SATIETY AND ALCOHOL CHALLENGE

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Satiety and Transdermal Alcohol Concentration (SatTAC)

Protocol Number: 24-1095

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Summary of Changes from Previous Version:

Date	Affected Section(s)	Summary of Needed Revisions
9-10-24	Study visit procedures	Change compensation from $240 to $230 to reflect shorter lab visit 2
10-30-24	Inclusion criteria	Changed BMI lower cutoff from 21 to 18.5 to include the full normal range.

1 CONTENTS

1. SUMMARY

1.1 SYNOPSIS

Title:	Satiety and transdermal alcohol concentration (SatTAC)
Study Description:	The proposed study is an inter-lab collaboration to gather pilot data on responses to alcohol in a controlled laboratory setting compared to a naturalistic setting. Alcohol is administered in the lab and alcohol exposure is measured with a wearable wrist monitor (Skyn) and a breathalyzer (BACtrack S80). Naturalistic drinking and alcohol-related harms are assessed during a 7-day remote assessment period. Additional aims assessed during laboratory visits include changes in satiety to alcohol after dietary manipulation and the relationship between responses to alcohol and biomarkers: GLP-1 and HMGB1.
Objectives:	**Aim 1:** Identify the correlations between transdermal alcohol concentration (TAC; Skyn) and breath alcohol concentration (BrAC; BACtrack S80) in controlled laboratory and natural settings and compare correlations across settings. **Aim 2:** Compare TAC and BrAC as predictors of self-reported number of drinks consumed and the odds and frequency of alcohol-related harms in natural settings. **Aim 3:** Model individual differences in alcohol-specific satiety using self-report and a paced-drinking alcohol administration laboratory model. **Aim 4:** Assess the effect of a dietary supplement on plasma GLP-1 levels and subjective and alcohol satiety. **Aim 5:** Assess the effect of acute alcohol exposure on a marker of peripheral inflammation (HMGB1)
Outcomes:	**Alcohol exposure:** Transdermal alcohol concentration, breath alcohol concentration. Questionnaires: Self-reported satiety questionnaire and other alcohol subjective response questionnaires. Tasks: Behavioral economic demand for alcohol, attentional bias to alcohol-related cues. Remote self-reported assessment of alcohol-related harms. Biomarkers: Plasma change in GLP-1 and HMGB1.
Study Population:	Adults from the triangle area (Chapel Hill, Raleigh, Durham) who meet NIAAA criteria for at-risk drinking; >7/14 standard drinks per week for women/men, with at least one past-month heavy drinking episode defined as 4/5+ standard drinks for women/men.
Description of Sites/Facilities Enrolling:	University of North Carolina at Chapel Hill
Participants:	55
Study Duration:	1 year
Participant Duration:	Each participant completes an online pre-screen eligibility survey, virtual visit, and two 5-6 hour lab visits within 2-3 days of one another, followed by a 7-day remote assessment period, and a final 1-hour discharge visit.

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Online Prescreen	Virtual Visit	Study visit 1	Study Visit 2	7 day Remote Assessment	Discharge visit
Online prescreen survey	X					
Informed consent		X				
DSM-5 SCID AUD and SUD		X				
Demographics Form		X				
Alcohol Use Identification Test (AUDIT)		X				
Inventory of Drinking Situations (IDS)		X				
Obsessive Compulsive Drinking Scale (OCDS)		X				
Reward-based Eating Drive Scale (RBEDS)		X				
Body Perception Questionnaire (BPQ)		X				
Drinking Motives Questionnaire (DMQ)		X				
Comprehensive Relative Autonomy Index for Drinking (CRAI Drinking)		X				
Alcohol Sensitivity Questionnaire (ASQ)		X				
Impaired Control Scale (ICS)		X				
Dietary supplement or placebo			X	X		
Administer alcohol priming drink			X	X		
Paced alcohol or control drinking			X	X		
Weight and height			X			
Pregnancy test			X	X		
Alcohol-specific satiety questionnaire			X	X		
Drug Effects Questionnaire (DEQ)			X	X	X	
Visual Analogue Scale (VAS)			X	X		
Biphasic Alcohol Effects Scale (BAES)			X	X		
Subjective Effects of Alcohol Scale (SEAS)			X	X		
Alcohol Urge Questionnaire (AUQ)			X	X		
Alcohol Purchase Task (APT)			X	X		
Dot Probe task			X	X		
Breath Alcohol Concentration (BrAC)			X	X	X	
Transdermal Alcohol Concentration (TAC), measured via Skyn			X	X	X	
Ecological Momentary Assessment (EMA)					X	
DEXA scan				X		
Venipuncture blood sample x2			X	X		
Fingerprick blood sample x3			X	X		
Timeline followback (TLFB)						X
Brief young adult alcohol consequences questionnaire						X
Importance of consequences of drinking short-form						X
Return Skyn monitor						X

2. INTRODUCTION

2.1 STUDY RATIONALE

Alcohol response can indicate differential risk for heavy drinking and the development of alcohol use disorder. Laboratory and naturalistic methods of data collection on acute responses to alcohol may be used in a complementary way to assess alcohol risk phenotypes. Satiety to the effects of alcohol is an understudied and ill-defined construct which may confer protective effects for heavy drinking. Satiety related hormones like glucagon-like peptide 1 (GLP-1) and the inflammatory biomarker, high-mobility group box 1 (HMGB1) may represent biomarkers of alcohol use disorder risk. However, researchers currently have a limited ability to accurately and non- invasively assess individuals' real-time alcohol use exposure. Transdermal alcohol concentration (TAC) sensors and ecological momentary assessment may be used to address this gap. Furthermore, it is not well understood how naturalistic alcohol data collection methods relate to drinking in a controlled laboratory setting. In an inter-lab collaboration TAC will be measured during both laboratory and naturalistic drinking contexts to assess the strength of the association between a novel TAC sensor (BACtrack Skyn) and breath alcohol (BrAC) measurements. Alcohol-specific satiety will be measured during alcohol drinking lab sessions and the biomarkers, GLP-1 and HMGB1 will be assessed as potential biomarkers of satiety and heavy drinking risk.

2.2 BACKGROUND

Introduction

Over half of U.S. adults consumed some alcohol in the past month, with 37% of college and 29% of non-college young adults ages 18-25 engaging in binge drinking (5/4+ drinks for men/women).[1] Many young adults also exceed binge drinking thresholds, with 1 in 20 consuming 10+ drinks and 1 in 33 consuming 15+ drinks during a single drinking bout.[2, 3] These excessive drinking behaviors increase risk for a multitude of severe acute consequences, including physical and sexual assault, hospitalization and death, hangovers, and cognitive impairment.[4-6] Long-term consequences of excessive drinking include alcohol dependence and risk of cancer and fatty liver disease. [5, 7, 8] Despite the significant public health burden associated with the short- and long-term harms of excessive alcohol use, researchers currently have a limited ability to accurately and non- invasively assess individuals' real-time alcohol use exposure. Accurately and non-invasively assessing real-time alcohol use exposure has the potential to inform just-in-time harm reduction interventions.

Transdermal Alcohol Concentration Sensor

The majority of research capturing real-time alcohol use exposure relies on participant self-reports or obtrusive alcohol sensors. Self-report is commonly criticized due to social desirability biases and the difficulty of accurately estimating drink volume and ethanol content,[9-12] is limited by the neuro-cognitive effects of alcohol, especially with excessive drinking, and [13] is burdensome for participants [12]. In contrast to self-report, wearable alcohol sensors enable continuous assessment of real-time biological alcohol exposure via transdermal alcohol concentration (TAC), an indirect index of blood and breath alcohol concentration (BAC and BrAC, respectively), which are typically assessed via breathalyzer.

Breathalyzer measurement of BAC or BrAC requires frequent repeated measures that may be too burdensome and invasive for participants [14-17]. In contrast, TAC sensors provide a mostly passive and non-invasive approach for continuously monitoring alcohol exposure. TAC sensors are worn on the ankle or wrist and measure the 1% of alcohol that is eliminated through the skin via insensible perspiration or sweat [16, 18-21]. One limitation of TAC is that it is not quantitatively equivalent to BAC or BrAC. TAC reflects an individual's relative alcohol exposure, whereas BAC/BrAC reflect absolute alcohol exposure, which provides actionable information about a person's likely level of cognitive and physical impairment due to alcohol use [18, 22]. Unfortunately, there are currently no reliable methods for directly estimating BAC from TAC, due to the variety of factors that can impact individual differences in TAC (e.g., sex, age, fat-free mass, skin temperature) [15, 21-26]. Translating TAC to BAC/BrAC is necessary prior to leveraging wearable TAC sensors to provide actionable knowledge to inform just-in- time harm reduction interventions. The most unobtrusive and user-friendly TAC sensor currently in use is the BACtrack Skyn (Skyn). The Skyn is a small, lightweight wrist-worn sensor that collects TAC data every 20 seconds and that participants are comfortable and willing to wear across extended time periods in natural settings [14-17, 22, 27-30]. The few studies testing the Skyn under controlled laboratory conditions suggest that Skyn TAC values strongly correlate with BrAC [15] and can be used to estimate BAC at low or moderate BAC levels [31]. However, it is often infeasible and unethical to dose participants in laboratory settings to the excessive levels they dose themselves in natural settings. Additionally, laboratory studies preclude examining whether TAC values predict next-day alcohol-related harms, such as hangovers or blackouts. While two studies have compared the Skyn to another commonly-used TAC sensor in natural settings and found moderate-to-strong correlations between the sensors, [27, 30] we are unaware of any studies comparing the Skyn to BAC or BrAC in natural settings or of any studies examining TAC relative to BrAC as a predictor of volume of consumption and alcohol-related harms (e.g., sickness, hangover). As such, it remains unclear whether correlations between Skyn TAC values and BrAC captured in controlled laboratory settings translate to alcohol use in real-world settings or whether TAC values perform similarly to BrAC in predicting next-day alcohol-related harms [17, 22, 27, 31].

Alcohol-specific satiety and GLP-1

While laboratory settings do not allow for dosing at the levels of natural settings, the laboratory setting provides a controlled context in which to verify the precise level of alcohol exposure, and to experimentally test the effects of alcohol on a person's internal state. The internal state plays an important role in regulating the incentive value of a reward, with satiety being a prime example of a motivational state which reduces reward-value and appetitive motivation [32-35]. Satiety is fundamental in regulating food intake, and resistance to satiety has been implicated in obesity-related overeating behavior [36]. Satiety in the context of drug and alcohol consumption is understudied, despite overlapping mesolimbic neurocircuitry involved in appetitive motivation for both food and drugs [37]. Observations from human lab studies suggest that a dose of alcohol can either prime further alcohol consumption or promote satiety, indicated by reductions in the desire to drink and attentional bias to alcohol-related cues [38, 39]. However, an alcohol-specific satiety construct has yet to be the subject of rigorous investigation. Resistance to satiety may be implicated in the binge-like consumption behavior symptomatic of alcohol and substance use disorder (A/SUD), warranting investigation of satiety-promoting factors.

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that increases subjective satiety and reduces food consumption [40] in part through inhibition of accumbal dopamine release [41], implicating

incentive motivation in GLP-1 satiety signaling. Through the same mechanism, GLP-1 receptor agonists (GLP-1RAs) reduce consumption of alcohol and other drugs in animal models [42, 43], making GLP-1RAs promising candidates for AUD pharmacotherapy [44]. An analysis of social media reports from our lab indicate that some patients prescribed GLP-1RAs for obesity or type-2 diabetes report reduced desire for alcohol and changes in subjective response which indicate increased satiety i.e. being satisfied with fewer drinks, reduced interest or desire for alcohol [45]. Alcohol-specific satiety may be a translational mechanism by which GLP-1 receptor agonists reduce alcohol consumption. However, alcohol-specific satiety as a construct has not been modeled in the laboratory.

Inflammation and HMBG1

Increasing evidence also suggests that chronic alcohol consumption promotes neuroinflammation. Increases in systemic inflammation due to alcohol consumption are proposed to contribute both to alcohol-related diseases (including liver disease and cancers) and negative affective states in AUD (e.g., pain, stress). Examination of postmortem human brain tissue demonstrates increased proinflammatory signaling molecules in AUD – one such marker being high-mobility group box 1 (HMGB1) [46, 47]. Evidence from both human and animal brain tissue shows that HMGB1 is a key marker of alcohol-induced immune activation [46-51].

Summary

The goal of the proposed study is to collect pilot data on factors which may predict risk for alcohol use disorder through an inter-lab collaboration using data from 2 alcohol drinking laboratory visits and a 7-day remote assessment period. Correlations between Skyn TAC and BrAC will be assessed in an internally valid, controlled laboratory setting and in an ecologically valid natural setting within the same individuals, and to examine correspondence between TAC and BrAC in predicting alcohol consumption and alcohol-related harms among 42 moderate-heavy drinking adults. During laboratory sessions, additional aims related to individual differences in alcohol risk phenotypes will be assessed. Satiety to the effects of alcohol will be assessed using a novel self-report measure of alcohol-specific satiety and a laboratory model of paced drinking, and the effect of a GLP-1 stimulating dietary supplement on alcohol-specific satiety. In addition, individual differences on an inflammatory biomarker, HGMB1 on drinking outcomes will be assessed.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risk of Confidentiality Breach: To avoid breaches in confidentiality, study documents that contain personal information and including the informed consent document are kept in locked filing cabinets in locked rooms separate from any source documents containing participant dummy identifiers. The document that links study ID numbers to personal identifying information is encrypted and protected using a password-protected document on a secure server provided by UNC Department of Psychology and Neuroscience. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers. Only study personnel will have access to the data. All study staff participate in

annual human participant training that includes education about responsibilities to the minimize risk of confidentiality breach. All patient identifiers will be stored in REDCap (or similar platform) until recruitment is over. When recruitment is over, all patients who do not consent or are not eligible for participation in the study will have their responses permanently deleted.

Risk of Embarrassment: Self-report assessments contain questions regarding sensitive personal information. This risk is necessary to assess psychological symptoms. Participants will be informed that they can decline to answer any survey questions that they're uncomfortable with by selecting '*Prefer not to answer'.* Participants will be assured upon intake that only study personnel will have access to study data, which will not be stored with any self-identifying information. Embarrassment and/or emotional distress may occur with the measurement of body composition, but this is rare (<1%). To minimize this risk, participants will be measured individually, with no one but the trained research staff present, in a private area.

Risk from Participation in Alcohol Administration Sessions: Other potential risks include typical risks related to participation in alcohol administration studies. For example, it is possible that participants may experience dizziness/nausea from drinking during these visits, or symptoms the following day (e.g., headache). Our group has considerable experience with alcohol administration procedures [80-84], and the safety precautions required in these studies. Across these studies, the incidence of adverse events such as vomiting has been exceptionally low. Our procedures will follow the NIAAA recommended guidelines for administering alcohol to human subjects (https://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm). Briefly, the NIAAA guidelines include recommendations for administering alcohol to participants who meet criteria for AUD. In particular, we have taken measures to protect against ethical concerns by *excluding treatment-seekers* (or those engaged in an active quit attempt), as per the NIAAA recommended guidelines. Additionally, we will screen out participants with severe AUD (defined as 6 or more of 11 symptoms). This approach allows us to generate data relevant to a clinical population while minimizing risks.

Risk from Dietary supplements: There is the infrequent and mild potential risk of gastrointestinal discomfort associated with dietary fiber and green tea extract supplements. To minimize these risks, effective doses of each supplement have been chosen which have been shown to be safe and tolerable for human subject research in prior studies [52, 53].

Risk from blood draws: There is a rare (<1%) risk of infection following blood draws. Trained personnel will conduct all procedures and the site of blood draws will be cleaned appropriately prior to data collection.

Potential physical risks: During the dual x-ray absorptiometry scan (DEXA) subjects will be exposed to very low doses of radiation. The amount of x-ray radiation that subjects will receive during the scan is approximately 0.8 mrems, which is extremely small. The amount of radiation is less than one tenth of the amount used during a normal chest X-ray and significantly less than the radiation received from natural background in a year (300 mrem).

2.3.2 KNOWN POTENTIAL BENEFITS

This study has not been designed to benefit the individual participants. However, the knowledge gained from this study will contribute to understanding about the psychological and biological basis of substance use disorder which may be used to develop future interventions. All participants will receive feedback regarding anthropometric and body composition measures.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks and benefits presented above are no more serious than for other observational studies in this population. Based on the need to discover mechanisms contributing to AUD, the potential risks outweigh the potential benefits.

3. OBJECTIVE AND OUTCOME MEASURES

Aim 1: Identify the correlations between transdermal alcohol concentration (TAC) and breath alcohol concentration (BrAC) in controlled laboratory and natural settings and compare correlations across settings.

- Outcomes measures: BrAC using the BACtrack S80 and TAC readings using the BACtrack Skyn monitor and light-based finger monitor during laboratory alcohol drinking sessions and a remote assessment period.

Aim 2: Compare TAC and BrAC as predictors of self-reported number of drinks consumed and the odds and frequency of alcohol-related harms in natural settings.

- Outcome measures: BrAC and TAC readings, self-reported number of drinks and alcohol related harms measured using a mobile app questionnaire (LifeData app).

Aim 3: Model individual differences in alcohol-specific satiety using self-report and a paced-drinking alcohol administration laboratory model.

- Outcome measures: Alcohol specific satiety questionnaire, BrAC readings.
- Secondary measures: Self-report alcohol subjective effects (stimulation, sedation, craving), behavioral economic demand for alcohol, attentional bias for alcohol related cues.

Aim 4: Assess the effect of a dietary supplement on satiety to alcohol

- Outcome measures: Blood plasma GLP-1 levels samples during lab sessions via venipuncture before and after supplement administration, alcohol-specific satiety questionnaire

Aim 5: Assess the effect of alcohol exposure on HMBG-1 marker of inflammation

- Outcome measures: Blood plasma levels of HMBG-1 will sampled during lab sessions via fingerprick at timepoints before alcohol administration, 30 minutes after an initial priming drink, and after the final drink.

4. STUDY DESIGN

4.1 OVERALL DESIGN

Study Design and overview: Aims related to alcohol response will be assessed using alcohol administration in the laboratory. Additional aims related to naturalistic drinking and alcohol related harms will be gathered using wearable alcohol sensors and ecological momentary assessments (EMA) and daily diaries. Transdermal alcohol concentration (TAC) will be measured during both laboratory and

naturalistic drinking contexts to assess the strength of the association between a novel TAC sensor (BACtrack Skyn) and breath alcohol (BrAC) measurements. In addition, we will also use a small non-intrusive light-based blood flow measurement device (placed on the participant's finger) and validate these measurements against the other metrics. These aims will be accomplished using data from two half-day visits to our lab at UNC campus, 1-2 days apart, followed by a 7-day remote assessment study and a final brief discharge visit (Figure 1). Lab visits involve a novel self-report questionnaire to assess alcohol-specific satiety during a paced alcohol challenge paradigm. In addition, on each of the two sessions in counterbalanced order, participants receive either a dietary supplement intended to stimulate postprandial GLP-1, or a calorically matched placebo to assess the effect of GLP-1 stimulation on alcohol-specific satiety. Two blood samples will be collected at each session to confirm plasma levels of glucagon-like peptide 1 (GLP-1). Blood fingerprick samples will be used to measure high-mobility group box 1 (HMGB1) inflammatory marker at three timepoints after alcohol administration. Additional measures of reward and incentive motivation for alcohol will be included to test the hypothesis that satiety is associated with reduced incentive motivation for alcohol reward. At the end of the second lab visit participants will be oriented to the 7-day remote assessment study. During the 7-day remote visit participants will be asked to wear the Skyn sensor continuously across 24-hours/day, except when bathing/showering or charging the device, and to initiate EMAs if they start an alcohol drinking bout. During drinking bouts, and for up to one hour following drinking bouts, participants will be prompted to record their BrAC every 20 minutes and to self-report the number of drinks consumed since the prior survey and subjective intoxication. Each morning, participants will complete daily diaries reporting alcohol-related harms experienced on the prior day. Following the 7-day remote visit, participants will complete a final discharge visit to return study devices, complete a timeline follow-back, and undergo a dual x-ray absorptiometry (DEXA) scan to assess fat-free mass, which will be included as a covariate in subsequent analyses to account for alcohol-elimination rate [56]..

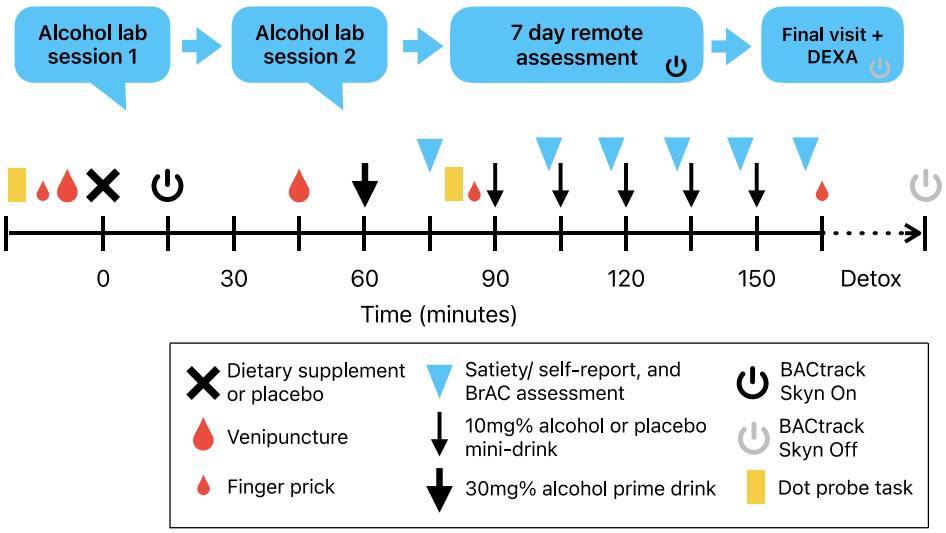

Figure 1. Diagram of lab session procedures

4.2 PARTICIPANTS

We will aim to recruit 42 adults who meet NIAAA criteria for at-risk drinking; >7/14 standard drinks per week for women/men, with at least one past-month heavy drinking episode defined as 4/5+ standard drinks for women/men. To ensure a range of alcohol use in the sample we will aim to recruit an even number of participants from AUDIT zones 1, 2 and 3 (AUDIT total score = 0-7, 8-15, and 16-19 respectively) which reflect different levels of alcohol use health risk severity [57]. The AUDIT is a validated screening tool that indexes alcohol use severity, but is not a diagnostic instrument. Typically an AUDIT score of 20 or greater indexes elevated risk for alcohol use disorder; those with scores of 20+ will be excluded. In addition, we will aim to recruit an even distribution of males and females across AUDIT zones. Participants will be recruited via flyers and social media ads from the triangle area (Chapel Hill, Raleigh, Durham). Interested participants will fill out an online pre-screen survey using Research Electronic Data Capture (REDCap) to determine initial eligibility. We estimate screening 250 people will yield 55 eligible participants to consent. Accounting for study drop-outs, we expect that 55 consents will allow for a final sample size of 42 who complete all study procedures, which is a feasible goal for the 12-month study. Potentially eligible participants will be contacted via email to schedule a virtual visit including additional screening and informed consent. A research assistant will explain the study requirements and both parties will sign the consent documents via REDCap if agreeing to enroll in the study. The DSM-5 SCID will then be administered to screen for alcohol and substance use disorder.

4.3 STUDY VISIT PROCEDURES

Participants will arrive to the lab at 9 AM fasted overnight prior to the alcohol administration study visits. Identity will be confirmed by verification of photo ID and pregnancy will be confirmed with a urine pregnancy screen. Abstinence from alcohol will be confirmed with a breathalyzer. Mode of transportation to the session will be confirmed. Participants will be encouraged to arrange for a ride or take public transportation to sessions to minimize the risk of driving while intoxicated. In the case that a participant drives themselves to the session, the participant will be required to sign an acknowledgment that their keys will be held by the research assistant during the session and returned after the subject's BAC reaches zero. Blood will be sampled with venipuncture to analyze baseline plasma GLP-1. Fingerprick blood sample will be used to measure HMGB1. Baseline measurements of study outcomes will be taken at this time. Participant will complete additional baseline measures at home including: demographics form, the Alcohol Use Disorder Identification Test (AUDIT) [57], Obsessive Compulsive Drinking Scale (OCDS) [58], Reward-based Eating Drive Scale (RBEDS) [59], Body Perception Questionnaire (BPQ) [60], Drinking Motives Questionnaire (DMQ) [61], Comprehensive Relative Autonomy Index for Drinking (CRAI Drinking) [62], Alcohol Sensitivity Questionnaire (ASQ) [63], and the Impaired Control Scale (ICS) [64], and the Inventory of Drinking Situations (IDS)[65] using REDCap to explore potential moderators in secondary analyses. Assessments will occur in a study room furnished to feel like a comfortable living room with a TV. Participants may watch TV or engage in relaxing recreational activities (e.g. reading, personal computer) during recovery from alcohol. Participants will be fitted with a Skyn TAC wrist monitor and finger-tip sensor to monitor alcohol exposure and be trained on using the BACtrack S80 for BrAC measures. Participants will download the Skyn app to sync the Skyn data during the session, and then will be instructed to refrain from using their phones for non-study related purposes.

Dietary manipulation

Participants will receive a beverage containing either a dietary supplement (10g Fibersol®-2 mixed with water and aspartame sweetener for taste + 725mg decaffeinated green tea extract capsule) or a calorically matched placebo supplement (Aspartame sweetener mixed with water + aspartame capsule) counterbalanced at two separate visits. Forty-five minutes after the dietary supplement, the second blood sample is taken. Next, a priming drink (calculated to achieve 30mg% BAC) is administered to stimulate craving for alcohol [66, 67]. Drinks will consist of 40 proof vodka and a sugar-free cranberry juice mixer at a 1:5 ratio. Doses are calculated to achieve target BACs based on sex and body weight using formulas established in prior research [68]. Fifteen minutes after the priming drink, a novel alcohol-specific satiety questionnaire will be administered followed by alcohol incentive motivation tasks (alcohol purchase task; APT [69], dot probe attentional bias to alcohol-related stimuli), additional validated alcohol subjective response questionnaires (Drug Effects Questionnaire; DEQ[70], Biphasic Alcohol Effects Scale; BAES [71], Alcohol Urge Questionnaire; AUQ [72], Subjective Effects of Alcohol Scale; SEAS [73]), *hunger, fullness, and satiety* visual analogue scale (VAS) items, a BACtrack S80 BrAC measure, and a fingerprick blood sample.

Alcohol-specific satiety paced drinking procedure

Then over a 2-hour period, 5 additional mini-drinks (calculated to achieve an estimated BAC increase of 10mg% each or placebo) are administered with 15 min absorption time between each drink to reach an estimated maximum BAC of 60-70mg%, reflecting a moderate level of alcohol exposure (80mg% is the conventional cutoff for "binge" exposure). Participants have 3 minutes to finish each drink (Average volume of a drink, alcohol+mixer at a 1:5 ratio is 8/5oz for a man/woman). This paradigm is designed to approximate a natural drinking pace, while controlling for the BAC during subjective satiety assessment. The control session will control for expectations of increased satiety with subsequent drinks. Control drinks contain cranberry juice with an alcohol mask (rim sprayed with vodka) matched in total volume to the alcohol drinks. Participants will be told that all drinks contain alcohol. Subjective response questionnaires are repeated 15 minutes after each drink. BACtrack S80 BrAC measures are repeated every 15 minutes.

After the paced drinking procedure, a final fingerprick blood sample will be taken and participants will remain in the lab until their BAC reaches 0mg% at which point they will be either dismissed. At the end of the second lab session, participants will receive instructions on using the Skyn and BACtrack S80 devices, using the Skyn app for syncing Skyn data and the LifeData app for completing drinking bout EMA surveys and morning surveys about past day alcohol use and consequences.

Remote assessment

During the 7-day naturalistic study, participants will be asked to wear the Skyn for 24 hours/day for 7-days (except when bathing or swimming). On days when participants choose to drink they will initiate drinking bout surveys via smartphone by indicating they have started drinking, after which they will prompted to provide a BrAC reading once every 20-minutes throughout the drinking bout and for up to 1-hour after the drinking bout ends. Every 60-minutes participants will also self-report alcohol amount and subjective intoxication during the drinking bout. Importantly, participants will be informed that they are not expected to change their drinking behaviors during the study and compensation is not contingent on self-reports or breathalyzer readings during drinking bouts. Participants will complete daily morning surveys about past day alcohol use and consequences and evening surveys about daily pain and stress.

After the 7-day protocol, participants will return their devices to the PI's lab and report past 7-day drinking behaviors (timeline follow-back; TLFB) and drinking consequences (Brief Young Adult Alcohol Consequences Questionnaire, Importance of Consequences of Drinking short-form) and undergo a DEXA scan. Participants will be compensated upon device return with up to $240 ($20 for baseline surveys, $50 for lab visit one, $50 for lab visit two, $70 for all 7-day EMA study procedures, $10 for device return, $10 for follow-up questionnaires, $10 for DEXA scan, and $10 study completion bonus).

Blood sampling: Blood is sampled at baseline and again 45 minutes after dietary supplement administration to assess the effect of the dietary manipulation on circulating GLP-1. Blood samples will be immediately placed on dry ice and centrifuged the same day. Extracted plasma will be stored at -80° C. Blood samples will be collected in a 2mL vacutainer pretreated with a DPP-4 inhibitor in accordance with manufacturer guidelines (EMD Millipore Corp., Billerica, MA). Only biologically active forms of GLP-1 will be measured which include GLP-1(7–36) and GLP-1(7–37) [74]. Blood samples will be processed in duplicate with the MILLIPORE Glucagon-Like Peptide-1 (Active) ELISA kit - 96-Well Plate (Cat. #EGLP-35K). HMGB-1 will be measured at three timepoints via a fingerprick blood sample. Plasma samples will be processed in duplicate using a deproteinization kit and the HMGB1 ELISA kit - 96-Well Plate (Cat. # EEL047).

Dietary supplements: commercially available supplements will be used to stimulate glp-1; 10g prebiotic fiber (digestive resistant maltodextrin; fibersol®-2) and 725mg decaffeinated green tea extract (https://www.vitaminshoppe.com/p/triple-strength-green-tea-extract-100-vegetarian-capsules/vs-1807). Dietary fiber [54, 55, 75-77] and green tea extracts [78, 79] separately have been shown to increase plasma levels of active glp-1 in randomized controlled studies. These supplements will be used together for the purposes of this research aim, which prioritize efficacy of the glp-1 manipulation over an investigation of any particular supplement. Effective doses of each supplement have been chosen which have been shown to be safe and tolerable for human subject research in prior studies [52, 80, 81]. Aspartame (Equal®) was chosen as a placebo based on prior research indicating that non-nutritive sweeteners are unlikely to stimulate GLP-1 release [82, 83].

BACtrack Skyn TAC Monitor: The BACtrack Skyn is a small, lightweight wrist monitor that measures alcohol exposure through the 1% of alcohol transmitted through perspiration (i.e., transdermal alcohol concentration). The device wirelessly syncs to the Skyn app on the participant's iPhone to collect TAC data every 20 seconds. Alcohol exposure is detected with an average delay of 35.6 minutes [84]. The following outcomes are derived from TAC data: *drinking intensity* (peak TAC and area under the curve [AUC]), *drinking duration* (hours with TAC >0 µg/L air), *rise rate* (average rate of all ascending point-to-point TAC values), and *fall rate* (average rate of all descending point-to-point TAC values).

BACtrack S80 BrAC Monitor: The BACtrack S80 is a portable, battery-operated professional breathalyzer that measures the percentage of alcohol in a person's breath (i.e., BrAC). Participants capture BrAC within seconds after following a series of automated instructions provided by the S80 and breathing into the mouthpiece. Participants will report their S80 readings in the EMA surveys. The outcomes derived from the BrAC data are the same as those described above for TAC data.

Behavioral tasks:

The alcohol purchase task (APT) measures the hypothetical behavioral economic demand for alcohol at 14 different price points. This measure is sensitive to the reinforcing effects of alcohol, and predictive of real-world alcohol consumption [69]. The following outcomes are derived from the APT: APT-intensity (consumption when drinks were free); APT-breakpoint (the first price at which consumption was suppressed to zero); and APT-Omax (maximum alcohol expenditure) [69]. The task takes no more than 5 minutes to complete and is administered on REDCap

The dot probe is a measure of cognitive attentional bias used in prior studies thought to reflect the incentive salience of alcohol related stimuli [85, 86]. This task will be administered on E-Prime software. Subjects are sat at a computer and shown left-right pairs of images on a screen for 1000ms followed by a white dot in place of one of the images. Participants are instructed to respond to the dot probe target with a key using their left hand if the dot is on the left side, and the right hand if the target appears on the right side. Pairs of images include alcohol related images matched with control images (non-alcohol beverages such as soda, a glass of water, etc.). 10 image pairs are presented four times each for a total of 40 critical test trials. 40 additional trials are randomly interspersed with critical trials which feature neutral filler images (office supplies, etc.). The target may either be congruent to the alcohol-related stimuli (target appears on the same side as the alcohol-stimuli) or incongruent (target appears on the side of the control stimuli). The task takes 5 minutes to complete. Faster reaction times to alcohol-related imagery on congruent trials (alcohol image displayed on the same side as the dot probe target) and slower reaction times on incongruent trials reflect increased attentional bias towards the alcohol-related stimuli. Therefore, reaction time to alcohol cues > neutral cues on incongruent > congruent trials reflect the attentional bias score [86]. Attentional bias will be assessed before and after alcohol administration and change scores will be calculated.

List of Measures (See section 1.3 for assessment time points)

1. Demographics form
2. Alcohol Use Disorder Identification Test (AUDIT)
3. Inventory of Drinking Situations (IDS)
4. Obsessive Compulsive Drinking Scale (OCDS)
5. Reward-based Eating Drive Scale (RBEDS)
6. Body Perception Questionnaire (BPQ)
7. Drinking Motives Questionnaire (DMQ)
8. Comprehensive Relative Autonomy Index for Drinking (CRAI- D)
9. Alcohol Sensitivity Questionnaire (ASQ)
10. Impaired Control Scale (ICS)
11. Alcohol-specific satiety questionnaire
12. Drug Effects Questionnaire (DEQ)
13. Visual Analogue Scale items (VAS)
14. Biphasic Alcohol Effects Scale (BAES)
15. Subjective Effects of Alcohol Scale (SEAS)
16. Alcohol Urge Questionnaire (AUQ)

17. Alcohol Purchase Task (APT)
18. Dot Probe attentional bias to alcohol related cues task
19. Breath Alcohol Concentration (BrAC)
20. Transdermal Alcohol Concentration (TAC)
21. Ecological Momentary Assessment Questions (EMA)
22. Timeline followback
23. Brief Young Adult Alcohol Consequences Questionnaire
24. Importance of Consequences of Drinking short-form

4.2 END OF STUDY DEFINITION

The participant is considered to have completed the study if they have completed all the listed study procedures in the Schedule of Activities (SoA), Section 1.2. The end of this study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

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

- Age 21-45
- Meeting NIAAA criteria for current at-risk drinking (i.e., >7/14 drinks in one week for women/men, with at least one episodes of 4+/5+ drinks in the past 30 days)
- Willingness to complete laboratory sessions involving blood draws and alcohol administration
- Ability to communicate and read in English
- Body mass index (BMI) of 18.5 - 30 kg/m^2
- Own an iPhone with Apple iOS 6 or higher compatible with the Skyn app

5.2 EXCLUSION CRITERIA

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

- Meets past-year criteria for severe AUD (>7 of 11 symptoms endorsed) or AUDIT score of 20+
- Meeting past-year criteria for a substance use disorder (with the exception of alcohol, tobacco or mild cannabis use disorder)
- Current engagement in alcohol treatments, or currently engaged in intentional efforts to quit alcohol use
- Current use of GLP-1 receptor agonist medication or weight control medications
- Lifetime diagnosis of severe mental illness (including schizophrenia and bipolar disorder)
- History of suicide attempt, or recent (past 30 day) suicidal ideation, or psychiatric hospitalization in the last 6 months
- History of diabetes
- Medical conditions or medications for which alcohol is contraindicated

- Pregnant, nursing, or trying to become pregnant
- Plans to travel during the duration of study participation

5.3 SCREEN FAILURES

The prescreen procedures should identify most participants who will become screen failures if consented to participate. The online prescreen and phone screen assess all previously stated eligibility and exclusion criteria except 1) SUD and psychiatric disorders 2) current use of prescription psychoactive medication 3) pregnancy. There is still a chance that the first session reveals that they do not meet study criteria. The study personnel completing the interviewing process will notify participants of their ineligibility.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will utilize multiple recruitment strategies to communicate this opportunity to as many potential participants as possible. We estimate that approximately 55 participants will be enrolled from the Triangle area. Potential participants will be informed of the study through email and listserv announcements with study information or a flyer/ brochure with a link to the prescreen survey on REDCap. Potential participants may also find study information through advertisements with a link to the prescreen survey on UNC research for me, social media (Facebook/Twitter/Instagram), and craigslist.com (in the gigs section). Interested individuals can then complete the prescreen survey, which will indicate whether they consent to be contacted about the study. Monetary incentives will be used for study retention as described in Section 4.1.

6. DISCONTINUATION OF STUDY / PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation of the study means that study participation is halted and study procedures are not completed. The study procedures will be discontinued for the following reasons:

- Any unanticipated problem, laboratory abnormality, intercurrent illness or other medical condition, or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).

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 or withdraw a participant from the study for the following reasons:

- Any unanticipated problem or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- The participant cannot complete study procedures or attend sessions as required.

The reason for participant discontinuation or withdrawal from the study will be recorded with the participant files. Participants who sign the informed consent form but do not fully complete study procedures will be replaced.

6.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to attend Study Day 2 and is unable to be contacted by the study site staff. All efforts will be made to ensure participants are not lost to follow-up, including developing rapport and ensuring enrolled participants are reminded of their session dates. Every effort will be made to contact participants who are lost to follow-up, including contacting via email and phone. Any participant that is lost to follow-up will be replaced.

7. UNANTICIPATED PROBLEMS

7.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (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.

7.2 UNANTICIPATED PROBLEM REPORTING

If an UP occurs, the IRB will be notified, and the study will be adjusted as needed to protect the health and safety of the participants. Depending on the nature of the UP, the research protocol, inclusion/exclusion criteria, and informed consent will be changed to reflect the possibility of this event reoccurring. During this time, no new participants will be recruited and the research procedures for currently enrolled participants will be stopped. Each UP will be recorded and reported throughout the study.

7.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any new information gained during the study that may affect a participant's willingness to continue in the study will be reported to all currently enrolled participants.

8. STATISTICAL CONSIDERATIONS

8.1 SUMMARIZE THE STATISTICAL ANALYSIS STRATEGY FOR EACH SPECIFIC AIM

Descriptive statistics (e.g., frequency, mean, standard deviation, variance, range) will be generated for all study variables. Continuous study variables will also be examined for normality and homogeneity of variances using visual inspection methods (e.g., histograms, box plots, residuals, Normal Q-Q plots) and quantitative methods (Shapiro-Wilk test). If these assumptions are violated, the continuous study variables will be transformed, as necessary (e.g., log transformation). Exploratory analysis of the association between participant characteristics and study outcomes will be tested using Pearson correlation coefficients, chi square, and analysis of variance.

To analyze study aims 1 and 2, multi-level regression models will examine the within-person correlations between TAC and BrAC measurements, including peak TAC/BrAC and area under the TAC/BrAC curves (AUC). Models will test within-person correlations between TAC and BrAC during the in-lab alcohol administration and naturalistic drinking bouts and will investigate whether correlations differ across conditions. Multi-level models will test TAC predicting drinks consumed and the odds and frequency of alcohol-related harms (e.g., hangover, missed classes), and will examine whether BrAC accounts for additional variance in those outcomes. Person-specific algorithms for predicting BrAC from Skyn TAC data will be developed using a backwards step- wise multiple linear regression approach starting with Skyn TAC data as the primary predictor and adding relevant covariates (e.g., fat-free mass, skin temperature) that result in statistically significant and/or clinically meaningful improvements to the model.

To analyze study aim 3, multi-level regression models will be used to assess within-person changes on repeated measures along with between-person individual differences. A linear growth curve model will be used to test the hypothesis that alcohol-specific satiety increases with time and additional drinks. Timepoint (1-6) and drug (alcohol or placebo) will be included in the model as within subject factors. Compared to placebo, alcohol is predicted to be associated with higher rates of change (slope) in satiety. Next, AUDIT will be included as a continuous predictor of slope in the model to test the hypothesis that participants with fewer alcohol dependence symptoms (lower AUDIT scores) report reduced satiety. Finally, subjective craving scores (Alcohol Urge Questionnaire; AUQ) from each timepoint will be included in the model. The effect of satiety over time is expected to remain significant after controlling for craving. Alcohol-specific satiety is expected to be negatively associated with measures of reward and incentive motivation for alcohol (BAES, APT, Dot Probe). Outcomes from each of these measures will be included in separate multi-level models with satiety scores as the primary dependent measure and timepoint (1-6) and drug (alcohol, placebo) as within-subject factors to determine the effect of additional dependent measures on within-person change in alcohol specific-satiety over time (slope).

To analyze aim 4, a repeated measures analysis of variance (ANOVA) will be used to assess the effect of a dietary supplement on alcohol-specific satiety in a 2(alcohol, placebo) x 2(timepoints) design. It is

predicted that compared to placebo, a GLP-1 stimulating dietary supplement will increase alcohol-specific satiety.

To analyze aim 5, linear regression will be used to assess the association between HMGB1 levels as a function of BrAC during the laboratory alcohol sessions. Data processing and analyses will be completed in R and SPSS.

8.2 SAMPLE SIZE JUSTIFICATION

An a priori power analysis was conducted using G*Power version 3.1.9.7 (Faul et al., 2007) to determine the minimum sample size required to test the study aims. Results indicated the required sample size to achieve 86% power for detecting a medium effect, at a significance criterion of $\alpha = .05$, was N = 42 for within-between interactions on repeated measures.

8.3 PLANS FOR DATA MANAGEMENT

Questionnaire data will be digitally captured via REDCap a secure, HIPAA compliant web-interface that connects to UNC. In case of a device malfunction, a paper copy will be used, followed by manual data entry into REDCap by a member of the study team. Protected health information (PHI) from the online prescreen survey will be stored in REDCap. Participants will be assigned a numeric code which will be used to identify the study participants. This follows best practices and will minimize the risk of accidental disclosure of study participation or study measurements.

BACtrack Skyn Data: Skyn data are uploaded into a cloud-based server that is password and user account protected. The user account will be created by the PI and data will only be accessible by using this account login information. Only investigators with the IRB clearance will be given access to the password-protected secured server, which will be administered by the PI. BACtrack Skyn personnel do not access or export data collected for research studies.

EMA/Daily Diary Data: EMA and daily diary data collected via the LifeData application are stored in the Microsoft Azure cloud environment on services located in the United States. LifeData uses encryption technology for all data, including those on mobile databases, web databases, and in transit. All data are stored in the cloud environment and are back-up. The LifeData platform is password and user account protected and the web application employs an idle timeout. The user account will be created by the PI and data will only be accessible using this account login information. We will use the Anonymous Data Collection mode, which allows participants to download and interact with the LifeData mobile application without having to provide PII by creating a unique LifeData ID code that is distinct from their participant ID code. The LifeData ID code will be stored in the participant's REDCap file to facilitate linking data upon study completion. Data for each participant will be stored with their unique study identifier to maintain confidentiality. The LifeData platform is HIPAA compliant, GDPR compliant, and certified with a Privacy Shield.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The informed consent procedures will be conducted in-person or remotely using a HIPAA-compliant virtual meeting platform (e.g., Webex, Zoom) and REDCap. Consent forms describing, in detail, the study procedures, and risks are given to the participant and written documentation of informed consent is required prior to the administration of any treatment. All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Participants must complete the consent documentation prior to any in-person study session procedures taking place. Participants will provide electronic signature (via REDCap) witnessed by research personnel. At several intervals during the consent review, the researcher will ask questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. The researcher will also pause several times during the consent process and ask if the participant has any questions about the study or their participation. If needed, the participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice or penalty. A copy of the signed informed consent document will then be given to the participant for their records.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform research staff, study participants, and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

The database will be password protected. Additionally, REDCap's unique features will be used to ensure that PHI cannot be exported from the database. Written records will be kept in locked files that are only accessed by study staff. All staff associated with this study have been trained in ethics and protection of personal health information. All identifiable data will be locked in cabinets (for hard copy) or on a password-protected secure server (for electronic data). All data storage methods noted above are password protected and will be accessed using secure devices that meet the IRB determined data safety level. Data will only be transmitted between members of the research team in de-identified form.

9.1.4 FUTURE USE OF STORED DATA

After the study is completed, the data collected for this study will be fully de-identified and archived within a locked file cabinet or an encrypted server maintained by the principal investigator. Physical files with linking or identifying information will be shredded and digital files with linking or identifying information will be permanently deleted.

9.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Co-Investigator**
Jimikaye Courtney, PhD	Christian Hendershot, PhD
The University of North Carolina at Chapel Hill - Department of Exercise and Sport Science	The University of North Carolina at Chapel Hill - Department of Psychiatry
919-445-1520	919-962-5565
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9.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the principal investigator and co-investigator. The PI and/or Co-I will review unanticipated problems in real time and make decisions as of participant's continuation of the study session. The PI will review AEs with the research team as soon as possible after identification. Any protocol deviations will be reviewed at regular intervals. The PI may request additional review by Co-I on a case-by-case basis. Additional information about reporting procedures are outlined in section 9.1.9.1.

9.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). This is a single site, investigator initiated, experimental research study so there will be no site monitoring plan in place.

9.1.7.1 STUDY MONITORING PLAN

The latest version of the approved IRB application for this study will be followed at all times. This responsibility falls in the hands of the trained research personnel. If at any time there is a deviation from protocol, the deviation from protocol log will be filled out. All team members will be trained on how and when to use this log. Deviations will be sent to IRB every 4-6 weeks (if necessary).

Data will be verified for completeness following every study session and all data will be entered into REDCap, a secure online database. After a participant has completed their participation (full completion through the in-person study visit or because they withdrew prior to completion), data will be rereviewed for completeness and accuracy. After all data has been collected, data will be re-reviewed by another lab member who was not involved with the data collection process.

The PI and Co-I will have read-only access to the REDCap database. This allows the PI and Co-I to view reports that provide information on any missing data on an individual participant basis, but does not allow them to add, change or input any data.

9.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The Study team will conduct internal quality management of study conduct, data collection, documentation and completion. Following written Standard Operating Procedures (SOPs), research personnel will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

9.1.9 DATA HANDLING AND RECORD KEEPING

9.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Trained research personnel will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, and CRF entries. Research personnel will be responsible for unanticipated problem documentation and reporting, while the PI will be responsible for the unanticipated problem assessment, review of the unanticipated problem documentation forms and overview of the research staff.

Clinical data (including unanticipated problems and concomitant medications) will be entered into a data capture system provided by TraCS Clinical Research Data Management Service (REDCap). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Trained research personnel will have complete access to the REDCap system, while the PI and Co-I will have read-only ability. This will enable the researchers to enter the data and the PI and Co-I to review.

As discussed in ***Section 9.1.3****,* data entered in REDCap is stored on servers that are maintained by TraCS. The data is encrypted during transmission. The servers are in a secure campus area with all appropriate physical security measures in place. The web and database servers are monitored by the TraCS IT staff, patched frequently, and scanned by a third-party vendor to ensure that they are protected against known vulnerabilities. The scanning application is the standard service for the entire campus.

9.1.9.2 STUDY RECORDS RETENTION

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule, records will be kept for 5 years after the completion of the study or grant end date, whichever is later.

9.1.10 PROTOCOL DEVIATIONS

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

9.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Data Sharing Policy.

9.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Any conflict of interest for any persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by the UNC Conflict of Interest Office. If necessary, for persons who have a perceived conflict of interest, management will be provided again by the UNC Conflict of Interest office.

9.2 ADDITIONAL CONSIDERATIONS

N/A

9.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

BAC	Blood Alcohol Concentration
BrAC	Breath Alcohol Concentration
GLP-1	Glucagon-like peptide 1
HMGB1	High-mobility group protein box 1
TAC	Transdermal alcohol concentration
NIAAA	National Institute on Alcohol Abuse and Alcoholism
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
AUD	Alcohol Use Disorder
SUD	Substance Use Disorder
AUDIT	Alcohol use identification test
IDS	Inventory of drinking situations
OCDS	Obsessive Compulsive Drinking Scale
RBEDS	Reward-based eating drive scale
BPQ	Body perception questionnaire
DMQ	Drinking Motives Questionnaire
CRAI	Comprehensive relative autonomy index
ASQ	Alcohol Sensitivity Questionniare
ICS	Impaired Control Scale
DEQ	Drug Effects Questionnaire
VAS	Visual Analogue Scale
BAES	Biphasic Alcohol Effects Scale
SEAS	Subjective Effects of Alcohol Scale
AUQ	Alcohol Urge Questionnaire
APT	Alcohol Purchase Task
EMA	Ecological Momentary Assessment
DEXA	Dual-energy x-ray absorptiometry
Tlfb	Timeline Followback
ELISA	Enzyme-linked immunosorbent assay
AUC	Area Under the Curve
BMI	Body Mass Index

9.4 PROTOCOL AMENDMENT HISTORY

MAINTAINED AT THE TOP OF THIS DOCUMENT

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