Biphasic Effects of Acute Alcohol Intoxication on Bystander Intervention for Sexual Violence

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STATEMENT OF COMPLIANCE

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

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

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

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

INVESTIGATOR'S SIGNATURE

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

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 11/22/2024

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0 PROTOCOL SUMMARY

0.0 SYNOPSIS

Title: Biphasic Effects of Acute Alcohol Intoxication on Bystander Intervention for Sexual Violence

Grant Number: R21AA029225

Study Description: The goal of this experimental study is to examine the effect of alcohol, gender, and bystander attitudes on bystander barriers and sexual violence intervention among young adult men and women (age 21-30). The main questions it aims to answer are:

Aim 1: Determine the main effects of alcohol and gender on bystander barriers and SV intervention.

Hypothesis 1a: There will be a main effect of beverage condition such that (1) intoxicated participants (AL and DL) will report greater bystander barriers and lower intervention intentions compared to no-alcohol controls and (2) participants on the AL, compared to DL, will report fewer barriers and greater direct intervention intentions.

Hypothesis 1b: There will be a main effect of gender such that men will report greater bystander barriers, lower indirect and direct intervention intentions, and more aggressive intervention intentions, compared to women.

Aim 2: Determine the interaction of alcohol, gender, and bystander attitudes on barriers and SV intervention.

Hypothesis 2a: The effect of gender on SV intervention will be moderated by alcohol intoxication, such that men, compared to women, on the AL will report fewer bystander barriers and greater intervention intentions.

Hypothesis 2b: The effect of prosocial bystander attitudes on SV intervention will be moderated by alcohol intoxication, such that among participants higher in prosocial bystander attitudes, participants on the AL will report greater direct and aggressive intervention intentions compared to sober and DL participants, in addition to fewer barriers to intervention and compared to DL participants.

Objectives:	Primary Objectives: • To determine effects of alcohol and gender on bystander barriers • To determine effects of alcohol and gender on intentions to intervene • Secondary Objectives: • N/A
Endpoints:	Primary Endpoint: • Articulated Thoughts of Barriers to Bystander Intervention Articulated Thoughts of Intentions to Intervene as a Bystander • Secondary Endpoints: • N/A
Study Population:	Participants will be 275 healthy individuals between the ages of 21 and 30 who identify as a man or woman from the Metro-Atlanta/Denver area. We will enroll up to 275 participants to account for screen failures and withdrawals and plan to randomize 192 participants.
Phase or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	The enrollment site is Georgia State University and the University of Colorado Anschutz Medical Campus.

Description of Study Intervention/Experimental Manipulation:

Beverage Condition: Participants will be randomly assigned to an alcohol or no alcohol control beverage condition. Participants in the alcohol condition (AL and DL) will be administered two drinks consisting of an overall dose of 0.75 g/kg (men) or .69/kg (women) of 95% USP alcohol mixed in a 1:5 ratio with juice. This dosage reliably produces a mean peak BAC of 0.08%[116] and was selected because rigorous experimental research has found it is associated with activating effects of the AL and sedating effects on the DL[1]. This dosage is also within NIAAA safety guidelines for the safe administration of alcohol. Participants in the no-alcohol control condition will receive an isovolemic beverage consisting solely of orange juice. All beverages will be poured into two glasses in equal quantities and served chilled with no ice. Participants in both alcohol conditions (AL or DL) will be told that they are receiving alcohol. Participants will be given their glasses at equally spaced times during a twenty-minute interval to control for drinking rate (10 minutes per beverage). BACs for participants in the alcohol conditions will be monitored every five minutes after finishing their beverages with the AlcoSensor IV breath analyzer. For participants randomized to the AL, the laboratory task will commence after they reach a criterion BAC of .055%, which will ensure participants are still on the AL at the end of the approximately 15-minute laboratory task. For participants randomized to the DL, the laboratory task will commence after two consecutive BAC descending readings, with the last reading $\leq$.07%. Participants in the no-alcohol control group will be yoked to an alcohol participant assigned to the same limb based on 'wait time'[25,117].

BAC Limb Condition: Participants will be randomly assigned to one of two BAC limb conditions: (1) ascending limb (AL) or (2) descending limb (DL). Upon reaching .055% BrAC (ascending limb condition), two consecutive descending BAC limb (descending limb condition), or a yoked wait time (sober condition for both ascending and descending limb), participants will project themselves into a heat-of-the moment risky sexual violence scenario depicting a high-risk, sexually violent situation.

Study Duration: 36 months

Participant Duration: 1 day

0.1 SCHEMA

Day -30 to -1: Prescreening

- Preliminarily online screen of potential subjects by inclusion and exclusion (*n*=2,500)
- Schedule laboratory visit

Time 1, Day 1: Laboratory Visit

- Obtain informed consent (n=275)
- Screen potential subjects by inclusion and exclusion
- Baseline assessment, see **Section 7.1 Endpoint and Other Non-Safety Assessments**
- Randomization (n=192; alcohol n=128, sober n=64)
- Assessment of study endpoints, see **Section 7.1 Endpoint and Other Non-Safety Assessments**

0.2 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent) Day -30 to -1	Time 1 Day 1
Review Eligibility	X	X
Informed Consent		X
Demographics		X
Baseline Assessment		X
Weight		X
Randomization		X
Experimental Manipulation – Beverage, BAC Limb Condition		X
Laboratory Based Heat-of-the-Moment SV Bystander Scenario		X
Adverse Events Reporting		X

1 INTRODUCTION

1.1 STUDY RATIONALE

One in five young adult women experience sexual violence (SV) victimization[8]. Bystander training programs (BTPs) are increasingly popular as part of a comprehensive approach to prevent SV but have yet to demonstrate reduced rates of SV[9-11]. A major gap in BTPs is that they fail to train bystanders in intervening when consuming alcohol, which may help explain the limited effectiveness of BTPs in SV prevention so far. SV behavior frequently begins (or occurs entirely) at bars and parties[12-14] where bystanders are present and could intervene. Indeed, ~35% of young adults report an opportunity to intervene in a risky SV situation involving alcohol[15]. Survivors of SV report that 88% of bystanders who could have intervened in their assault, but did not, were consuming alcohol at the time[16]. Thus, research is urgently needed to inform BTPs on how alcohol intoxication influences SV intervention, including when and with whom these alcohol effects are most pronounced.

1.2 BACKGROUND

SV victimization results in severe mental and physical health problems[39-42] and a financial cost of $3.1 trillion over the course of survivors' lifetimes[43]. Male-to-female SV warrants particular attention given that 1 in 5 women experience attempted or completed rape[8,44]. Given that alcohol plays a significant role in SV[45], targeting alcohol in SV prevention efforts is essential. Although perpetrators ultimately are responsible for SV, SV prevention stands to benefit from comprehensive approaches that target perpetrators, potential victims, and bystanders[46]. Indeed, SV bystander training programs (**BTPs**) are a promising form of prevention[47-49]. BTPs recently gained widespread traction among adolescent, college, and military populations[50,51] despite the limited evidence base supporting their effectiveness[9] and no measurable reduction of SV rates since their widespread introduction in the early 2010s[9-11]. One major shortcoming of BTPs is their failure to account for bystander alcohol use. Our research suggests that 88% of bystanders were drinking when they could have, but did not, intervene in SV[16]. Only two evidence-based programs include alcohol use reduction content[52,53] and no evidence-based programs train bystanders on how to intervene while drinking. Importantly, BTPs teach participants how to intervene during high-risk sexual situations, including instances where drinking takes place (e.g., fraternity party), but it is unclear whether bystanders can or do intervene using the strategies they are taught (i.e., distracting the perpetrator). Both theory and our preliminary data suggest that one's own drinking may hinder or embolden intervention, and rigorous research is needed to understand and leverage the barriers and behaviors of intoxicated bystanders. Without such work, BTPs are unlikely to reach their full potential in preventing SV[50,54,55]. Specifically, a significant gap exists in our understanding of when and how bystanders make decisions to intervene in SV when they are intoxicated. This proposal addresses that gap and will identify specific barriers that intoxicated bystanders experience and strategies that can be used to intervene in SV while drinking.

Prior research shows that alcohol intoxication is central to bystander intervention. Alcohol associated with (1) greater difficulty noticing SV and interpreting it as warranting intervention[17] and (2) decreased SV intervention among men who report high intentions to intervene in SV when sober[18]. Conversely, research indicates that alcohol intoxication is also associated with an increase in prosocial behavior[2,3], including SV intervention[4-6], likely due to the disinhibiting effects of alcohol that decrease intervention barriers. The proposed research addresses four notable limitations in our current understanding of alcohol's effect on SV intervention. First, research on intoxicated bystanders has been limited to the ascending limb (AL) of the breath alcohol concentration (BAC) curve (i.e., when BAC is rising), thereby focusing on the disinhibiting and activating effects of alcohol only. However, alcohol has biphasic effects on behavior and neurocognitive function,[19-28] and is sedating on the descending limb (DL) of the BAC curve (i.e., after BAC has peaked and is now decreasing). Understanding these effects could redirect BTPs towards encouraging bystanders to act when experiencing the activating effects of alcohol, and conversely, to heighten their awareness and recognition of SV when impaired by the sedating effects of alcohol. Neither are addressed in established BTPs. Second, gender differences have not been examined among intoxicated bystanders whereas cross-sectional research clearly indicates that SV intervention varies by gender (e.g., men report greater barriers[29-32] and less SV intervention[15,32,33] than women). Third, extant research has only examined the effect of alcohol on direct bystander intervention, such as intervening with the perpetrator, although indirect strategies (e.g., distraction) are more commonly used[34]. Finally, it is unclear how alcohol intoxication may interact with modifiable individual-level predictors (e.g., prosocial bystander attitudes) of SV intervention. This information will allow BTPs to tailor program content based on baseline individual attitudes.

1.3 RISK/BENEFIT ASSESSMENT

1.3.1 KNOWN POTENTIAL RISKS

We foresee the following immediate risks to participants: (1) risk of breach of confidentiality, (2) risks associated with drinking alcohol and (3) psychological discomfort associated with contemplating the hypothetical SV scenario.

1. **Breach of confidentiality.** It is possible that data could be breached or that a participant could be identified as being a part of our research study. However, we think such a likelihood, including a breach of confidentiality, is highly unlikely because the investigative team will strictly adhere to the guidelines for research outlined by the Institutional Review Board (IRB), and the DHHS Federal Policy for the Protections of Human Subjects (45 CFR, Part 46).

2. **Risks associated with drinking alcohol.** Alcohol administration will follow the guidelines stipulated by NIAAA. The investigative team, including Drs. Leone (PI) and colleagues have tested nearly 1,150 participants using similar alcohol administration parameters with no serious adverse consequences or complaints. Dr. Leone (PI) has extensive experience in alcohol administration research and is fully informed about the ethical and practical issues in these areas. In addition, Dr. Leone's laboratory also has an IRB-approved protocol for minimizing the likelihood of intoxicated participants leaving the laboratory prior to reaching a safe BAC level

(i.e., .02%). The laboratory has never experienced an instance where a participant left the laboratory prematurely and in an unsafe state that required notification of local law enforcement.

3. **Psychological discomfort associated with study measures and tasks.** It is possible that participants will feel psychological discomfort when completing a baseline questionnaire battery about sensitive subjects or when contemplating the hypothetical SV bystander scenario. With respect to participants interacting with content involving a woman's experience unwanted sexual advances, Dr. Leone (PI) has tested approximately 400 subjects using laboratory paradigms in which subjects have the opportunity to intervene in a female's unwanted sexual experience (i.e., being "forced" to watch a sexually explicit video). An adverse response has never occurred (e.g., subject requesting to terminate the study, 'extreme' psychological distress). Further, Dr. Leone's colleagues, Drs. Stappenbeck and Davis, have extensive experience using similar heat-of-the-moment scenarios and protocols to assess SV risk and sexual decision making and no prior participants have experience events involving emotional distress.

1.3.2 KNOWN POTENTIAL BENEFITS

Participants will receive a better understanding of behavioral science research and knowledge about how such research is conducted. However, the main benefit of this research will be to society as a whole. The central aim of this research program is to investigate the biphasic effects of acute alcohol intoxication on SV bystander intervention. This fact underlies the significant benefit that this line of research may provide—the first investigation of the acute effects of alcohol on behavioral barriers and intervention. As such, this line of research has the potential to provide (1) the foundation for future research that will examine other factors that influence intervention among intoxicated bystanders (e.g., gender, intoxication level of victim and perpetrator, different peer norms) and (2) the evidence base from which intervention programming can draw from to better teach bystanders how they can successfully intervene.

As noted above, this study involves no risks to participants other than the risk of breach of confidentiality, potential discomfort associated with drinking alcohol, and psychological discomfort from the hypothetical scenario. Given our safety protocols and our safety history, we feel that the scientific and societal benefits gained from results of this study far outweigh the minimal risks involved in conducting such research.

1.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The potential risks in this study are minor and we will take steps to minimize risk to participants.

Confidentiality. The screening questionnaire uses a secure, online HIPAA compliant platform (e.g., the CU Qualtrics or REDCap platforms) that does not require the participant to enter any identifying information, unless they are deemed potentially eligible. Once the participant has been deemed potentially eligible, they will be given the opportunity to enter their contact information in order to allow the research team to contact them for scheduling. Participants who are deemed potentially eligible will also be asked to provide their legal first name, legal last name, date of birth, telephone number, email address, and home address to obtain or create a Medical Record Number (MRN) with UCHealth to potentially schedule their inpatient visit at the CTRC for the laboratory visit prior to

informed consent. Those who are not eligible or who choose not to provide contact information are never identified. Participants' name and contact information will be entered into an electronic spreadsheet and kept in a password protected file in a HIPPA compliant, secure OneDrive folder that only the PI and research team will have access to.

Data collected during the laboratory session is also anonymous. Although we will check the identity and age of the participant prior to beginning the study, the participant's name will not be connected to the datafile in any way. All members of the research team have received or will receive training that includes emphasis upon the importance of confidentiality of information, and all personnel on the project (including research assistants and study staff) will complete the required NIH training in protection of human research participants. Data transfer will be protected using a Secure Socket Layer with 128-bit encryption. This is the same level of encryption used for most banking transactions and offers the highest degree of protection available for data transfer. Electronic protection is provided by a commercial-grade firewall, with continuous monitoring of the server for any attempts at electronic invasion.

Data that is collected will be stored (1) in locked file cabinets in Dr. Leone's (PI) laboratory, (2) on a secure, online HIPAA compliant platform (e.g., the CU Qualtrics or REDCap platforms), and (3) on a secure, OneDrive folder that is password protected. All data will be identified only by numerical code rather than participants' names. Names will never be stored with or linked to study data. Names will only be saved on a password-protected electronic spreadsheet for pre-screening, scheduling, and on consent forms. Names will be removed from the scheduling spreadsheet after completion of the study session. Consent forms will be kept in a locked cabinet located in a separate room from all other study data in Dr. Leone's laboratory. Data will also be stored electronically on a secure OneDrive folder that only the research team has access to. Aside from the temporary scheduling spreadsheet and pre-screening leads log, participants' names will not appear in any computer files and cannot be linked in any way to their responses. All computers and servers are password-protected. Only individuals with a correct password can gain access to individual computers and departmental servers (e.g., OneDrive). User accounts are created and maintained by the University's IT Support team. In addition, the entire campus WAN is behind a firewall that blocks direct outside access to all servers for FTP or direct logon without a designated hole created by the campus IS group. These holes are IP-to-IP specific. All research workstations are password-protected to further limit unauthorized user access. Dr. Leone's laboratory space is only accessible by badge access to authorized personnel. The department, as well as the University, maintains a list of individuals with authorized access.

Alcohol Administration. Steps have been taken to minimize the possibility that participants will experience adverse reactions to alcohol. Abstainers (see Inclusion and Exclusion Criteria above) will be excluded. Furthermore, participants who self-report that they are currently seeking treatment or in recovery for an alcohol use disorder will be excluded because of the potential for relapse that may occur after alcohol consumption. Individuals receiving any prescription medications that may contraindicate the use of alcohol and those reporting a condition in which alcohol consumption is medically contraindicated, will also not be tested. In addition, the pre-experimental guidelines and beginning of experiment breath alcohol test serve to ensure that we do not administer alcohol to anyone who is already intoxicated. We will also administer a pregnancy test to ensure that we do not administer

alcohol to anyone who may be pregnant and confirm female participants have not had sexual intercourse without effective contraception in the past two weeks. In the event of a positive or inconclusive pregnancy test, the participant will be informed that the pregnancy test was not clearly negative and, as such, we cannot allow her to participate in our study at this time. We will inform the participant that an ambiguous test result does not necessarily indicate pregnancy and recommend that she seek an additional pregnancy test from a medical facility.

The alcohol will be administered in the Department of Psychiatry's Research Suite, which includes dedicated clinical interview rooms for alcohol administration located on the 5th floor of the Anschutz Health Sciences Building (AHSB). This space has been used in other studies for alcohol administration within the Department of Psychiatry (Schacht Protocol# 19-1658 and 19-2335). We will follow standard security procedures for alcohol administration visits, including having two staff members present at each visit, along with 24-hour phone access to campus police and silent panic alarms in all AHSB 5th floor clinical interview rooms. As recommended by University Police, research staff also have the SafeZone app installed on their cell phones: https://www.cuanschutz.edu/police/divisons/emergencymanagement/cuanschutzsafe. A silent alert can be activated using this app and will be received within seconds and responders will start moving to the exact location of the alert. Current and previous Department of Psychiatry studies using this space for alcohol administration visits have never had to call the police or trigger an alarm or alert. The PI and other division faculty also have offices in the Psychiatry Research Suite and will be close by if any issues arise. All entrances to the Psychiatry Research Suite offices are badge access only.

After IRB approval of the research protocol the study team will submit an Investigational Product Management Plan (IPMP) for the storage and administration of alcohol in this study. Data collection will not begin until this is approved by the Research Product Review Committee (RPRC) and this approval has been submitted to the IRB. The IPMP will be modeled after already approved IPMPs with alcohol accountability and inventory logs, temperature monitoring, alcohol storage in a locked cabinet in a restricted badge access room, and a ceiling-mounted facilities camera in the hallway that monitors access and activity. Alcohol administration will occur in the morning (before noon) and participants will be required to refrain from consuming food for a time period of four hours prior to testing. Participants in the alcohol condition will be administered two drinks consisting of an overall dose of 0.75 g/kg (men) or .69/kg (women) of 95% USP alcohol mixed in a 1:5 ratio with juice. Participants in the Alcohol groups (AL and DL) will be told that they are receiving a 'moderate' dose of alcohol. Participants in the No-Alcohol Control group will receive an isovolemic beverage consisting solely of orange juice in two separate glasses. All beverages will be served chilled with no ice. The beverages will be poured into two glasses in equal quantities and participants will have ten minutes to drink each glass (twenty minutes total). This single alcohol dose has been used in past studies and reliably produced blood alcohol levels of .08%, which is within NIAAA safety guidelines *(*https://www.niaaa.nih.gov/research/guidelines-and-resources/guidance_conducting_alcohol_administration_studies_human_participants*)* for the safe administration of alcohol. Inasmuch as alcohol dosing is based on body weight, it is important to ensure that participants are not given excessively large amounts of alcohol due to high levels of body fat. As such, the following parameters were derived based on past consultation with healthcare professionals.

Participants will be excluded if they are under 6 feet tall and over 230lbs or if they are over 6 feet tall and over 250lbs. It was determined that a healthy drinker within these height/weight limits will be able to easily tolerate our dose of alcohol (0.75 g/kg or .69/kg) without any danger of adverse effects or excessively high breath alcohol concentrations. A chart determining which height/weight category our participants fall into will be included in each participant's data folder and will be referenced during the laboratory paradigm by study staff. Parenthetically, body mass index charts are not advisable for determining alcohol administration parameters in as much as they would consider a muscular 6'3" 240lb person to be "obese" and a 6'3" 200lb person to be "overweight." Thus, use of BMI would result in an inappropriate dosing method because it would not be able to discriminate between a healthy, muscular individual and a physically-"hearty", stocky individual.

Please see the "Dealing With Adverse Reactions" section below for a detailed description of the procedures for handling participants if they become ill and the "Discharge from the Laboratory" section below for a detailed description of the procedures for handling participants if they attempt to leave prior to being discharged.

Dealing With Adverse Reactions.

Physical Discomfort – Illness. During informed consent, participants will be informed that they may experience some physical discomfort associated with drinking alcohol. They will also be told that if, at any time they feel uncomfortable, they can stop drinking and quit the study. If they do feel sick, they will be allowed to remain in a quiet, private room until they feel well enough to leave (provided that their BAC is below 0.02%). Participants will also be given immediate access to a bathroom in case they need to vomit. Other than some mild nausea and vomiting (which is very rare), none of our participants have ever experienced any adverse reactions to our procedures. Nevertheless, we have added the following safety precautions in order to protect participants against even highly unlikely medical situations. A standard operating procedure (SOP) will be in place for dealing with emergency medical situations which include notifying the PI immediately. All experimenters will be familiar with this protocol and are trained to respond in the case of an unlikely medical event. The protocol clearly explains when to call 911 for medical emergencies as well as how to deal with events such as fainting, arrested breathing, choking, convulsions, bleeding, fractures, and cuts and abrasions (it should be noted that the Emergency Room at UCHealth is only 2 blocks away from Dr. Leone's laboratory). Again, these precautions have been added to increase participant safety. None of the above adverse events have ever occurred in the laboratory of Dr. Leone (PI) or other divisions PIs who have used these alcohol administration procedures for the past 5 years at CU and previously at MUSC (Schacht Protocol# 19-1658 and 19-2335).

Psychological Discomfort. Although experience shows that the risk is quite low, we recognize that the sensitive subject matter of some of the survey questionnaires and the heat-of-the-moment scenario may precipitate emotional distress for a participant. In order to minimize possible harm from answering these questions, we do the following:

(1) Participants will be made aware verbally through the informed consent procedure, and in writing on the informed consent document and on the questionnaires themselves that they are free not to answer any question for any reason.

(2) Research assistants will monitor participants for signs of distress. Notably, if a subject communicates being upset during the task (even if he does not explicitly state that he would like to stop the study), the experimenter will reiterate to the subject that he has the right to withdraw from the study at this time and still receive compensation. An offer will be made to discontinue the study at that time. If the subject accepts this option, the study will be stopped, and debriefing will immediately commence.

(3) Participants are provided with contact information (telephone and email) for the PI and encouraged to contact them with any questions, complaints or concerns.

(4) At the conclusion of the laboratory session, each participant is offered the opportunity to ask questions in person. At any point, any report of stress, discomfort, or negative reaction will be monitored directly by Dr. Leone. Dr. Leone completed her doctoral training in clinical psychology and has extensive training in interviewing, counseling, referral, and crisis management with particular expertise with substance use and violent populations. Dr. Joseph Schacht, a licensed clinical psychologist in Dr. Leone's division, will serve as a clinical back up in the event she is unavailable or needs to consult.

Discharge from Laboratory. To minimize the possibility that participants will drive a motor vehicle after leaving the laboratory, they will be transported home via pre-arranged transportation (e.g., a ride from a family member or friend) or via public transportation (e.g., Uber/Lyft) at no cost to the participant. Moreover, they will not be allowed to leave the laboratory until their BAC has fallen to 0.02% (in accordance with NIAAA guidelines) and have also passed a field sobriety test. All participants will be given a standard field sobriety test upon entering the laboratory in the sober state and will be given the same test when they reach a descending BAC of 0.02%. Participants will only be discharged from the laboratory if this test score is the same or better as when they entered the laboratory.

Although these measures will minimize risk to participants upon discharge from the laboratory, it is also possible, though highly unlikely, that participants may attempt to leave the laboratory prior to reaching a BAC of 0.02% and passing a field sobriety test. To guard against this remote possibility, participants will be required to surrender their keys and valid ID (e.g., driver's license) upon providing informed consent. In addition, upon completion of experimental testing (i.e., at the outset of the 'detoxification' phase), a sign will be posted on the inside of the detoxification room door (i.e., the side of the door facing the participant) that reminds participants that: 1) The experimenter has their keys and license in a locked drawer in the laboratory; 2) These items will be released to the participant after his BAC reaches 0.02 and he passes a field sobriety test, and 3) The police may be contacted in the event that the participant leaves the laboratory without the experimenter's approval. Thus, should the participant attempt to leave the room, this sign will be at eye level and clearly visible. The purpose of this sign is to provide a salient cue that inhibits a premature exit. Finally, all participants will also be told in the consent form that they will be paid after reaching the specified BAC level and passing a field sobriety test. Thus, the longer they stay in the laboratory, the more money they will earn (at a rate of $15 per hour). This can be viewed as yet another incentive to remain in the lab and, simultaneously, a measure that would minimize the risk of participants leaving prematurely.

It is possible, though highly unlikely, that a participant will still leave the laboratory despite not having their keys or valid ID, reading the sign, and not being paid. Again, in such an event, campus police may be contacted if Dr. Leone deems this individual a danger to themselves or others. Our laboratory's possession of the participant's ID will facilitate the ability of law enforcement to locate the individual. Alternatively, a participant could request that their keys or ID be returned to them in order to leave the lab without the approval of the experimenter. If this occurs, our staff will be trained to avoid

any adversarial interaction and return the participant's keys and ID. However, this contact between the participant and the experimenter will provide the opportunity for the experimenter to clearly outline the consequences of leaving the laboratory (i.e., the police may be contacted). Participants who opt to leave early will sign a form stating they are leaving against the research team's advice. In the very few instances in which this has occurred in previous studies, participants were behaviorally contracted to answer a phone call from the lab at a predetermined time on that evening and/or the next day to confirm participants' safety.

The proposed investigation will provide data that is critical to developing (1) an evidence base upon which existing bystander intervention programming is based (2) a foundation for future work on the effects of acute alcohol intoxication on bystander intervention for SV. Given that SV occurs at bars and parties at high rates, it is vital for researchers to consider the role of bystanders' own intoxication to inform prevention programming efforts, including the biphasic effects of alcohol. Not only will the findings from the proposed study examine gender differences and the biphasic effects of alcohol intoxication on intervention, it will also provide data on how modifiable bystander attitudes targeted in bystander training programs interact with alcohol use to predict alcohol-related SV intervention. Again, these positive societal benefits outweigh the very minimal risks involved in conducting this research.

2 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine effects of alcohol and gender on bystander barriers	Articulated Thoughts of Barriers to Bystander Intervention	Articulated thoughts in simulated situations is a proxy for understanding barriers to intervention
To determine effects of alcohol and gender on intentions to intervene	Articulated Thoughts of Intentions to Intervene as a Bystander	Articulated thoughts in simulated situations is a proxy for understanding intervention intentions.
Secondary		
N/A	*N/A*	N/A
Tertiary/Exploratory		
N/A	N/A	N/A

3 STUDY DESIGN

3.1 OVERALL DESIGN

The following hypotheses are advanced:

- **Hypothesis 1a.** There will be a main effect of beverage condition such that (1) intoxicated participants (AL and DL) will report greater bystander barriers and lower intervention intentions compared to no-alcohol controls and (2) participants on the AL, compared to DL, will report fewer barriers and greater direct intervention intentions.
- **Hypothesis 1b.** There will be a main effect of gender such that men will report greater bystander barriers, lower indirect and direct intervention intentions, and more aggressive intervention intentions, compared to women.
- **Hypothesis 2a.** The effect of gender on SV intervention will be moderated by alcohol intoxication, such that men, compared to women, on the AL will report fewer bystander barriers and greater intervention intentions.
- **Hypothesis 2b.** The effect of prosocial bystander attitudes on SV intervention will be moderated by alcohol intoxication, such that among participants higher in prosocial bystander attitudes, participants on the AL will report greater direct and aggressive intervention intentions compared to sober and DL participants, in addition to fewer barriers to intervention and compared to DL participants.

Participants will be randomly assigned (following confirmation of eligibility at the laboratory session) to one of two beverage conditions (alcoholic, control beverage) using a 2:1 randomization and one of two BAC limb conditions (AL, DL). Bystander barriers and intervention intentions will be assessed using the articulated thoughts in simulated situations (ATSS) think-aloud paradigm.

3.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A larger sample size for the alcohol (n=128), compared to sober (n=64) is needed to provide adequate power to detect limb effects (n_{AL}=64, n_{DL}=64).

Participants in the no-alcohol control will be yoked to an AL or DL alcohol wait time to reduce error variance in intoxication levels[35].

A no-alcohol control beverage (i.e., told no alcohol, receive no alcohol) was selected due to compensatory effects associated with the use of an alcohol placebo in SV research[114], and research suggesting a placebo condition is not an appropriate control for moderate to high dosage alcohol conditions[115].

3.3 JUSTIFICATION FOR INTERVENTION

Administering alcohol is necessary to test the acute effects of alcohol on SV bystander behavior. Beverages will be delivered orally and must be consumed within 20 minutes. The PI has used these procedures in previous studies.

3.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment and the experimental session.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and lifestyle considerations (see **Section 4.3, Lifestyle Considerations**)
3. Between the ages of 21 and 30
4. Identifies as a man or woman
5. Report that on at least 3 days in the past year they have consumed an alcohol quantity on a single occasion that was equal or greater to the dose administered in the lab

4.2 EXCLUSION CRITERIA

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

1. Currently seeking treatment or in recovery for an alcohol or substance use disorder
2. Any medical or psychiatric condition, as well as current use of a medication, that would contraindicate alcohol administration via self report:
    - Head Injury: any past serious head injuries
    - Acute Psychiatric Symptomatology: elevated psychological distress as indicated by a score greater than 65 on the Brief Symptom Inventory
3. Self-report that a participant is trying to get pregnant, currently pregnant, or currently breastfeeding, or has engaged in sexual intercourse without effective contraception in the past two weeks or a positive pregnancy test
4. If the participant is less than six feet tall and weighs over 230 pounds or is over six feet tall and weighs over 250 pounds as measured during the lab visit

4.3 LIFESTYLE CONSIDERATIONS

Prior to the study assessment visit, participants are asked to:

1. Refrain from consuming drugs or alcohol within the last 12 hours
2. Refrain from eating food within 4 hours

4.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because they do not meet one or more exclusion

criteria or fail to meet one or more inclusion criteria that are likely to change over time will not be rescreened.

4.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Strategies for Recruitment: Recruitment for our study will utilize methods used previously by the research team for this grant and will be passive in that we will utilize advertisements via multiple media outlets to ensure we have adequate reach of our target population of drinking men and women ages 21-30. We will use a broad recruitment strategy that includes advertising online (e.g., Facebook, Instagram, Snapchat), local radio stations, local transportation (e.g., RTD buses) and community flyers that will target young adults in Denver, CO. Ads will include a website link and/or QR code that directs participants to an online eligibility screener. They may also be provided a telephone number and email address to the PI's laboratory for the option to complete the eligibility screener over the phone with a member of the study team. When we reach our target sample size for any given group (e.g., women), we will stop recruitment for that group. Any subsequent callers with those characteristics will be told we have reached our quota for some study aspects. Potentially eligible and interested participants will be contacted by study staff to verify their eligibility, provide information about the study, and confirm their interest in participating. During this eligibility phone call, participants will be informed of and have to agree to pre-session guidelines including not eating 4 hours prior to the session and not consuming alcohol/drug 12-hours prior to their session. They will also be required to not drive home from the laboratory. The research team may also use the online scheduling platforms (e.g., Microsoft Bookings, Calendly) to schedule pre-screening calls with participants and send calendar invites with email reminders for participants' in-person lab visit.

The proposed research will include racial/ethnic minority and non-minority participants. It is expected that the participants recruited into this study will reflect the general racial and ethnic composition of Atlanta/Denver's population. Among our currently recruited sample from Atlanta, GA, approximately 38% identify as Black, 30% as White, 19% as Asian, and the remain identify as another racial group. We estimated that at least 50% of our sample will be Non-Hispanic/Latiné White that is recruited from Denver. The remainder will be Black (approximately 9%) or of another racial group. We expect approximately 30% of participants will identify as Hispanic/Latiné. Other minority groups will not be excluded. However, they do not comprise a significant percentage of Denver's population.

The current study does not include all ages due to scientific reasons. Specifically, adults aged 21-30 will be considered eligible for the study. Both children and older adults will be excluded. Participant age is restricted to 21-30 due to the scientific premise of the research which includes a focus on sexual violence (SV) bystander intervention among young adults who engage in alcohol use. Further, because the present study will employ an alcohol administration method, adults under 21 are excluded for legal reasons.

Compensation and Incentives: Participants who present to the laboratory, provide consent, and are not eligible for the full study will be compensated $15/hour. Participants who are eligible for the full study will be paid up to $120 for completing all study procedures. Payments will be sent via electronic gift cards (e.g., Amazon). Participants may choose to stop the study at any time and will be paid for their participation so far at a rate of $15/hour. All participants who are paid over $100 will complete a W9 form per CU's policy, noting their name, home address, social security number, date, and signature.

Participants will be transported home from the laboratory session using a rideshare service (e.g., Uber or Lyft) or by a family member or friend. The research team will pay for or compensate the participant for transportation home if assigned to the alcohol condition.

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

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

5.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Beverage Condition— Participants will be assigned to one of two beverage conditions: (1) alcohol or (2) no-alcohol control. The target BrAC for the alcohol condition is .08.

BAC Limb Condition— Participants will be randomly assigned to one of two BAC limb conditions: (1) ascending limb (AL) or (2) descending limb (DL). Upon reaching .055% BrAC (ascending limb condition), two consecutive descending BAC limb (descending limb condition), or a yoked wait time (sober condition for both ascending and descending limb), participants will project themselves into a heat-of-the moment risky sexual violence scenario depicting a high-risk, sexually violent situation.

5.1.2 ADMINISTRATION AND/OR DOSING

Alcohol participants (AL and DL) will be administered two drinks consisting of an overall dose of 0.75 g/kg (men) or .69/kg (women) body weight of 95% USP alcohol mixed in a 1:5 ratio with juice. This dosage reliably produces a mean peak BAC of 0.08%[116] and was selected because rigorous experimental research has found it is associated with activating effects of the AL and sedating effects on the DL[1]. Participants in the no-alcohol control condition will receive an isovolemic beverage consisting solely of orange juice. All beverages will be poured into two glasses in equal quantities and served chilled with no ice. Participants in both alcohol conditions (AL or DL) will be told that they are receiving alcohol. Participants will be given their glasses at equally spaced times during a twenty-minute interval to control for drinking rate. BACs for participants in the alcohol conditions will be monitored every five minutes after finishing their beverages with the Alco-Sensor IV breath analyzer. For participants randomized to the AL, the laboratory task will commence after they reach a criterion BAC of .055%, which will ensure participants are still on the AL at the end of the approximately 15-minute laboratory task. For participants randomized to the DL, the laboratory task will commence after two consecutive BAC descending readings, with the last reading less than or equal to .07%. Participants in the no-alcohol control group will be yoked to an alcohol participant assigned to the same limb based on 'wait time'[25,117].

5.2 FIDELITY

5.2.1 INTERVENTIONIST TRAINING AND TRACKING

N/A

5.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will be predetermined by the PI and is stratified by gender. All members of the study team will be unblinded.

5.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

N/A

5.5 CONCOMITANT THERAPY

For this protocol, participants may not use any medication that would contraindicate alcohol administration. Medication usage will be assessed at each study visit and documented in the participant's study folder.

5.5.1 RESCUE THERAPY

N/A

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

6.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from drinking their beverage (i.e., they opt not to finish their beverage) but not from the study, remaining study procedures will be completed as indicated by the study protocol.

6.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Any event or medical condition or situation occurs such that continued collection of study data would not be in the best interest of the participant or study staff and would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

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

6.3 LOST TO FOLLOW-UP

N/A

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Upon arrival to the laboratory session, a trained research assistant will check the participant's ID to verify the participants' age, verify that they adhered to the pre-session guidelines, administer a breathalyzer test to ensure a BAC of 0.00% and conduct a field sobriety test. Participants who enter the laboratory with a BAC above 0% as determined by a breathalyzer will be prohibited from completing the study at that time. Participants will either be asked to reschedule or if their BAC is at 0.02% or below they will be given the option to remain in the laboratory until their BAC is 0% as determined by a breathalyzer to begin the study (participants will not be paid for their time until their BAC is at 0%)

Informed consent will be obtained and participants will sign an IRB-approved "Drive Home Agreement", in which participants agree to remain in the laboratory until they reach a predetermined BAC level (0.02%), to surrender their ID and keys (if they have keys) to the experimenter until the end of the study, to not operate a vehicle for the remainder of the day, and laboratory staff will arrange a rideshare (e.g., Uber or Lyft) home from the laboratory if assigned to the alcohol condition. All participants will surrender their cell phones, any smart watches or personal belongings (e.g., backpack) to the laboratory staff to be stored in a locked space until the end of the study. Female participants will provide a urine sample for a pregnancy test and an RA will confirm a negative result to determine eligibility.

A questionnaire battery will be administered to re-verify eligibility (see In-Person Eligibility Screener) and answer questions about alcohol use, social behavior, beliefs, and attitudes (see Baseline Survey). Participants will complete the Brief Symptom Inventory (BSI; Deragotis, 1993) to ensure the absence of acute psychiatric symptomatology and to confirm participants' reported absence of acute psychiatric symptomatology. Any participant who obtains a T-score above 65 on the Global Severity Index of the BSI will be excluded from participation. Importantly, this measure is not intended to diagnose participants with a psychiatric disorder. Rather, the purpose of administering the BSI is to identify acute psychiatric symptomatology that would contraindicate alcohol administration – even if the participant would not meet DSM-V criteria for a given psychiatric disorder. Thus, targeting general symptomatology – rather than diagnostic status – as a threshold for exclusion represents a more conservative (and safe) approach. Finally, all self-report criteria assessed during the online screening (described above) will be re-verified and participants will be weighed to determine their correct alcohol dose.

Participants will then be randomly assigned to one of two beverage conditions (alcoholic, control beverage) in addition to one of two BAC limb conditions (ascending limb (AL) or descending limb (DL)). Participants in the no-alcohol control will be yoked to an AL or DL alcohol wait time to reduce error variance in intoxication levels. Participants will be informed of their condition (i.e., if they will be consuming alcohol). Those in the alcohol condition will be asked to sign a form attesting to the fact that they will not drive a motor vehicle nor operate any heavy machinery until the next morning (see Drive Home Agreement). Participants will then receive detailed instructions for the remaining portions of the study and consume beverages based on beverage condition.

Baseline and Eligibility/Ineligibility Measures. Following consent, participants will complete a questionnaire battery, which includes the following.

- Eligibility/Ineligibility Measures:
  - The Brief Symptom Inventory[55] will be used to ensure the absence of acute psychiatric symptomatology and to confirm participants' reported absence of acute psychiatric symptomatology. Any participant who obtains a T-score above 65 on the Global Severity Index of the BSI will be excluded from participation.
  - A demographics questionnaire will be used to confirm eligibility for gender, alcohol use, and alcohol contraindications (i.e., treatment for alcohol/drug use, medical contraindications).
  - NIAAA's Alcohol Consumption Questions[109] will assess participants' frequency in which they consumed their expected laboratory dose of alcohol during the past year
- Baseline Characteristics:
  - Daily Drinking Questionnaire
  - NIAAA's Alcohol Consumption Questions
  - Timeline followback
  - Bystander Barriers Scale
  - Sexual Experience Short-Form (Perpetration)
  - Revised Sexual Experience Survey-Short Form (Victimization)
  - Intent To Help Friends Scale
  - Rape Myth Acceptance Scale
  - Bystander Efficacy Scale
  - Cannabis Use Identification Test-Revised (Cudit)
  - Revised Conflict Tactics Scale (Cts-2)
  - The Conformity To Feminine Norms Inventory
  - The Conformity To Male Role Norms Inventory
  - Acceptance And Action Questionnaire II (Bond Et Al., 2011)
  - Ceoa
  - Knowledge of Effective Consent for Sex

Eligibility/Ineligibility Determination. Some participants will not qualify for the study based on the inclusion/exclusion criteria after completing the baseline assessment. It will be clearly explained to the ineligible participant why s/he is ineligible to participate. Laboratory staff will refrain from using any value judgments when conveying this information. If it is determined that the participant endorses acute psychiatric symptomatology on the BSI that will preclude them from participation, laboratory staff will tactfully, and in a relaxed manner, inform the person of this fact. It will be clearly explained that this measure does not provide a diagnosis of a psychiatric disorder. Laboratory staff will then ask the participant whether s/he is receiving treatment for these symptoms. If not, laboratory staff will encourage the individual to seek treatment from a mental health professional (referrals will be made if requested). If a pregnancy is detected, laboratory staff will inform the subject in a tactful and relaxed manner. The participant will be told that her test was positive and that she should visit her physician to confirm the result (referrals to health care centers will be provided). If it is determined that she is excessively distressed about the result, the experimenter will contact the PI for assistance.

If an individual is deemed actively homicidal or suicidal based on statements they make to research staff, they would not be enrolled in the study and the PI would provide appropriate medical or

psychiatric referrals and report the information to police to keep the individual safe. If an individual reports information about someone hurting someone else, the PI would also report this information to the police. If suicidal or homicidal ideation, unusual anxiety or depression develops during or after the study, the PI, will be informed and appropriate referrals for intervention will be offered, if needed. If an individual report information about child neglect or abuse, the PI would report the information to Social Services.

Randomization. After eligibility is confirmed, participants will be randomly assigned to an alcohol (target BAC .08%) or no-alcohol control beverage using a 2:1 randomization. They will then be randomly assigned to complete the study on the ascending or descending alcohol limb, or an equal yoked wait time (sober condition). Participants will be seated in a where they will drink an alcoholic or no-alcohol control beverage.

Beverage Administration. Participants in the alcohol condition (AL and DL) will be administered two drinks consisting of an overall dose of 0.71 g/kg (men) or .65g/kg (women) body weight of 95% USP alcohol mixed in a 1:5 ratio with juice to reach a peak target BAC of .080. Participants in the no-alcohol control condition will receive an isovolumic beverage consisting solely of orange juice. All beverages will be poured into two glasses in equal quantities and served chilled with no ice. Participants will be given their glasses at equally spaced times during a twenty-minute interval to control for drinking rate. BACs for participants in the alcohol conditions will be monitored every five minutes after finishing their beverages with the Alco-Sensor IV breath analyzer. For participants randomized to the AL, the laboratory task will commence after they reach a criterion BAC of .055%. For participants randomized to the DL, the laboratory task will commence after two consecutive BAC descending readings, with the last reading less than or equal to .07%. In other words, both conditions will be assigned a dose of alcohol to reach a BAC of .080; those in the AL condition will start the experiment at .055% BAC and those on DL will start the experiment after their BAC has peaked and then descending with two consecutive descending readings of .07. Those assigned to drink alcohol will complete the attached "effects of alcohol" measure to assess effects on each limb. Participants in the no-alcohol control group will be yoked to an alcohol participant assigned to the same limb based on 'wait time'. Yoking will be done by recording the time it takes participants to reach the target BAC on an excel spreadsheet. Participants in the sober condition will be matched to these participants on wait time. For example, if the last alcohol, ascending limb participant took 15 minutes to reach their target BAC, the next sober participant will wait 15 minutes before starting the task.

Heat-of-the-Moment SV Bystander Scenario.

Participants will project themselves into a drinking situation (e.g., you are at a party with friends) based on scenarios used in previous research by the research team[35,36,118,119], modified to assess bystander barriers and intention, and piloted by the investigative team (*n*=50). Participants will read and project themselves into a series of events that pose a risk for SV perpetration, which they are witnessing as a bystander. Specifically, this story depicts a male friend who is drinking and makes sexually suggestive comments to an intoxicated woman, and then begins to kiss and grope her while dancing. As the party continues and the woman gets visibly more intoxicated, the male friend states that he is getting a ride share to take her back to his place to "hook up". We will use a modified ATSS think-aloud paradigm to capture real-time affective and cognitive components of participant's bystander decision-making process. This ATSS paradigm is a well-validated and rigorous procedure to capture ongoing thoughts in response to small-dosage situations and has previously been paired with hypothetical scenarios[106,120-122] and used to study cognitive decision making[123]. In this modified version, participants will be promoted during five

strategic stopping points in the scenario to verbally articulate their thoughts and affective reactions to the current situation for 30 seconds. Participants will think out loud until they hear a tone signaling the end of the articulation period. The ATSS paradigm was selected following initial pilot data by the research team wherein participants were asked to write their reactions to the scenarios, yielding response rates of only 66% in a sample of 30 young adults. The ATSS is less cumbersome than writing and has numerous strengths including the ability to collect unconstrained responses and unlimited choice of data coding approaches. These thoughts will be audio-recorded, transcribed, and later coded by two trained coders to understand barriers and bystander intentions using a deductive coding scheme developed by the research team following pilot data collection (see section C8). Coders will be trained and supervised by Dr. Leone's colleague, Dr. Stappenbeck, who has extensive experience using the ATSS paradigm (F31AA017563, PI: Stappenbeck)[106]. Coders will review transcripts to add new inductive codes (e.g., new intervention strategies that do not fit exclusively into direct or indirect intervention) that appear in more than 50% of transcripts. Next, responses will be coded using the revised coding manual. A subset (20%) of the transcripts will be coded by both coders. They will code separately and then come together for discussion and reconciliation. This will be done until inter-rater dependability is reached (kappa>0.8). Coders will not have access to any participant information or to the other coders' ratings and will be blinded to beverage condition.

At the end of the heat-of-the-moment scenario, secondary barrier and behavioral intention outcomes will be collected using a series of close-ended Likert-type scale questions designed and piloted by the research team to assess (1) each of the five barriers to intervention (e.g., Barrier 2, Failure to Identify Risk: "I am concerned that Marcus will sexually take advantage of Kim") and (2) direct, aggressive, and indirect bystander intervention behavior (e.g., indirect behavior: "How likely are you to try to distract Marcus to prevent him from following Kim"). Pilot data indicates that each scenario will take approximately 10 minutes to complete, which ensures that participants assigned to the AL condition will still be on the AL following completion of this paradigm.

Debriefing, Detox, and Compensation. Following this procedure, participants will respond to closed-ended questions assessing secondary bystander barriers and behavior intention outcomes. A breathalyzer test will then be administered to confirm that the task occurred on the AL or DL as intended. All participants will then be debriefed by a trained staff member. Participants in the no-alcohol control condition will be compensated at the rate of $15 per hour and discharged from the laboratory. Participants in the alcohol condition (AL or DL) will be required to remain in the laboratory in the Department of Psychiatry's dedicated lab space for alcohol administration in the Psychiatry Research Suite located on the 5th floor of the Anschutz Health Sciences Building (AHSB) or at the inpatient unit at the Clinical and Translational Research Center (CTRC) until they reach a BAC of 0.02% and pass a field sobriety test. Dr. Tyle Coyle, a licensed psychiatrist in Dr. Leone's division, will be the medical provider with admitting privileges at UCH for participants who utilize the inpatient CTRC. It is noted that in prior studies by the PI with individuals and colleagues (Dr. Dominic Parrott), participants were sent home at a BAC of .04. Thus, we are taking a more conservative approach to further minimize any risk in this study. Participants will detoxify in a room equipped with adequate seating. They will also be offered snacks, a full meal, and non-alcoholic beverages at that time. Upon reaching the target BAC, they will be compensated at the rate of $15 per hour and discharged according to their arranged private or public transportation. Participants will be provided a copy of the Informed Consent Form and Debriefing Statement before leaving.

7.2 SAFETY ASSESSMENTS

Participants assigned to the alcohol beverage condition will be monitored near continuously via livestreaming by a staff member per NIAAA's alcohol administration guidelines.

7.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from NIAAA: Adverse events (AEs) are defined as any untoward medical occurrence that may present itself during treatment or administration of an intervention, and which may or may not have a causal relationship with the treatment.

7.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are defined as any medical occurrence that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; creates persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

7.3.3 CLASSIFICATION OF AN ADVERSE EVENT

7.3.3.1 SEVERITY OF EVENT

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

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

7.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by the PI or an appropriately-trained staff member based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Unrelated—** There is not a reasonable possibility that the adverse event may have been caused by participation in the study.
- **Possibly Related—** The adverse event may have been caused by participation in the study; however, there is insufficient information to determine the likelihood of this possibility.
- **Related—** There is a reasonable possibility that the adverse event may have been caused by participation in the study.
- **Seriousness—** Results in death, is life threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, or any other event that may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

7.3.3.3 EXPECTEDNESS

Trained staff members will consult with the PI, who will determine whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during the laboratory session.

All AEs, not otherwise precluded per the protocol, will be recorded on an adverse event and unanticipated problems log maintained by the research team. Information to be collected includes event description, time of onset, assessment of severity, relationship to study procedures, and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

A trained staff member will record events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the in person study session.

7.3.5 ADVERSE EVENT REPORTING

Dr. Leone will be responsible for monitoring data and participant safety. Dr. Leone will have weekly meetings with research personnel that interact with research participants (e.g., staff who serve as experimenters for the laboratory session). All aspects of the laboratory session and participant safety, including adverse events, will be discussed during these meetings. Further, Dr. Leone will be "on call" and available should an adverse event occur during a laboratory session.

All study personnel will be trained regarding how to handle adverse events. Research staff will be trained to do the following if an adverse event occurs: (1) take any and all appropriate medical actions necessary that are detailed in the protocol for dealing with emergency medical situations, including calling 911 if needed; (2) immediately contact Dr. Leone to notify them of the occurrence; and (3) provide a detailed description of the event on a standardized "Unexpected Problems Checklist" contained in each participant's data folder. They will keep a written log of all events and ensure that the IRB, DSMB, and NIH Project Officer are contacted. They will also keep a log of the outcome of IRB decisions regarding adverse events and apprise the research team of any changes that need to occur as a result of IRB decisions.

In the case of an AE, a written deidentified report will be prepared for submission to the IRB Chair at the University of Colorado, the DSMB Chair, and to the NIH Project Officer for the study. In the event of an SAE, the same procedures will be followed and, in addition, the SAE will be reported to the NIAAA Program Official within 24 hours by phone and/or email and a written report of the SAE will be submitted to that same Program Official no more than 48 hours later. Any such AEs or SAEs will be presented as quickly as possible. The report of such AEs or SAEs will include whether they were expected or unexpected, a rating of severity of the event, a brief narrative summary of the event, a determination of whether a causal relationship existed between the study procedures and the event, whether the informed consent document should be changed as a result of the event, and whether all enrolled participants should be notified of the event. Finally, as part of the annual progress report to the DSMB and NIAAA, we will provide summary information regarding all AEs and SAEs occurring during that year. COMIRB will determine whether it is appropriate to stop the study protocol temporarily or will provide suggestions/modifications to the study procedures as necessary.

Internal Adverse Events. An internal adverse event is reportable if the occurrence meets all three of these conditions: 1) is unexpected, 2) is related or possibly related to participation in the research, and 3) is serious or places participants or others at greater risk of physical/psychological harm than was previously known or recognized. Internal adverse events are not reportable under these conditions: 1) expected and not more prevalent than expected, whether related or unrelated, and 2) unexpected and unrelated, regardless of seriousness, aside from death.

Internal Deaths. All internal deaths occurring during the conduct of the study or 30 days post-termination from protocol are required to be reported as adverse events even if they are expected or unrelated.

IRB Reporting Schedule for Adverse Events. For any unexpected and related or possibly related, serious or more prevalent event occurring during a research study, a report must be made through COMIRB's reporting system as soon as possible but no later than 5 working days after the investigator first learns of the event. All other (expected adverse events) are reported as aggregate data at the time of IRB continuing review.

Report of Changes or Amendments to the Protocol. The annual DSM report will describe any minor actions or changes with respect to the protocol. In the unlikely event that major changes are required, the Principal Investigator will discuss the needed changes with the NIAAA Program Official first, reach a consensus agreement on the changes with the Program Official, and then provide a written description of the changes to NIAAA.

7.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the DSMB, NIAAA, and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 3 working days after the investigator first learns of the event.

7.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

7.3.8 EVENTS OF SPECIAL INTEREST

N/A

7.3.9 REPORTING OF PREGNANCY

N/A

7.4 UNANTICIPATED PROBLEMS

7.4.0 DEFINITION OF UNANTICIPATED PROBLEMS

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

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

7.4.1 UNANTICIPATED PROBLEMS REPORTING

Unanticipated problems (UPs) will be reported to the reviewing Institutional Review Board (IRB) within 3 working days of the PI learning of the UP. The UP report will include the following information:

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

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to NIAAA within 3 working days of the investigator becoming aware of the event
- Any other UP will be reported to the IRB within 72 hours of the investigator becoming aware of the problem

7.4.2 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

8 STATISTICAL CONSIDERATIONS

8.0 STATISTICAL HYPOTHESES

- Primary Endpoint(s):
  - **Hypothesis1a:** There will be a main effect of beverage condition such that (1) intoxicated participants (AL and DL) will report greater bystander barriers and lower intervention intentions compared to no-alcohol controls and (2) participants on the AL, compared to DL, will report fewer barriers and greater direct intervention intentions.
  - **Hypothesis1b:** There will be a main effect of gender such that men will report greater bystander barriers, lower indirect and direct intervention intentions, and more aggressive intervention intentions, compared to women.
  - **Hypothesis2a:** The effect of gender on SV intervention will be moderated by alcohol intoxication, such that men, compared to women, on the AL will report fewer bystander barriers and greater intervention intentions.
  - **Hypothesis2b:** The effect of prosocial bystander attitudes on SV intervention will be moderated by alcohol intoxication, such that among participants higher in prosocial bystander attitudes, participants on the AL will report greater direct and aggressive intervention intentions compared to sober and DL participants, in addition to fewer barriers to intervention and compared to DL participants.

- Secondary Endpoint(s):

- N/A

8.1 SAMPLE SIZE DETERMINATION

For the primary outcomes, we plan to recruit and randomize 192 participants who are deemed eligible. To reach this sample size, we anticipate consenting up 275 people into the study, 70% of whom will meet eligibility criteria. A power analysis using GLIMMPSE was conducted to determine the sample size needed to detect a two-way interaction (H2a), which requires the highest number of participants to detect the hypothesized effects. Prior research suggests a large effect of alcohol on bystander barriers[17], and a small[83] to large[126] effect on SV intervention. With an alpha of .05 and power of .80, we determined that we would have adequate power to detect a medium effect, with a sample size of 190. We selected a sample size of 192 to ensure equal sized groups across beverage conditions.

8.2 POPULATIONS FOR ANALYSES

Participants will be included in analyses if they complete the laboratory analogue and had no adverse reactions to alcohol while completing the experimental task (i.e., vomiting).

8.3 STATISTICAL ANALYSES

8.3.0 GENERAL APPROACH

Prior to inferential statistics, scale scores will be calculated for each of the background measures following validated procedures. Urn randomization will ensure equal distribution of pertinent variables (See **Table 2**) across beverage condition groups. To confirm this assumption, 4 X 2 ANOVAs and chi-square analyses will be conducted on pertinent study variables to ensure group equivalency. If significant differences are detected, the variable will be included as a covariate in subsequent analyses. Further, all statistical test assumptions will be assessed. To ensure trustworthiness of the qualitative data, we will use established content analysis methodology, multiple trained coders, and memos[127]. ATSS responses will be coded using a combination of deductive and inductive codes[128] by two coders who will be extensively trained and supervised by Dr. Leone's colleague, Dr. Stappenbeck. The research team has developed a preliminary deductive coding scheme based on pilot data and pertinent bystander theory to rigorously evaluate bystander barriers and behavioral intentions. This coding manual may be modified to include additional codes using an inductive coding scheme as described previously.

8.3.1 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Primary dependent measures from the ATSS will include dichotomous (absent/present) codes for (1) each of the five barriers and (2) the three types of intervention behaviors at each time of the five breakpoints. Secondary dependent measures from the quantitative data will include continuous measures of (1) bystander barriers (i.e., the extent to which they perceived barriers at each of the five steps to intervene) and (2) the likelihood of engaging in bystander intervention (i.e., bystander intentions). To test

Aim 1, multilevel linear mixed-effects models using the repeated measures ATSS codes (collected during five breakpoints in the scenario) as dependent variables will be conducted to examine the main effect of beverage condition (no alcohol, AL, DL; **H1a**), and gender (**H1b**) on bystander barriers and intervention strategies. Dummy codes for beverage condition will be created to first evaluate differences between no alcohol controls and both AL and DL participants, and differences between AL and DL participants (**H1a**). To evaluate **Aim 2**, interactions will be added to the mixed-effects models including Gender x Beverage Condition dummy codes (**H2a**) and Bystander Attitudes x Beverage Condition dummy codes. Secondary analyses with continuous outcomes will be tested using a series of ANOVAs. Planned pairwise comparisons will be examined using the Sidak procedure.

8.3.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

N/A

8.3.3 SAFETY ANALYSES

N/A

8.3.4 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be used to compared baseline characteristics across conditions.

8.3.5 PLANNED INTERIM ANALYSES

N/A

8.3.6 SUB-GROUP ANALYSES

The proposed recruitment strategy includes an equal representation of men and women. The randomization strategy includes a stratification process to ensure equal representation of gender within each beverage condition (AL, DL, sober control). As part of our study aims, we will conduct analyses to understand the effects of gender on bystander barriers and intervention. Additionally, we will conduct exploratory analyses to elucidate the effects of racial/ethnic identification on pertinent study outcomes.

8.3.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

No individual participant data will be listed by measure and timepoint.

8.3.8 EXPLORATORY ANALYSES

N/A

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.0 INFORMED CONSENT PROCESS

9.1.0.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The consent materials are submitted with this protocol.

9.1.0.2 CONSENT PROCEDURES AND DOCUMENTATION

Participants who are eligible to participate in the study, and choose to do so, will be asked to come to the laboratory. Upon arrival, a trained experimenter will tell participants that the purpose of the study is to assess the effects of alcohol on social behaviors. Participants will be required to show a photo ID verifying age and take a breathalyzer to ensure BAC=.00. They will again be informed about the procedures of the study and notified that their responses/data will be confidential, and that they can refuse to answer any questions or quit the study at any time and still receive payment at the rate of $15 per hour. The experimenter will then ask the participant to read the informed consent form in its entirety. Study personnel will allow each participant sufficient time to review the consent form and then will verbally reiterate the most critical aspects of consent before asking the participant if s/he has any questions. The participant will be encouraged to ask any questions they may have. Following this, both the participant and the experimenter will sign the form. Participants will receive a copy to take home. The original signed consent form will not indicate the participant's ID number and will be kept in a locked cabinet, separate from study data. All experimenters will have completed an NIH-approved human subjects training course in addition to extensive training in the laboratory protocols. Dr. Leone will closely supervise these individuals.

9.1.1 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Determination that the primary endpoint has been met

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy NIAAA, sponsor, IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).

9.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor, and NIAAA. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of the sponsor or funding agency (NIAAA) and representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or NIAAA requirements.

Names of participants completing the screening will be stored in a password protected document. Individuals will be deleted after two months of no communication regarding scheduling, or they express they are no longer interested in participating.

All study data will be identified only by numerical code rather than participants' names. Names will never be stored with or linked to study data, with one exception. A password protected codebook will be maintained connecting participants' names and ID numbers. This codebook is necessary to link participants study ID number to create their GUIDid for NIAAA data sharing, and ensure participants have not already participated in the study. The codebook linking participants to their names will be destroyed after data collection is completed and a GUIDid has been created for data sharing.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

9.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Colorado. De-identified data will be transmitted to and stored at The National Institute on Alcohol Abuse and Alcoholism Data Archive ($NIAAA_{DA}$), for use by other researchers including those outside of the study. Data will be uploaded twice annually per NIAAA's policy. Permission to transmit data to the $NIAAA_{DA}$ will be included in the informed consent. Participants may notify the PI if they do not wish to share their data at a later date. Once participant's data is part of $NIAAA_{DA}$ it cannot be removed.

9.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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Amanda Gilmore, Ph.D., Co-Investigator: Dr. Gilmore is an expert in the development and evaluation of integrated prevention programs for alcohol and sexual violence victimization, perpetration, and bystander intervention. She has over 70 peer reviewed publications on the topics of alcohol use and sexual assault. Specific to the current project, Dr. Gilmore has expertise in utilizing experimental and alcohol administration research findings to inform integrated prevention programs for alcohol and sexual assault (R01AA028813, PI: Gilmore; R34AA025691, PI: Gilmore; F31AA020134, PI: Gilmore; K23DA042935, PI: Gilmore). She received training with Drs. George and Davis (Consultant) in the development and testing of heat-of-the-moment scenarios where she was heavily involved in the scenario development process, data collection using an alcohol administration paradigm, and data analysis (n=436; R01AA016281; MPIs: George/Davis). Further, she was actively involved in the dissemination of findings from an alcohol administration study assessing the effects of acute alcohol intoxication on sexual risk behavior among men and women (n = 412; R01AA013565; PI: George). For the proposed research, she will collaborate with the investigative team to ensure that the heat-of-the-moment scenarios, assessments, and findings can directly inform prevention programs. Towards this end, she has contributed to the development of the heat-of-the moment scenarios and will be actively involved in the study design, assessments, and dissemination of study findings. She has demonstrated successful collaboration with Dr. Leone (PI) for the past three years and members of the investigative team (Drs. Stappenbeck [Co-I] and Davis [Consultant]) for over a decade. Dr. Gilmore will provide expertise to ensure that the heat-of-the-moment scenarios, assessments, and findings can directly inform prevention programs.

Cynthia Stappenbeck, Ph.D., Co-Investigator: Dr. Stappenbeck has a strong foundation in alcohol research with expertise in using heat-of-the-moment scenarios to assess sexual risk decision-making processes, as well as use of the articulated thoughts in simulated situations think aloud paradigm making her an ideal fit to serving as a Co-I of this study. Moreover, Dr. Stappenbeck has statistical expertise analyze data using these research methods. Dr. Stappenbeck received her Ph.D. in clinical psychology from the University of Texas at Austin in 2011, completed a postdoctoral fellowship on a National Institute of Alcohol Abuse and Alcoholism (NIAAA) T-32 training grant awarded at the University of Washington. She is a licensed clinical psychologist and Associate Professor in the Department of Psychology at Georgia State University. Throughout her career, she has served as Co-I on multiple NIAAA-funded projects that include alcohol administration, as well as the use of heat of-the-moment scenarios (e.g., R01AA017608, 2R01AA016281, R37AA025212 with Drs. Davis [Consultant of proposal]) and use of the articulated thoughts in simulated situations think aloud paradigm (F31AA017563, PI: Stappenbeck). Relevant to the current project, she has published several manuscripts in top-tier journals examining the effects of acute alcohol intoxication on sexual decision-making, and has been the lead statistician on numerous manuscripts analyzing data using the articulated thoughts in simulation situations paradigm and heat-of-the moment scenarios. Thus, she has a deep understanding of and experience with designing, implementing, and analyzing data from laboratory-based paradigms. She has demonstrated a successful and long-term collaboration with Drs. Gilmore (Co-I) and Davis (Consultant) for over a decade. As a Co-I, Dr. Stappenbeck will work with Dr. Leone to oversee the conceptual and methodological decisions related to the use of the heat-of-the-moment scenarios to assess bystander decision-making and intervention. She will statistical analyses and assist with the dissemination of the study findings.

9.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) and will be led by Dr. Kathleen Baggett, the Director of the Mark Chaffin Center for Health Development at Georgia State University. Dr. Baggett will serve as the Security Officer and will convene the DSMB annually to review and ensure the on-going safety of the participants. Other members of the DSMB will include Dr. Dominic Parrott (Professor in Psychology at GSU), expert in alcohol administration, and Dr. Anne Marie Schipani (Research Scientist in Public Health at GSU), expert in sexual violence. The members, who will all be voting members, are chosen based upon their knowledge of clinical trial methodology, their experience with the topical area (i.e., alcohol administration protocols), and absence of conflicts of interest. Members of the DSMB will be independent from the study conduct and free of conflict of interest. They will be appointed for the life of the project. The NIH Project Officer will serve as an ex-officio member of the DSMB. Serious adverse events will be reported to the Chair as soon as they occur. The Chair of the DSMB will determine whether an in-person meeting or teleconference is needed. Prior to the meetings, a written report containing any study preliminary findings will be sent to DSMB members. Preliminary findings will not be made available to individuals outside of the DSMB. Each meeting will include time to review the progress of the study and to answer questions from members of the DSMB. Members of the DSMB will disclose any potential conflicts of interest, either pre-existing or those that develop during their tenure, to the Principal Investigator and the NIH Project Officer.

Members of the Data Safety Monitoring Board (DSMB) will perform the following activities:
1. Review the research protocol and plans for data and safety monitoring.
2. Review progress of the trial, including analysis of data quality and timeliness; subject recruitment and retention; subject risk versus benefit; and other factors that may affect outcome.
3. Review serious adverse event reports, provide commentary, and provide oversight to ensure that reports are relayed to individual IRBs and to the Office of Human Research Protections (OHRP), as indicated.
4. Review analyses of outcome data and review reports of related studies to determine whether the current study needs to be changed or terminated.
5. Determine whether the trial should continue as designed, should be changed, or should be terminated based on the data and make recommendations to the NIH and the Institutional Review Board considering conclusion or continuation of the study.
6. Review proposed modifications to the study prior to their implementation.
7. Protect the confidentiality of the trial data and the results of the monitoring.
8. Determine whether and to whom outcome results should be released prior to the reporting of study results.
9. Following DSMB meetings, provide appropriate NIH staff with written information concerning their findings.

In addition to the DSMB, diligent safety monitoring will be conducted by Dr. Leone (PI) throughout this study in compliance with the following required elements of COMIRB's continuing review process:
1. Tracking of subject accrual (enrollment, drop-outs, demographics).
2. Timely and appropriate reporting of informed consent process deficiencies, protocol deviations, privacy breaches, conflicts of interest, and/or changes in personnel.

3. Ongoing monitoring and appropriate reporting of adverse event activity:
    a. Internal:
        i. frequency of unexpected, related or possibly related, and serious or more prevalent than expected adverse events
        ii. frequency of internal deaths occurring during the study or within 30 days of study termination, even if expected or unrelated
    b. External: frequency of unexpected, related or possibly related, and serious adverse events
4. Interim assessment of risk/benefit relationship in reference to adverse event occurrences, preliminary observations, and emerging information.
5. Timely and appropriate IRB submission of safety-related documents such as audit reports, sponsor progress reports, and other materials or communications that might impact the safe conduct of this study.
6. Active cooperation with the IRB and other applicable entities in the event of a random or for-cause internal or external audit.

The Institutional Review Board at the University of Colorado Denver Anschutz Medical Campus (UCD) will serve as the IRB of record and will approve all Informed Consent documents for the study and will provide additional oversight of data and safety issues. The study protocol will be approved prior to soliciting or consenting any participants. Moreover, the study will be reviewed on an annual basis by COMIRB with regard to recruitment and retention, and quarterly reports will be made to the DSMB Chair regarding the progress of the proposed project, including any issues pertinent to recruitment, retention, confidentiality, and safety of human subjects. Any incidents that involve a breach of this plan or serious accident/injury will be reported to the DSMB Chair, the IRB chair at COMIRB, and the NIAAA Safety and Monitoring Board.

9.1.6 CLINICAL MONITORING

N/A

9.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 9.1.8, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

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

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by NIAAA.

9.1.8 DATA HANDLING AND RECORD KEEPING

9.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Hard copies will be entered into an electronic database (e.g., SPSS) and will contain no identifying information. Data will also be collected electronically via REDCap and Qualtrics.

Regarding data management and storage, all data will be collected using computerized self-report questionnaires. The codes that link the name of the participant and the study ID will be kept confidential by the research team on a password protected document on secured university servers. The self-report measures will be administered in the laboratory using CU Qualtrics or REDCap survey software, which will be programmed to check data at the time of entry to ensure that entered values are within the specified range and that items are not inappropriately skipped. CU Qualtrics provides the highest level of internet security available and offers Transport Layer Security (TLS) encryption (HTTPS) and survey security options like password protection and HTTP referrer checking. Data is stored in data centers that are audited and SAS 70 certified and all data is protected with real-time data replication. Data is transmitted by 128-bit SSL encryption, which is the same level of security used for most e-commerce applications. All customized security requirements are enveloped in the software developed by Qualtrics. The data is stored in secure servers behind a firewall and access to collected data is limited to password-enabled research staff as designated by Dr. Leone and the limited necessary Qualtrics IT professionals required to maintain their servers and infrastructure. The data from Qualtrics will be imported directly into a password-protected SPSS data file stored on a UCD OneDrive that is only accessible to the research team. Dr. Leone will control access to this folder. In addition to these precautions, all personnel will have experience in conducting research. All research personnel collecting and manipulating data will have completed a Human Subjects

Research Training course and will meet weekly with Dr. Leone to ensure strict compliance with the DSM plan. All de-identified data will be released as outlined in the data sharing plan.

9.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 7 years after the grant is closed out per IRB regulations.

9.1.9 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

It will be the responsibility of the PI to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation. All deviations will be addressed in study source documents and reported to the NIAAA Program Official per the DSMP on record with NIAAA. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

9.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed

journals. Data from this study may be requested from other researchers by NIAAA$_{DA}$. Considerations for ensuring confidentiality of these shared data are described in Section 9.1.2.

The Principal Investigator for this study will adhere to The National Institutes of Health (NIH) Policy on Dissemination of NIH-funded Clinical Trial Information. The University of Colorado Denver Anschutz (UCD), the recipient institution for this award, has an internal policy in place that ensures all clinical trials are registered and results reporting are publicly posted. UCD's Office of the Vice Chancellor for Research provides support services for registering clinical trials, maintaining these records, providing timely updates, and close-out of clinical trials with ClinicalTrails.gov.

In Year 1, we registered the trial at ClinicalTrials.gov prior to enrollment of participants (NCT05701865). This timeframe is in compliance as registration must be submitted within 21 days after the first human subject is enrolled. We will transfer NCT05701865 to the UCD.

We will include a specific statement in our study's informed consent documents relating to the posting of clinical trial information at ClinicalTrials.gov.

Following the completion of the study and data analyses, we will submit summary results for public posting. This timeframe is in compliance as results must be posted no later than 1 year after the study's Primary Completion Date, as described in 42 CFR 11.44(a) of the final rule.

The project team is committed to the open and timely dissemination of research outcomes. Findings will be presented at scientific meetings and published in peer review journals. Published manuscripts will be submitted to the digital archive PubMed Central. The publication plan at minimum includes 1-2 manuscripts from the proposed research.

9.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIAAA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

9.2 ADDITIONAL CONSIDERATIONS

N/A

9.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
AL	Ascending Limb
BAC	Breath Alcohol Concentration
BTP	Bystander Training Programs
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
CRF	Case Report Form
DHHS	Department of Health and Human Services
DL	Descending Limb
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IRB	Institutional Review Board
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SV	Sexual Violence
UP	Unanticipated Problem
US	United States

9.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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