consult with family members, and be fully informed of all aspects of the study before signing the informed consent and beginning the study.

Potential Risks: Two potential risks associated with involvement in the study include: (1) potential threats to confidentiality, and (2) potential distress from responding to questions that involve sensitive topics including alcohol use. These risks are discussed in greater detail as follows**.**

Confidentiality. Every effort will be made to protect participant's confidentiality and privacy. Due to the nature of some of the questions it is unlikely, although possible, that there may be instances in which confidentiality could be breached (e.g., suspected child abuse, harm to self or others). Participants will be informed of these risks prior to completing the assessments. We will make all possible efforts to protect the privacy and confidentially of study participants by using only code-linked data in the database, and only subject number will be included on source documents. A password protected file will be saved on Box that links the subject to their code. Only the research team will have access to the password. No name, birthdate or other identifying information will be included on any assessment. Participants will be provided with a written informed consent document, which specifies the risks and confidentiality protections and limits of study procedures. Further, data will not be stored on the person's phone. Data for the EMA assessments will be stored within REDcap, an MUSC secured web-based survey system.

Distress or Discomfort. Some participants may experience distress by questions pertaining to their alcohol use. All participants will be informed at the outset that the study is voluntary, and they may terminate participation at any point. Our past and ongoing research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms. This experience includes substantial research with younger and older adults, active duty service members, military Veterans, rape victims, victims of other forms of violence (e.g., natural disasters, car accidents), and work on large-scale studies asking questions about similar topics with general population samples.

In the event that subjects experience psychological distress secondary to participation, subjects will be encouraged to contact the PI (Dr. Hahn). Dr. Hahn is a licensed mental health care provider. Subjects will be given contact information for the Dr. Hahn at the time of consent, as well as resources for local and national 24-hour hotline numbers. In addition, participants will have access to urgent care services at MUSC. The research team is comprised of licensed clinical psychologists and psychiatrists with extensive experience working with adults who have experienced significant life stressors and drug/alcohol addiction. If the candidate, assessors or project staff believes that a participant is significantly distressed by participation, the investigator team will be notified immediately, and Dr. Hahn will contact the participant to assess distress and assure participant safety. If called by a participant, the PI will attempt to address all participant concerns and will set up an alternate referral for clinical services outside the project if desired.

With regard to potential alternative treatments, current "standard of care" exists in Women's Health in screening, brief, intervention, and referral to treatment. In addition, residents and psychology interns are available for behavioral health treatment. Participants will be able to participate in standard of care at Women's Health. When the study is being described to potential participants, it will be made very clear that the participants have the right to choose not to participate in the study and they will be

provided with appropriate referrals. All subjects in the study will be given a list of local resources and mental health agencies that may be helpful.

2. ADEQUACY OF PROTECTION AGAINST RISKS

Informed Consent: Informed consent (IC) will be collected at the study research offices, in a private and interruption-free enviornment. The PI or Research Assistant will obtain IC. The IC form will outline: a) the sponsponsorship of the study; b) the nature, purpose and procedures of the study; c) the voluntary nature of participation (i.e., participation is not required; participation can be discontinued at any time); d) the duration of the study; e) potential risks and discomforts, as well as benefits of participation; f) that all information will be kept confidential subject to the provisions of the state and federal law; g) compensation; and h) alternative treatements. The IC form will specifically review the potential for psychological distresss, and the risks associated with completing assessments and treatment that may occur as a result of study participation. The IC form will be explained to participants in easy-to-understand language, and participants will be instructed to read the form carefully prior to signing it. The IC form will include emergency contact information for the PI (Dr. Hahn). Any questions pertaining to the study or consent process will be answered fully. Potential participants will not be required to make a decision to participate at the initial contact, though that possibility will be available. If participants wish to discuss study participation with their family and/or significant others, they will be encouraged to do so. Participants will be informed that they can discontinue their participation in the study at any time and that this decision will not influence the care they receive at MUSC. Consent will be documented by the signature of the participant on the IC document, accompanied by the signature of the individual obtaining the consent. Participants will be given a copy of the informed consent.

Protection Against Risk: Planned strategies have been identified to manage and potential risks**.**

Confidentiality. Risks to confidentiality will be minimized by using initials and code identifiers. Linkage between a participant's identity and their responses will be through a random number code. There will be only one master list of participants code (not linked to any participant responses) which will be kept locked, separate from all data, and will be available only to the PI and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the PI or research assistant's (RA's) research office) to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff. The PI is well trained in the confidential nature of research subjects' records, and complete annual courses on confidentiality protection and most recently on HIPAA regulations. These procedures are highly effective in protecting confidentiality issues. Names will not be used on specimens, assessments or be available in the research laboratory. The investigators and all study personnel will sign a confidentiality agreement that no identifying information of specific individuals will appear in any internal reports or external documents (e.g., peer-reviewed publications, presentations). Research subjects' data will be entered in a computer database with only number codes for identifiers and will not identify study subjects by name. These procedures have proved highly effective in preventing breaches of confidentiality in our previous research studies.

Assessments. Several steps will be taken to assess for suicidal ideation and safety plan. During the baseline and follow-up appointment participants complete the PHQ-9 item about suicidal ideation with the assessor, rather than in self-report. In addition, at baseline they complete the DIAMOND suicidality module to complete a thorough assessment of suicide risk. If participants endorse suicidal ideation, they will engage in safety planning with a member of the research team, all who have ample experience assessing and responding to suicide. Participants who report suicidal ideation without intention, plan, or recent attempts, may still be eligible for the study. The participant will complete a safety plan template (see attachment). This will include providing crisis numbers and instructions to go

to the ED or call 911 if suicidal ideation increases. At each study visit participants complete the PHQ-9 suicidality item with the assessor and suicide assessment and safety plan is reviewed as indicated. Participants will also be asked to provide the name of a social support person to contact if there is concern for participants safety. Participants who report a plan or intention at baseline may not be eligible for the study, but regardless will receive safety planning. If the PI is not the one completing the assessment, she will be immediately notified when someone endorses a plan and/or intention for suicide. Depending on risk level, safety planning may include calling mobile crisis and/or 911, informing current care providers of suicide risk, voluntary agreement to go to the local emergency department, or other necessary steps to ensure safety. At the start of every visit, participants will be asked to inform the assessor of their current location. This information will only be stored for the duration of the study visit to use in case of an emergency. If immediate intervention from mobile crisis, police, ED, is not indicated, a suicide safety template will be completed. In addition, referrals to appropriate services will be provided and if indicated follow-up contact will be provided to ensure the person connected with referrals. During the consent process, participants are informed that confidentiality can be broken if there are concerns about the person's safety. Risk assessment and safety planning information will be documented in redcap in study visit notes. if safety is in question in the minds of any project staff, the Mobile Crisis unit of Charleston County, which involves a team of police and psychiatric workers, or the EMS unit will be dispatched to the participant's home to assure safety. In the co-PI's NIH, VA- and DoD-funded clinical trials of comorbid PTSD and substance use disorder treatments, Dr. Back has not had any problems related to participation that could not be safely resolved with these methods.

3. POTENTIAL BENEFITS OF RESEARCH TO SUBJECTS AND OTHERS

Potential benefits of participation in this study may include a reduction in alcohol craving and consumption. However, there is no guarantee or promise that participants will receive any benefit from participation in this study.

4. IMPORTANCE OF KNOWLEDGE TO BE GAINED

The potential benefits of the knowledge to be gained from the proposed study are considerable. This study proposes to test a brief visual cognitive test to reduce alcohol craving and consumption. Alcohol misuse is common and under-treatment among women. The proposed research is an essential step in informing evidence-based practices for reducing alcohol misuse among women. The plans for monitoring risk as described above warrant the conduct of this study for the knowledge that may reasonably be expected to result.

DATA AND SAFETY MONITORING (DSM)

A Data and Safety Monitoring Plan (DSMP) has been developed in accordance with the National Institutes of Health (NIH) Office of Human Research Protection (OHRP) to assure the appropriate clinical safety monitoring of study subjects participating in this study. Recruitment and safety data are monitored according to the schedule established by the monitoring board. Quality control and assurance of data entered into the database is discussed above as part of Protections Against Risk. Missing data will be considered as part of the plan for statistical analysis.

Summary of the Protocol: This application proposes to test the efficacy of a visual cognitive interference task using ecological momentary assessments to reduce alcohol craving and consumption. The primary outcomes of interest include: (1) alcohol craving, (2) alcohol consumption.

Trial Management: The study will be conducted and managed in the National Crime Victims Research and Treatment Center in the Department of Psychiatry at Medical University of South Carolina (MUSC), College of Medicine, in Charleston, SC.

Data Management and Analysis: The PI will oversee data management, quality control procedures and data analysis conducted by the PI. Data will be entered by trained research assistants directly into Redcap and exported to standard database software (SPSS; STATA). Quarterly audits of at least 10% of data entry will be completed. A detailed data analysis plan is outlined in the Statistics Analysis section of the Research Plan.

Regulatory Issues: All unexpected Adverse Events (AEs) will be monitored, recorded, and reviewed by the PI at weekly study team meetings. AEs are reportable to the IRB if the event is unexpected AND related or possibly related AND serious or more prevalent than expected. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug~~,~~ device or intervention. Serious AEs (SAEs) will be reported within 24-business hours. Follow-up of all unexpected and serious AEs will also be reported to the study sponsor and the MUSC IRB. All AEs are reviewed weekly by the PI, and annually by the Data Safety Monitoring Board (DSMB) and the IRB. AEs and SAEs occurring during the course of the trial will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. The PI and Research Assistant will identify any potential AEs during the course of the study from participant self-report and administration of assessments and procedures. This information will be provided to the co-investigators, who will also be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

Definition of AE and SAE: An Adverse Event (AE) is defined as any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the study that may or may not be related to study participation. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, OR requires intervention to prevent one of the above outcomes.

Documentation and Reporting: Any clinical study event that is judged to be an AE will be recorded on the AE Form during the course of the study. The PI ensures this information is captured during every study visit. SAEs are also recorded on the AE Form, managed medically as appropriate, and followed until resolution or stabilization.

AEs/SAEs are documented and reported as per protocol and MUSC requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are documented on AE Logs and additional relevant AE information, if available, will be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study.

When a reportable SAE is identified, the research assistant will initiate an SAE form, and the following individuals will be notified within 24 hours of the site's initial notification of the SAE:

a) The PI will notify the MUSC IRB and complete the AE report form. Both committees meet monthly. Communication with the MUSC IRB is through email, memos, official IRB forms, and online reporting.
b) The data safety monitoring board members.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The PI will attach copies of source documents to the SAE report for review by the DSMB and for forwarding to the sponsor as appropriate.

All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated.

Trial Safety: The potential risks and methods to minimize these risks are outlined above. Protocols for reporting AEs and SAEs are outlined above. All unexpected AE and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly meetings (or before if urgent), the PI will report any premonitory symptoms of clinical deterioration to the investigative team. Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to the PI. All requests by participant's physicians and other medical providers will be referred directly to the PI.

DSM Plan Administration: The PI will be responsible for monitoring the study. Dr. Hahn will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSM report will be filed with the IRB and sponsor on a yearly basis, unless greater than expected problems occur. The report will include subject characteristics, retention and disposition of study subjects, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report results at the end of the trial.

DSM Board: We will create a DSMB to monitor the overall participant safety, the rate and severity of adverse events, and the validity and integrity of the data. The panel will include three researchers with experience in treating patients with alcohol use disorders, women's health, and a statistician. The board will meet annually, but may be called at any point if needed for unexpected AEs, etc. Modification will be made in the procedures and/or the protocol if necessary, based on the recommendations of the board.

ClinicalTrials.gov Requirements: In accordance with Public Law 110-85, the proposed trial will be registered with ClinicalTrials.gov. Applicable requirements regarding results reporting will be adhered to.

RECRUITMENT AND RETENTION PLAN

Recruitment. In order to have 32 participants complete the proposed pilot randomized controlled trial (see power analysis) we will recruit 40 participants to accommodate for expected attrition rates of 20%. Participants will be recruited nationally from online campaigns, the community, and from primary care/Women's Health at the Medical University of South Carolina (see Letter of Support from Vice Chairman of the Department of Obstetrics and Gynecology). IRB approved research staff (e.g., Anna Foster, Sara Del Mas, Christine Hahn) will also meet with interested patients in a private room within Women's Health to inform them about the research study. Research staff will only meet with potential participants who indicate to someone directly involved in their clinical care (e.g., nursing staff) that they agree to talk with research staff about the study. Research staff will provide a brief overview of the study and those who are interested in learning more will be provided with a link to the online screener. Flyers will be posted throughout Women's Health to recruit potential participants. Prospective subjects will be informed of the study by someone directly involved in their clinical care via a flyer that includes research staff contact information. The candidate has used these methods successfully in the past to recruit subjects for her dissertation research in a fertility and reproductive medicine clinic. In addition, potential participants will be identified through EPIC and contacted by research staff via phone, email, and mail. IRB-approved study flyers and other approved study materials will be placed in prominent locations in MUSC and community-based clinics (e.g., Charleston Center, CDAP, Sleep and Anxiety Clinic) and central hubs (e.g. Coffee shops). All appropriate permissions will be obtained prior to displaying any recruitment materials at community-based clinics and outside of MUSC. In addition, participants from past MUSC research studies who have consented to be contacted for future research studies will be recruited via telephone screening and/or e-mails. These individuals will be referred to us via other MUSC researchers.

Retention. In order to facilitate completion of scheduled and in-vivo assessments, participants will receive reminders, compensation in the form of ClinCards, amazon gift cards, or cash, and messages that reinforce completion of assessments. Specifically, in the baseline phase participants will be compensated $2.00 for each morning assessment completed and if they complete 90% of assessments (i.e., 6 assessments), they will receive a bonus of $10.00. Participants will receive $1.00 for each random in-vivo assessment completed from the hours of 2PM -9PM (each participant will receive four assessments at random times between the hours of 2 PM – 9PM), and a bonus of $10 if they complete 75% of in-vivo assessments (i.e., 21 of the 28 assessments) during the one-week period. The total potential compensation for morning baseline in-vivo assessments is $24.00 and for random in-vivo assessments is $38.00. In the experimental phase participants will also be compensated $2.00 for each morning assessment completed and if they complete 90% of assessments (i.e. 13 of the assessments), they will receive a bonus of $15.00. In the experimental phase, participants will also receive $1.00 for each random in-vivo assessment completed from the hours of 2PM -9PM (each participant will receive four assessments at random times between the hours of 2 PM – 9PM), and a bonus of $15 if they complete 75% of in-vivo assessments (i.e., 42 of the 56 assessments) during the two-week period. The total potential compensation for morning in-vivo assessments is $43.00 and for random in-vivo assessments is $71.00 during the experimental phase. Participants will receive messages to reinforce completion (e.g., "Great job, you have completed 60% of the assessments and earned $20.00. If you complete 75% of assessments, you will earn an extra $15.00). Participants will also receive messages reminding them to complete their morning assessments. Participants will be compensated $30.00 for baseline visits and $25.00 for post-experiment visits. They will be compensated $30.00 for the 1-month follow-up phone call. The total compensation for visits is $75.00. Participants can earn up to $261.00 if they complete all study procedures and ecological momentary assessments. Participants will receive two reminders for the post-experiment questionnaires and follow-up call (e.g., emails, text message, phone calls) and will receive a calendar with appointment times and dates at their first visit. Further, participants will

be asked to provide updated contact information (i.e., phone, email, and physical address) during the baseline teleconferencing visit. Payments to ClinCards, amazon gift cards, or cash will be distributed after the baseline visit, baseline EMA period, experiment EMA period, post-experiment questionnaires, and one-month follow-up visit. Gift cards will be electronically sent. To support consistent engagement in the study, participants will be encouraged to identify a social support person that can help them attend to study tasks and visits as needed.

Compensation for visits

Visit	**Compensation**
Baseline visit	$30.00
Post-experiment questionnaires	$25.00
1-month follow-up visit	$30.00
Total	**$85.00**

Compensation for in-vivo assessments

Day	**Morning assessment**	**Random in-vivo assessment**
Baseline Day 1	$2.00	$1.00 x 4 = $4.00
Baseline Day 2	$2.00	$1.00 x 4 = $4.00
Baseline Day 3	$2.00	$1.00 x 4 = $4.00
Baseline Day 4	$2.00	$1.00 x 4 = $4.00
Baseline Day 5	$2.00	$1.00 x 4 = $4.00
Baseline Day 6	$2.00	$1.00 x 4 = $4.00
Baseline Day 7	$2.00	$1.00 x 4 = $4.00
Baseline Bonus	$10.00	$10.00
Baseline Totals	**$24.00**	**$38.00**
Experiment Day 1	$2.00	$1.00 x 4 = $4.00
Experiment Day 2	$2.00	$1.00 x 4 = $4.00
Experiment Day 3	$2.00	$1.00 x 4 = $4.00
Experiment Day 4	$2.00	$1.00 x 4 = $4.00
Experiment Day 5	$2.00	$1.00 x 4 = $4.00
Experiment Day 6	$2.00	$1.00 x 4 = $4.00
Experiment Day 7	$2.00	$1.00 x 4 = $4.00
Experiment Day 8	$2.00	$1.00 x 4 = $4.00
Experiment Day 9	$2.00	$1.00 x 4 = $4.00
Experiment Day 10	$2.00	$1.00 x 4 = $4.00
Experiment Day 11	$2.00	$1.00 x 4 = $4.00
Experiment Day 12	$2.00	$1.00 x 4 = $4.00
Experiment Day 13	$2.00	$1.00 x 4 = $4.00
Experiment Day 14	$2.00	$1.00 x 4 = $4.00
Experiment Bonus	$15.00	$15.00
Experiment Totals	**$43.00**	**$71.00**
Baseline & Experiment Totals	**$67.00**	**$109.00**
Total		**$176.00**

DISSEMINATION PLAN

We will register our trial in ClinicalTrials.gov within the timeframe specified in the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information. We will submit results of the trial to ClinicalTrials.gov no later than 1 year after participants have completed the trial, including the 6-month follow-up assessments. We will include a statement in our Consent and Assent forms regarding ClinicalTrials.gov.

MUSC's Office of Research and Integrity & Assurance Responsibilities administers ClinicalTrials.gov accounts and monitors research community activity and responsibilities within ClinicalTrials.gov. PI Dr. Hahn will be responsible for creating records on ClinicalTrials.gov.

STATISTICAL DESIGN AND POWER

In the proposed study, 40 eligible participants will be initially recruited, assuming an estimated 20% dropout rate, in order to obtain data on 32 treatment completers. A moderate effect size is expected in the current study. Previous research testing visual cognitive interference tasks reported a medium effect size for models estimating craving strength ($f^2 = 0.12$; $n = 31$).[5-6] A power analysis was conducted using G*Power 3.1 to detect a medium-sized between groups effect ($d = .50$, $\alpha = .05$) with a power of .80, a total sample of 24 is needed (i.e., 12 participants per group). However, due to this developmental nature of this study and the objectives to demonstrate preliminary efficacy, the proposed sample size is larger. The proposed study will therefore enroll 40 participants to be randomized to treatment to estimate an 80% study retention rate with a 95% confidence interval of ± 13%.

Descriptive analyses will be used to describe the sample. Clinical outcomes of interest are defined as: (1) decrease in craving measured by a single item from the Visual Analogue Scale immediately after task completion and from baseline to 2-week intervention phase (2) decrease in number of standard drinks (amount) from baseline to 2-week intervention phase and at 1-month follow-up measured by daily reports of “how many standard drinks did you consume yesterday?”. In order to establish feasibility, descriptive analyses will be used to measure the proportion of prompts participants responded to and response time to complete prompts. Intent to treat mixed-effects regression will be conducted to test differences in craving items after completing the task, nested within individuals. We will use a random effects mixed modeling approach using maximum likelihood estimation to test differences in mean craving and drinking outcomes (i.e., alcohol consumption) between baseline and post-experiment. We will also test differences in alcohol consumption between baseline and one-month follow-up. The participants will be modeled as random factors and the group allocation will be a fixed factor. We will examine the intervention between intervention and study time (baseline versus follow-up). Maximum likelihood estimation will provide unbiases estimates assuming missingness at random. Dr. Hahn will be attending a summer statistical workshop in ecological momentary assessment data analysis and receive consultation from statisticians housed within the South Carolina Clinical & Translational Research Institute to support the proposed analyses in this project.

STUDY TIMELINE

Overview of Study Timeline					
	Months				
	1	2	3-11	12	13+
Tasks/Activities					
Study Start Up	↔				
Recruitment		↔	↔		
Conduct Randomized Controlled Trial		↔	↔		
Data Cleaning/Analysis			↔	↔	
Dissemination			↔	↔	↔

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