Biobehavioral Pathways Underlying Alcohol Use and Health

ClinicalTrials.gov Identifier: NCT05135767

Sponsor:

Brown University

Collaborators:

National Institute of General Medical Sciences (NIGMS)
Rhode Island Hospital

Information provided by (Responsible Party):

Brown University

Brown University
Human Subjects Research Application

Instructions on how to complete this application can be found in our guidance tool.

Study Title: Biobehavioral Pathways Underlying Alcohol Use and Health

Principal Investigator: Hayley Treloar Padovano, PhD
If PI is a graduate/medical student, please upload Appendix I: Human Subjects Research Advisor.

1. **Provide the scientific background of the study.**
   Alcohol-associated liver disease (AALD) and alcohol use disorder (AUD) are intersecting diseases. This project unites a team of Brown and Lifespan researchers to demonstrate the feasibility of implementing a brief, psychosocial AUD intervention in patients with AALD and AUD. The intervention includes personalized feedback from liver function tests, interviews of drinking patterns, and self-monitoring of craving for alcohol and negative mood states via smartphone reports in daily life.

2. **Identify the research question(s) of the study and how the study will contribute to generalizable knowledge.**
   We will compare groups of participants; half will have AALD and AUD, and half will have AUD only. There is a 1-week screening phase, brief intervention followed by 3-week intervention phase, and 3-month follow up. As a feasibility study, the total sample size is small (n = 44; 22 per group). This project is funded under P20GM130414, an NIH-funded Center of Biomedical Research Excellence (COBRE).

3. **Describe each participant population for the study and list all eligibility criteria.**
   Drinkers exceeding moderate drinking guidelines in the past 3 months will be recruited from local clinics and the community.

General Inclusion Criteria. To be eligible, the interested volunteer must:
1. Be at least 18 years of age.
2. Meet the Diagnostic and Statistical Manual-5 criteria for alcohol use disorder, indicated by meeting 2 or more symptom criteria, as assessed using the MINI.
3. If male, report 14 or more standard alcoholic drinks per week, or if female, report 7 or more standard alcoholic drinks per week at any point in the 90 days prior to enrollment.
4. Be able to speak and read English or Spanish in order to provide written informed consent and understand written and oral instructions in English or Spanish.

General Exclusion Criteria. Interested volunteers must not have any of the following:
1. Meet the Diagnostic and Statistical Manual-5 criteria for a current diagnosis of psychotic disorders, as assessed using the MINI.
2. Currently receiving specialized psychosocial treatment for an alcohol-use or drug problem.
3. If female, pregnant or nursing.
4. Be anyone who, in the opinion of the investigative team, could not currently be safely withdrawn from alcohol without medical detoxification.
5. A BMI of 40 or more, or 35 or more and experiencing obesity-related health conditions, such as high blood pressure or diabetes.

6. Known medical conditions that, in the opinion of the investigative team, would confound results (e.g., uncontrolled infections, multiorgan failure, uncontrolled upper gastrointestinal bleeding, hepatocellular carcinoma or other active malignancies except skin cancer).
7. Patients who have received a liver transplant or are too ill to participate.
8. Pre-existing loss of kidney function with estimated glomerular filtration rate < 30.
9. Any other condition that, in the opinion of the investigative team, would make the interested volunteer unsuitable for the study or unable to comply with the requirements.

Additional Inclusion Criteria for AALD/AUD patients.
To be eligible in the AALD/AUD group, the interested volunteer must be diagnosed with advanced alcohol-associated liver disease (i.e., either alcoholic hepatitis or alcoholic cirrhosis). AALD will be defined by chart review. Interested volunteers must have one of the following:

1. Positive liver biopsy, or
2. Fibroscan® score > 12.5 kPA, or
3. Evidence of a nodular liver or portal hypertension on abdominal imaging, or
4. Presence of portal hypertensive complications such as hepatic encephalopathy, ascites, or varices, or
5. Fibrosis-4 index (FIB-4) >= 3.25, or
6. Aspartate transaminase-platelet ratio index (APRI) >= 1.0.

Additional Exclusion Criteria for the AUD-only, comparison group.
To be eligible in the AUD-only group, the interested volunteer must not show the following diagnostic test results indicating advanced, alcoholic fibrosis >=F3.

1. Fibrosis-4 index (FIB-4) >= 3.25*, or
2. Aspartate transaminase-platelet ratio index (APRI) >= 1.0**, or
3. GGT-to-platelet ratio >= 0.32.

*The FIB-4 index will be calculated as: age (years)×AST (IU/L)/platelet count (×109/L)×√ALT (IU/L).
**The APRI score will be calculated as: (AST/upper limit of normal)/platelet count (expressed as platelets×109/L)×100.

3.1 Select all vulnerable populations you intend to target for recruitment.

☐	Brown Faculty, Staff, or Students	☐	Children (30 days – 17 years)	☐	Justice-Involved	☐	Decisionally-Impaired	☒	At Risk for / Experiencing Substance Use Disorder
☐	Students	☐	Known Interpersonal Relationships	☐	At Risk of / Experiencing Homelessness	☐	Unauthorized Immigrants	☐	Refugees
☐	LGBTQ+	☐	Pregnant People	☐	Fetuses / Neonates	☐	American Indian / Alaskan Native	☐	Disabled People / People with Disabilities

4. Describe the recruitment methods. ☐ N/A

Collaborator, Kittichai Promrat, M.D., directs hepatology clinics in Providence, RI, one of which is expected to be the primary recruitment site for alcohol-associated liver disease (AALD) patients, i.e., the Lifespan Hepatology Clinic. Another is the Providence VA Medical Center, where Dr. Promrat is the Chief of Gastroenterology. The project Primary Investigator, Hayley Treloar Padovano, Ph.D., and her research assistant, will work directly with Dr. Promrat and fellows and interns under his supervision to facilitate recruitment. Potential participants will be identified by chart review at their regular clinic visit using a checklist of criteria.
Under HIPAA, as members of the covered entity, Dr. Promrat and other fellows or interns under the supervision of Dr. Promrat may utilize information in medical records as part of routine clinical care to identify potential interested volunteers for this research project. Dr. Promrat or another fellow or intern under the supervision of Dr. Promrat

will review the Eligibility Checklist for all patients seen in their routine clinical visits. The Eligibility Checklist does not include any protected health information, i.e., an individual cannot be identified from the information.

If the visit is being conducted via telehealth, i.e., over phone or video conference, Dr. Promrat, or a fellow or intern under the supervision of Dr. Promrat, will introduce the study to the patient. If the patient is interested after hearing about the study, and they give their verbal permission, Dr. Promrat or a fellow or intern under his supervision will ask a few initial screening questions. If the patient appears eligible and remains interested, they will be scheduled for an in-person screening at Brown University. If the patient is interested but is not able to answer the initial screening questions at that time, they may be asked for verbal permission to mail or email them a Consent to Contact and Screening form to be completed, signed physically or electronically, and returned to the Brown University research study.

We may ask prospective participants who meet basic eligibility criteria to self-report to us whether they have been diagnosed with alcohol-associated liver disease, prior to the in-person screening session, and if so, what clinic and/or provider oversees their care. This procedure supplements our efforts to identify participants directly through their medical records at our participating clinic(s). Prospective participants with alcohol-associated liver disease who are recruited from the community based on their self-reports will complete the currently approved Brown HIPAA authorization form at their in-person screening session or via Brown-approved DocuSign to confirm their liver diagnosis. This will enable us to request records from the clinics and/or providers they identify that can confirm the specific eligibility criterion of advanced, alcohol-associated liver disease.

If the patient is in the clinic for an in-person visit, Dr. Promrat, or a fellow or intern under the supervision of Dr. Promrat will introduce the study to the patient. If the patient is interested after hearing about the study, Dr. Promrat, or a fellow or intern under his supervision, will offer the patient the option of signing a Consent to Contact and Screening form, HIPAA Authorization Form, and Medical Release Form. The Consent to Contact and Screening form gives permission for the interested volunteer's contact information (i.e., name, phone number, and email address) to be shared with the Brown University research study. This form also gives permission for a study representative to ask initial screening questions in the clinic, over the phone, or via video conference. Interested volunteers who are not able to meet with the study representative the day of their clinic visit will be given the option to meet with the representative at their next visit or be contacted by a study representative over the phone or via video conference. They will also be given the option to access our study landing page and initial screening survey online via Brown-approved Qualtrics. Interested volunteers who appear to be eligible based on the initial screening, via either in-person, phone, videoconference, or online-survey methods will be invited to the Brown laboratory for an in-person screening to confirm eligibility.

The HIPAA Authorization Form and Medical Release Form are required to share protected health information from the medical record with the Brown University research study. This information is necessary to characterize patients who are recruited to the study. The HIPAA Authorization Form and Medical Release Form may be signed at any time but must be signed before protected health information from the medical record can shared with the Brown University Research Study.

The AUD-only comparison group will be matched on drinking level. Interested volunteers will be enrolled at a pace to match recruitment of AALD/AUD patients. The AUD-only group will be recruited via a variety of standard tactics for research projects conducted by our investigative team. These will include the following:

1. Posting print or digital advertisements via flyers in local businesses (with permission) and other public places, such as public kiosks, the Department of Motor Vehicles, and community boards.
2. Posting advertisements on social media.
3. Posting advertisements via other methods of media, such as newspaper and radio advertisements.
4. Posting advertisements on public transportation.
5. Posting flyers in socioeconomic disadvantaged areas.
6. Sending mailings to local health-care professional offices describing the study and providing flyers that can be placed or posted in their waiting rooms.

Initial Screening. Interested volunteers may respond to recruitment advertisements by completing a set of pre-screening questions online (*i.e., Qualtrics*) or they may respond to recruitment materials by phone, email, or text message. Those who complete the online pre-screening questions will be asked to leave contact information including their phone number and email address, as well as their contact preferences. Interested volunteers who complete the online pre-screening and appear eligible will be contacted to complete a phone or video conference (*i.e., Zoom*) screening. Those who appear eligible will be invited to schedule an in-person screening in our laboratory at 121 South Main Street, Providence, RI. All aspects of this study protocol including all recruitment and screening materials and procedures will be offered in English or Spanish, at the preference of the participant. As described above, two postdoctoral interventionists who are fluent in English and Spanish will deliver the intervention and may

also assist with screening and recruitment. Any information collected as part of online pre-screening or phone or video conference (i.e., *Zoom*) screening prior to receiving written informed consent will be stripped of any personally identifiable information and will be saved only for the purposes of tracking feasibility of screening, recruitment, and enrollment.

In-Person Screening. All interested volunteers who appear to be eligible based on an initial screening will be invited to the CADRE laboratory at 121 South Main Street, Providence, RI, for an in-person screening to confirm eligibility. In-person screening processes will follow written informed consent, and all in-person screening data saved for research purposes will be safeguarded as attested herein.

5. Explain the informed consent process. ☐ N/A

Overall Process. Informed consent for in-person screening and participation will be obtained at the in-person screening session at CADRE laboratory at 121 South Main Street, Providence, RI. Interested volunteers will be given the opportunity to read an informed consent document in a private exam/assessment room. After the interested volunteer has verbally stated that they have read the informed consent document, the research assistant will review the document with the interested volunteer, highlighting each bullet point and soliciting questions from the interested volunteer at pre-specified checkpoints. A breathalyzer test will be administered prior to the interested volunteer signing and dating the informed consent document, and a reading of .000 will be required prior to obtaining the potential participant's signature. The research assistant will witness informed consent signing with their own written signature and date. In order to ensure voluntary participation and minimize possibility of coercion or undue influence, the research assistant will take care to highlight that (1) involvement in research is entirely voluntary, (2) the interested volunteer can withdraw from the screening process or participation in the research at any time, and (3) the interested volunteer is welcomed to ask questions at any point during their research involvement. Those who express hesitation to proceed with any portion of the in-person screening or study protocol will be reminded that participation in research is entirely voluntary and that they may withdraw at any time. Participants who indicate a desire to withdraw from the study will be compensated for their participation to that point. The research assistant will have completed all applicable CITI and HIPAA training and will be trained by the PI in informed consent procedures. **Facilitate Understanding**. The start and stop time of the informed consent procedures will be documented on a project manual with the research assistant's initials to ensure that adequate time was taken to provide informed consent and review the consent document. Interested volunteers will be encouraged to ask questions throughout the informed consent process at pre-specified checkpoints. Those who provide written informed consent and proceed with the study protocol will be encouraged to ask questions at each study visit. We plan to oversample individuals of Hispanic ethnicity and expect approximately one-third of our participants will be of Hispanic ethnicity. Therefore, the research assistant will be fluent in both English and Spanish, and all aspects of the informed consent process, including the informed consent document, will be available in both English and Spanish. Interested volunteers will be required to have ability to read and comprehend the informed consent document in either English or Spanish. Comprehension will be assessed via a short, 4-item quiz assessing understanding of key aspects of the study procedures. The quiz will be embedded in the informed consent document, which is attached with this IRB application. **Documentation**. The interested volunteer will provide their written signature on the informed consent document. The research assistant will witness informed consent signing with their own written signature and date. The original signed consent form will be kept in a locked filing cabinet separate from any data, and the potential participant will be offered a copy of the signed form.

5.1 To request a waiver or alteration of consent, at least one box must be checked ☒ N/A

☐ The research involves public benefit and service programs, is conducted by or subject to the approval of state or local officials, and could not practicably be carried out without the waiver or alteration;

☐ The research meets all requirements for a general waiver or alteration of consent

☐ For the purpose of screening, recruiting, or determining eligibility of prospective participants, the investigator will obtain information or biospecimens either through oral or written communication with participants, or by accessing records or stored identifiable biospecimens.

5.2 To request a waiver of documentation of consent, at least one box must be checked ☒ N/A

☐ The only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality.

☐ The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

☐ Participants or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk of harm and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

6. Describe if the study design involves deception or incomplete disclosure. ☒ N/A

Click or tap here to enter text.

7. Describe the study procedures.

If study procedures involve asking participants about depression, suicide, or the risk of harm to self or others; may result in participants experiencing emotional distress; include populations at high risk for self-injury; administer study medications with a side effect of suicidal ideation, or involve other research components that could increase suicidal risks, please upload Appendix F: Mental Health Safety Plan.

7.A. Overall Design.

This prospective, two-arm intervention trial will include drinkers who exceed moderate drinking guidelines (n = 44; i.e., 7 or more drinks per week for women and 14 or more drinks per week for men, at any point in the past 3 months) recruited from local hospitals, clinics, and the greater community. We will aim to recruit 22 patients with alcohol-associated liver disease (AALD) and alcohol use disorder (AUD) and 22 with AUD only, oversampling women and individuals of Hispanic ethnicity. Biological sex, Hispanic ethnicity, and age and BMI will be *a priori* covariates. Patients with other confounding factors will be excluded as indicated in Section 3 above. In the AUD-only comparison group, indices of liver fibrosis available from routine diagnostic blood tests will rule out AALD and non-alcoholic liver disease. Drinking will be corroborated with timeline follow-back, direct ethanol (EtOH) biomarkers from blood, urine, and breath collected in the laboratory, and self-monitoring via ecological momentary assessment (EMA) smartphone reports (*i.e., Metricwire*). The protocol, summarized graphically in Figure 1, includes a 1-week screening phase, 3-week intervention phase, and 3-month follow-up. Primary efficacy endpoints include endophenotypic markers of drinking outcomes used in clinical trials, i.e., craving elicited by alcohol cues and alcohol demand. Secondary efficacy endpoints are drinking outcomes. An exploratory aim relates biomarkers of immune activation and inflammation to behavioral endophenotypes of AUD and compares these in AALD/AUD patients versus those with AUD only.

7.B. Research Procedures and Materials.

7.B.1. General Procedures.

The primary research site will be the human laboratory at the Center for Alcohol and Addiction Studies (CAAS) at Brown University, School of Public Health, 121 South Main Street, 4th floor, Providence, RI, 02903. All study procedures will be approved by the Brown University Institutional Review Board (IRB) prior to enrolling any human subjects in this research. Additionally, investigators will apply for an IRB authorization agreement (IAA) for Lifespan and submit a separate IRB application for the Providence VAMC, as these will be the primary recruitment sites for alcohol-associated liver disease patients, with recruitment (described below) including chart review and on-site screening. All aspects of this study protocol will be offered in English or Spanish, at the preference of the participant.

Screening. All interested volunteers who appear to be eligible based on an initial screening (*described in Section 5. Recruitment Methods*) will be invited to the CADRE laboratory at 121 South Main Street, Providence, RI, for an in-person screening to confirm eligibility. The in-person screening will ideally be completed by the designated research staff within two weeks of the initial inquiry. Potential participants will be informed that they will receive free behavioral counseling and that their therapist would receive results of their laboratory tests and information on their self-reported feelings and drinking behaviors in daily life. After the study procedures are described in detail, participants will provide written informed consent. After obtaining written informed consent, participants will be asked to complete a locator form which details their contact information as well as the contact information of two friends or relatives who can be contacted for assistance in locating the participant. In-person screening processes will follow written informed consent, and all in-person screening data saved for research purposes will be safeguarded as described in *Part VI. Data Security Assessment.*

Intervention. All participants will receive psychotherapy utilizing manualized principles of motivational interviewing (MI) and cognitive-behavioral skill-building techniques, with an initial session (60min), two brief (10-15min) check-ins at weeks 1 and 2, and a 30-min booster session at 3 weeks. Dr. Treloar Padovano (PI) is a licensed psychologist and has extensive experience delivering MI in the context of research and clinical practice. She will train and supervise postdoctoral interventionists in the specific study intervention. It is customary for brief interventions to include personalized drinking feedback. A research assistant will create a personalized feedback report including a summary of the participants' self-reported drinking patterns, results of selected laboratory tests, and summary visual reports of drinking, craving, and negative affect from smartphone reports. Interventionists will use the feedback report to develop discrepancies between a goal of halting or reversing health risks versus continuing to consume alcohol. Participants will be given the option of in-person or telehealth sessions to allow for flexibility in the event that Brown University restricts laboratory access. The intervention will be offered in English or Spanish, at the preference of the participant. Sessions will be audio recorded for the purpose of coding treatment fidelity.

7.B.2. Research Materials Obtained from Human Subjects.

A key strength of this research project is the integration of research materials obtained from human subjects via multiple data sources. These include (a) self-reported data collected by research staff via interviews and questionnaires, (b) self-reported data collected via a HIPAA-compliant smartphone application implemented in human subjects' natural environments, stored on a HIPAA-compliant, cloud-based server, and monitored by research staff using a HIPAA-compliant web application (*i.e., Metricwire*), (c) biological specimens collected via research staff in our laboratory and processed either in house or at HIPAA-compliant local clinical laboratories (*e.g., Eastside Clinical Laboratories or Quest)*, (d) breathalyzer readings, height, weight, blood pressure, and heart rate, all collected by research staff in our laboratory, and (e) human subjects' performance on laboratory tasks assessing cognitive functioning. An additional strength of the research is the synergy with other CADRE projects, which is made possible through the implementation of a common set of core assessments. Measurement and data properties for behavioral markers and biomarkers specifically chosen to meet the project aims are listed in Tables 1 and 2, respectively. Additional questionnaires included to test ancillary research questions specific to this research project are included in the attached data collection materials. Additional measures that are included in all CADRE projects are listed and described in the attached data collection materials.

Table 1. ***Behavioral Markers: Measurement and Data Properties***

Behavioral markers	Abbrev.	Source	Measure	Scale
Primary Endpoints				
Ecological Momentary Assessment	EMA			
Alcohol craving	AC-EMA	App	Self-report	Continuous
Negative affect (PANAS-X guilt, sadness subscales)	NA	App	Self-report	Continuous
Morning report of yesterday's total standard drinks	MRSD	App	Self-report	Count
Human Laboratory	CRP			
Alcohol craving (*In Vivo* Cue Reactivity Paradigm)	AC-HLAB	VAS	Self-report	Continuous
Heart rate (*In Vivo* Cue Reactivity Paradigm)	HR	Print-out	Criticare system	Continuous
Blood pressure (*In Vivo* Cue Reactivity Paradigm)	BP	Print-out	Criticare system	Continuous
Alcohol demand (Alcohol Purchase Task)	APT	Paper	Self-report	Continuous
Secondary Endpoints				
Percent days abstinent per week	PDA	TLFB	Interview	Continuous

Percent heavy drinking days per week[a]	PHDD	TLFB	Interview	Continuous
Standard drinks per heavy drinking day	DPHDD	TLFB	Interview	Count

Note. Abbrev.= Abbreviation; App = Smartphone application; LP-MC = Liquid chromatography – Mass spectrometry; ELISA = Enzyme-linked immunosorbent assay; VAS = Visual Analogue Scale; TLFB = Timeline follow-back.
[a] A heavy drinking day is defined as 4 or more drinks for women or 5 or more drinks for men.

Table 2. ***Biomarkers: Measurement and Data Properties***

Biomarkers	Abbrev.	Source	Measure	Scale
Direct Markers of Alcohol Consumption				
Ethanol	EtOH	Breath	Breathalyzer	Continuous
Ethyl glucuronide	EtG	Urine	Urinalysis	Continuous
Phosphatidylethanol	PEth	Plasma	LC-MS	Continuous
Diagnostic markers used for screening				
Alanine transaminase	ALT	Serum	Clinical Lab	Continuous
Aspartate transaminase	AST	Serum	Clinical Lab	Continuous
γ-glutamyl transferase	GGT	Serum	Clinical Lab	Continuous
Platelet count (from clinical blood chemistry)	CBC	Serum	Clinical Lab	Count
Creatinine (to estimate glomerular filtration rate)	GFR	Serum	Clinical Lab	Continuous
Markers of Inflammation				
Lipopolysaccharide	LPS	Plasma	ELISA	Continuous
LPS binding protein	LBP	Plasma	ELISA	Continuous
Brain-Derived Neurotrophic Factor	BDNF	Plasma	ELISA	Continuous
Interleukin-6	IL-6	Plasma	ELISA	Continuous
Interleukin-10	IL-10	Plasma	ELISA	Continuous
Interleukin-17A	IL-17A	Plasma	ELISA	Continuous
Interferon gamma	IFN-γ	Plasma	ELISA	Continuous
Tumor necrosis factor alpha	TNF-α	Plasma	ELISA	Continuous
Monocyte chemoattractant protein 1	MCP-1	Plasma	ELISA	Continuous
Markers of Immune Activation				
Soluble cluster of differentiation 14	sCD14	Plasma	ELISA	Continuous
Soluble cluster of differentiation 163	sCD163	Plasma	ELISA	Continuous

Note. Abbrev.= Abbreviation; App = Smartphone application; LP-MC = Liquid chromatography – Mass spectrometry; ELISA = Enzyme-linked immunosorbent assay; VAS = Visual Analogue Scale; TLFB = Timeline follow-back.
[a] A heavy drinking day is defined as 4 or more drinks for women or 5 or more drinks for men.

7.B.3. Laboratory Measures and Procedures.

Self-reported Alcohol Use and Disorder Status. Drinking patterns will be assessed at in-person screening and updated at all timepoints using timeline followback (TLFB) methodology[1,2]. Screening timeline will include the past 90 days and be updated at the baseline session and weekly visits. The 3-month follow-up timeline will also be for 90 days. The Mini-International Neuropsychiatric Interview (M.I.N.I.; paper version 7.0.2) is a brief, 15-min, structured diagnostic interview that will be used to confirm eligibility[3]. Items of the Alcohol Use Disorder module will be asked at in-person screening and repeated at baseline, 3-week, and 3-month timepoints. The full MINI is part of the CADRE core battery (*see attached data collection materials*) and will be used to rule-out psychiatric exclusions. Procedures for suicidality and mental health monitoring are described in *Appendix F.* Breath alcohol concentrations (BrAC) will be assessed with an Alcoholsensor IV instrument (Intoximeters, Inc., St. Louis, MO) prior to participants signing informed consent and at the start of all study visits.

Biomarkers. Direct and indirect biomarkers of drinking and AALD will be used to confirm drinking status and eligibility[4]. Direct, objective biomarkers of alcohol use include ethanol (EtOH) and metabolite levels in blood, breath, and urine samples. EtOH and metabolite levels are the most sensitive and specific biomarkers of alcohol intake, but reflect only very recent use. Phosphatidylethanol (PEth) is an abnormal phospholipid nonoxidative metabolite generated only in the presence of EtOH[5,6]. PEth is detectible for a period of 2-3 wks and can be detected up to >2 wks, maybe to 6 wks[7]. PEth has been validated in AALD patients with higher sensitivity/specificity[8,9]. Indirect markers, such liver enzymes including alanine transaminase (ALT), aspartate transaminase (AST), and γ-glutamyl transferase (GGT), are used to detect chronic, heavy drinking. Immunologic biomarkers are summarized in Table 2. Biospecimens listed in Table 2 will be collected by our CADRE nurse practitioner at screening and all

study visits. EtG will be tested on site. Blood vials will be placed in a cooler with an icepack for pickup by a courier from a local clinical laboratory who will analyze samples and upload results to an online web portal within 24 hrs. Inflammatory markers listed in Table 2 will be collected at all visits except screening and stored in a -80C freezer prior to immunoassays using Ella™.

***In Vivo* Cue-Elicited Craving Paradigm**. Participants will be exposed to alcohol and water cues in the human laboratory via our in vivo cue reactivity paradigm. The participant's preferred alcoholic beverage is used as the in vivo alcohol cue. The procedure includes pouring the beverages into a glass in the presence of the participant. To standardize cue exposure, audio recordings will instruct participants to bring the glass to their nose and smell the beverage when high-pitched tones are presented and put the glass down and stop smelling the beverage when low-pitched tones are presented. Each cue exposure lasts approximately 90 seconds. An initial relaxation period is followed by exposure to the water cue, a second relaxation period, and finally two repeated exposures to the alcohol cue. This order is used to avoid carry-over effects of the alcohol cue. A visual analogue scale from 0 to 10 will assess craving, i.e., "How strong is your craving to drink alcohol right now?". Participants' blood pressure and heart rate will be measured during the task via an automatic blood pressure cuff and finger heart rate monitor. A Criticare VitalCare™ 506N3 Series vital signs monitor with be used to obtain a printed record of blood pressure and heart rate measurements repeated every 3 minutes during the cue reactivity paradigm.

Alcohol Purchase Task. A 15-item APT will assess indices of alcohol demand as follows: intensity, breakpoint, $O_{max,}$ $P_{max,}$ and elasticity. The instructional set will follow Jacobs and Bickel's original procedure, modified to fit alcohol treatment rather than drug treatment[13]. A recent met-analysis supported the validity of the APT alcohol demand indices in light and heavy drinkers[14].

Qualitative Exit Interview. A brief exit interview will be conducted at the Week-3 visit to provide information on feasibility and acceptability of the present research. The semi-structured interview will include questions about likes and dislikes of participating in the study, intervention, and smartphone application, as well as future plans for reducing or abstaining from alcohol and openness to additional assistance with reducing drinking. The interview will be audio recorded for the purpose of qualitative response coding. In addition to collecting this qualitative data, two questionnaire measures will provide a quantitative assessment of usability of the smartphone application (i.e., the 10-item System Usability Scale) and satisfaction with the research project and intervention more broadly (i.e., the 8-item Client Satisfaction Questionnaire).

Use of the CADRE Clinical Laboratory Core. The CLC provides a core assessment battery to promote CADRE synergy and measure common mechanisms underlying chronic disease. Many of the biomarkers will overlap with other CADRE projects. Neuropsychological testing is included in the core assessment battery and will be repeated at week 3 and 3-month follow-up laboratory visits. While our primary aims focus on biobehavioral assessments, we will also consider socioeconomic and psychosocial influences. Socioeconomic measures will include employment status and educational level, income, home ownership, and perceived neighborhood disadvantage. Psychosocial measures will include perceived stress, discrimination, and life satisfaction. The CLC core battery also includes additional psychosocial measures of pain, trauma, family history, medical history, behavioral dysregulation, physical activity, sleep, and health-related quality of life. Additionally, drug toxicology, pregnancy testing, vital signs, and height/weight will be assessed at baseline. Please see the attached data collection materials for a list and description of CLC core assessments.

7.B.4. Natural Environment Measures and Procedures.

Ecological Momentary Assessment (EMA). EMA is a method for collecting self-monitoring data using smartphones. We will use EMA during a 1-week screening phase and 3-week intervention phase. Dr. Treloar Padovano has expertise in complex EMA sampling schemes to assess mechanistic components of substance misuse[15,16,25–34,17,35,36,18–24]. Participants may use their own smartphone or have one provided to them, with data transmitted wirelessly to the vendor's HIPAA-compliant server. The sampling strategy will be relatively minimal to maximize compliance and ensure valid data.

- Morning reports will be the primary assessment of drinking, cannabis, nicotine, and other substance use the previous day and will query quantity and type of alcohol and other substances consumed. Sleep quality the prior night will also be assessed. Three morning-report questions will also assess meaning and purpose in life as follows, "How meaningful does your life feel?", "How much do you feel your life has purpose?", and "Are you searching for meaning in your life?", with responses recorded on a sliding scale from 0 to 10. Participants will indicate the amount of physical pain and pain interference they felt yesterday with two items rated on sliding scales from 0 to 10. Four items will relate to yesterday's drinking, i.e., "How intoxicated were you from alcohol yesterday?" "How much did you enjoy drinking alcohol yesterday?" "How much did you dislike drinking alcohol yesterday?" and "Did you drink more than planned yesterday?", all rated on sliding scales from 0 to 10. Next day drinking effects will be assessed with three items assessing hangover, regret, and severity of alcohol problems, all rated on sliding scales from 0 to 10. A single text-entry item will assess primary reason for drinking yesterday (for those who reported 1 or more alcoholic drinks) or primary reason for not drinking yesterday (for those who reported 0 alcoholic drinks). Last, participants will be asked to indicate the number of standard drinks of alcohol they plan to use that day. Importance and confidence to avoid or limit drinking will be assessed with two items rated on sliding scales from 0 to 10. Last, plans to use other substances will be assessed via a multiple checkbox item where they can check all that apply. Importantly, responses to these questions will not be monitored in real time by study staff, and there will be no mechanism for immediate intervention if a participant indicates substance-use plans.

- Audible signals will prompt reports of craving, affect, and situational influences “right now”, with prompts delivered randomly in four, 3.5hr blocks stratified by time of day between 8am and 10pm. Participants will self-monitor and rate the intensity of their alcohol craving in daily life using a sliding scale from 0 to 10 via the question, “How strong is your craving to drink alcohol right now?”. Craving for cannabis and nicotine will also be assessed, i.e., “How strong is your craving to use cannabis right now?” and “How strong is your craving to use nicotine/tobacco right now?” Participants will also indicate recent drinking and other substance use, the presence of visible alcohol cues, situational factors (e.g., presence of others, presence of others drinking alcohol), and setting (e.g., home, public place). Participants will self-monitor and rate the intensity of their negative feelings in daily life, as assessed by items selected from the PANAS-X guilt and sadness subscales, i.e., guilty, angry at self, sad, and lonely[37]. In order to avoid priming negative feelings, these will be balanced with items from the joviality subscale: happy and energetic. Other feeling states will be assessed by the following: angry at others, hungry, tired, anxious, stressed, and irritable. All will be rated on sliding scales from 0 to 10. Physical pain will be rated with one item, “How intense is your physical pain right now?” on a sliding scale from 0 to 10.

8. Describe the compensation. ☐ N/A

Click or tap here to enter text.

Total participant compensation will include in-person screening, baseline visit, progressively increasing payments for weekly visits, 3-month follow-up visit, initial telehealth session, booster session, and EMA daily payments and weekly bonuses. The duration of involvement (in minutes) and associated payment (in U.S. dollars) for each study component is as follows: in-person screening (75 min; $20), baseline visit (90 min; $50), Week 1 Visit (45 min; $40), Week 2 Visit (45 min; $45), Week 3 Visit (75 min; $50), 3-month follow-up visit (75 min; $60), EMA reports (up to 10 total min per day; up to $4 per day for 28 days, total up to $112). EMA daily amounts and weekly bonuses are contingent on compliance with EMA protocols. Daily EMA amounts will be pro-rated based on compliance as follows: 80% or greater compliance = full $4 amount; 60% compliance = $3; 40% compliance = $2; $20% compliance = $1. EMA compliance rates of 80% or greater as a weekly average will incur a $20 bonus for that week. Frequent feedback regarding compliance will be provided to encourage reporting and be clear with participants about their expected compensation based on their compliance. Total compensation will be a maximum of $457 per participant for a total expected involvement of about 12 hours over 3.25 months.

Participant compensation schedule.

Study component	Estimated time to complete (in minutes)	Compensation	*Note.*
In-person Screening	75	$20	
Baseline Visit	90	$50	
Week 1 Visit	45	$40	
Week 2 Visit	45	$45	
Week 3 Visit	75	$50	
3-month Follow-up Visit	75	$60	
EMA daily payments	~ 10 total min / day	$112	*Up to $4 per day for 28 days.*
EMA weekly bonuses	Not applicable	$80	*Up to $20 per week for 4 weeks.*
	Total Compensation:	**$457**	

The method of compensation will be a reloadable debit card, i.e., ClinCard, managed through Greensphire, specialists in global clinical payment technologies, and MasterCard. It can be used wherever MasterCard is accepted. This system confers several improvements over a manual payment system in terms of enhanced efficiency, security, and confidentiality. The use of the system has been approved by Brown IRB for several existing projects. Compensation will be loaded onto the ClinCard on a weekly basis during the baseline and intervention phases (4 weekly compensation amounts). A final balance of compensation for the 3-month follow-up will be loaded onto the Clincard at that time as one final compensation amount. This method and amount of compensation is appropriate for the participant population age (18 years or older) and study activities based on time commitment and number of study visits. This method is used by other current CADRE projects at the Center for Alcohol and Addiction Studies (CAAS) and compensation is commensurate with other similar projects at CAAS.

Interested volunteers are compensated $20 for their time spent completing the in-person screening, regardless of whether they are enrolled. There is a $3.50 fee to acquire each Clincard and a load fee of $1.00 per load. For this reason, we will provide interested volunteers who are not eligible for the project a one-time $20 Amazon gift card compensation amount rather than using the Clincard. The PI uses Amazon gift cards in other

Brown IRB-approved projects, and this process has worked well. Interested volunteers will be informed prior to in-person screening that if they are not eligible for the project, they will be provided a one-time $20 Amazon gift card as compensation for their time. We may also provide a nominal ($1) gift to interested volunteers who complete an initial screening in a clinic, regardless of whether they enroll.

Based on our prior research projects recruiting heavy drinkers for protocols with similar compensation and effort, we expect that approximately half of participants will require assistance with transportation to our laboratory. Bus passes or reimbursement for rideshare services will be offered. For those participants who prefer to drive themselves to our laboratory, we will provide covered parking a garage with free valet, when allowed per health safety regulations.

9. Is the study a clinical trial? ☒ Yes ☐ No

10. Describe the possible research risks to participants.

Click or tap here to enter text.

10.A. Potential Risks.

Potential risks to human subjects participating in the proposed Research Project are minimal and as follows:

1. Breach of Confidentiality.
2. Psychological discomfort from answering questions about alcohol and other drug consumption patterns and psychiatric symptoms.
3. Physical risks associated with blood draw procedures including and not limited to pain or discomfort, venipuncture, or fainting.
4. Risk of coercion.
5. Elevated alcohol craving in response to *in vivo* cue exposure.

10.B. Adequacy of Protection against Risks.

All procedures will be in accordance with 45 CFR Part 46 and will be approved by the Brown University Research Protections Office IRB. Every effort will be made to protect participants from potential risks, and risks will be closely monitored throughout the research project as described in the data safety and monitoring plan, *Section 7. C.*

10.B.1. Informed consent. Due to eligibility criteria listed above, in-person screening requires questions about alcohol and drug use patterns and associated problems. Therefore, informed consent will be obtained at the start of the in-person screening session prior to engaging in any further activities. BrAC of .00g% will be confirmed when obtaining consent. The nature of the study will be described verbally and in writing via an informed consent document written to an 8th grade reading level in English or Spanish, depending on the interested volunteer's preference. A brief quiz will be administered to assess comprehension of the procedures and risks described in the informed consent document. Interested volunteers will be informed that participation in research is entirely voluntary, and that they have the right to terminate study procedures at any time without risk of penalty. The names and office phone numbers of the project leader, Dr. Treloar Padovano, and on-site primary mentor, Dr. Monti, and research assistant will be provided on the consent document. Contact information for the Brown University IRB will also be provided on this document. Participants will be offered a signed copy of the consent document, and the original form will be kept in a locked filing cabinet.

10.B.2. Protections against Risk.

1. Breach of Confidentiality. Multiple protections will be implemented to minimize risk of breach of confidentiality as follows:
    a. Access to personally identifiable information collected in the proposed research project will be strictly limited to Dr. Treloar Padovano and trained research staff.
    b. Personally identifiable information, i.e., name, phone number, and email address, will be obtained initially for the purposes of screening and assigned a unique screening identification (ID) number.
    c. Information obtained during screening from interested volunteers who are ineligible for the study will be stripped of all personally identifying information and retained only for providing meta-data on research activities, e.g., number of screens completed, reasons for ineligibility, documenting attempts to contact interested volunteers to schedule in-person screening visit.
    d. Once interested volunteers provide written informed consent to participate in the research project, participant data and samples will be identified using a participant identification number (herein referred to as "ID number") that does not contain any personally identifiable information (e.g., the number is not a birth date, social security number, or other identifying number).

e. All personally identifiable information will be kept in a separate location from the participant's data. Hard-copy data containing personally identifying information, i.e., Locator Form and signed informed consent form, will be stored in a locked file cabinet drawer used solely for this purpose and accessible only to Dr. Treloar Padovano and trained research staff.
f. Links between personally identifiable information and the participant's unique ID number will be kept in a separate location from the participant's data in a password-protected file that is saved on a secure server maintained by Brown University Computing and Information Services (CIS).
g. At the conclusion of the study, the file containing participant identifiers linked with unique participant IDs will be destroyed by Dr. Treloar Padovano.
h. The COBRE CLC Data Analyst and Data Systems Management Coordinator will ensure that digital data protection measures utilize the highest industry standards.
i. Data collected for this research project will be de-identified, password-protected, and stored in one of the two following manners: (1) HIPAA-compliant, cloud-based servers managed by outside vendors that are vetted and approved by Brown University CIS, with procedures approved by the Brown University IRB; (2) Brown University's secure servers managed by our CIS department.
j. Biological samples collected in the course of the study will be marked with the participant ID number and will not be associated with personally identifiable information. Blood samples will either be (1) sent out for same-day processing by a local, HIPAA-compliant laboratory, or (2) stored in a freezer designated for this purpose in a locked room in the secure CAAS laboratory until transported to a local research laboratory for batch assays.

2. Psychological discomfort from answering questions about alcohol and other drug consumption patterns and psychiatric symptoms. All interviews and assessments will be conducted in a private room by trained research staff in a supportive manner, offering to explain to participants why certain questions are being asked. Research staff will be extensively trained in administering alcohol and other drug interviews in a manner that is nonresponsive and nonjudgmental, and they must pass this training and be approved by Dr. Treloar Padovano in order to administer these assessments. In addition, participants will be informed in writing and reminded through the protocol that they may withdraw from the study at any time without penalty or consequence. Participants who decide to withdraw from the study prior to completion will be paid for their participation up to that point.
3. Physical risks associated with blood draw procedures including and not limited to pain or discomfort, venipuncture, or fainting. Blood collection has a risk of pain or discomfort and venipuncture. Precautions are taken to minimize this risk during blood collection. All blood collection is implemented by a licensed nurse practitioner who is a trained phlebotomist and has extensive medical training, thus minimizing risk of venipuncture. Risk of fainting is considered low and participants will be seated for all blood draws to minimize any potential for physical harm.
4. Risk of coercion. The risk of coercion is low. The total amount of compensation during the study is modest given the study requirements and time commitment. All research staff will be specifically instructed in the need to avoid coercion. Participants will be assured that they are free to refrain from answering any questions or completing any tasks. Participants will be assured that participation in this research is strictly voluntary and that they may withdraw from the study at any time without penalty. Participants will be reminded of this at all phases of the study.
5. Elevated alcohol craving in response to *in vivo* cue exposure. The *in vivo* alcohol cue reactivity protocol is designed to experimentally induce short-term elevations in alcohol craving. Prior to ending each in-person study session where the *in vivo* alcohol cue reactivity protocol is implemented, trained research staff will assess any residual elevations in craving. If the participant reports residual urge, Dr. Treloar Padovano or another trained clinician will speak with the participant and complete a structured protocol authored by study collaborator, Peter Monti, Ph.D., and published in *Treating Alcohol Dependence: A Coping Skills Training Guide* (Monti, et al., 2002). The protocol involves multiple components, including discussing reactions to the session, assessing urge, and, if necessary, talking down the urge prior to the participant leaving our laboratory.

11. Describe the anticipated benefits to participants.

11.A. Potential Benefits of the Research to Human Subjects and Others. Participation in this research poses minimal risk, resulting in a favorable cost-benefit ratio. There are no demonstrated benefits to participants from participating in this study. Potential benefits, however, may include assistance with reducing harmful drinking patterns. Additionally, participants who express interest in receiving formal addictions treatment upon completion

of the study protocol will be offered the opportunity to speak with Dr. Treloar Padovano or another licensed clinical psychologist, who will review a list of local treatment options with the participant. Benefits to society are expected to stem from generation of new scientific knowledge informing our understanding of how reductions in alcohol use can reduce health risks, such as alcohol-related liver disease.

11.B. Importance of the Knowledge to be Gained. Harmful use of alcohol leads to multiorgan damage, injuries, and cognitive-behavioral alterations causing 3 million deaths per year worldwide, and alcohol misuse is a leading cause of preventable liver disease. This research project will contribute important scientific knowledge concerning the intersection of biobehavioral markers of liver function, inflammation, and alcohol use. The research has the potential to increase our understanding of the specific pathways by which excessive alcohol consumption exacerbates the development of alcohol-associated liver disease. The risks to participants, which are considered minimal, are reasonable in relation to the importance of the knowledge to be gained.

12. Does the study involve the use of secondary data (identifiable information or identifiable biospecimens)? ☐ Yes (complete Questions 12.1-12.3) ☒ No (skip to Question 16)

12.1 Provide the source of the data.
Click or tap here to enter text.

12.2 Describe the type(s) of data / biospecimens and date range(s) of the data you will use and the characteristics of the study research population (e.g., age range, sex, and any other pertinent demographic information.
Click or tap here to enter text.

12.3 Describe how will you use, study, or analyze the data / biospecimens.
Click or tap here to enter text.

13. Does the study involve the use of PHI from a HIPAA-covered entity?
☒ Yes (complete Question 13.1-13.2) ☒ No (proceed to Question 14)
If "yes," please upload Appendix G: Use of Protected Health Information (PHI) in Research. If applicable, upload a HIPAA Authorization form.

13.1 Describe how authorization to access the data will be obtained.
The HIPAA Authorization Form and Medical Release Form are required to share protected health information from the medical record with the Brown University research study. This information is necessary to characterize patients who are recruited to the study. The HIPAA Authorization Form and Medical Release Form may be signed at any time but must be signed before protected health information from the medical record can shared with the Brown University Research Study.

13.2 Is the data considered a limited data set? ☐ Yes ☒ No

14. Does the study involve the use of Family Educational Rights and Privacy Act (FERPA) or Protection of Pupil Rights Amendment (PPRA) data?
☐ Yes (complete 14.1-14.2) ☒ No (proceed to Question 15)

14.1 What type of FERPA or PPRA data will be accessed for this research?

☐ Directory information

☐ Education records

☐ Instructional material

☐ Personally identifiable information (PII)

☐ Data involving a PPRA-protected category

☐ Other, please describe: Click or tap here to enter text.

14.2 Describe how authorization to access the data will be obtained.

Click or tap here to enter text.

15. Is a Data Use Agreement (DUA), Material Transfer Agreement (MTA), or other agreement required by the source to obtain, use, study, or analyze the data / biospecimens?

☐ Yes ☒ No

If "yes," please upload a copy of the Agreement(s) (draft or executed).

16. What type of data will be collected?

☒ Identifiable biospecimens

☒ Personally identifiable Information (PII)

☒ Coded data and the study team has access to the linking file / key

☐ Coded data and the study team does not have access to the linking file / key

☐ Anonymous data

☐ Publicly available data

☒ Other, please describe: Metricwire is used to collect data via smartphone reports in daily life.

This data type and procedures to maintain the confidentiality of participant data are described below.

17. Briefly describe your plan for managing the integrity of the data and monitoring the safety of participants. ☐ N/A

Identifiers. Data and biospecimens collected for this project will be deidentified, meaning that identifiers will be stored separately from study data and biospecimens. Research staff will maintain a password-protected file that contains links of personal identifiers with unique participant identification (ID) numbers. This file will be stored on our secure departmental server that is managed by Brown CIS. This file will be kept for the duration of the study and will be destroyed at the conclusion of the study by the PI. **Justification.** This is a study of biobehavioral mechanisms of addiction and chronic disease and requires biospecimen collection for screening eligibility and addressing the project aims. Identifiers are needed because the study involves multiple sessions. **Proposed use.** Identifiable contact information will be used to schedule laboratory visits and follow-ups. Audio recordings can be used to code fidelity of postdoctoral interventionists to the manualized treatment and evaluate treatment process. **Audio recordings.** Audio recordings will be collected via Zoom videoconferencing software ONLY for the counseling sessions with postdoctoral interventionists. At the conclusion of the Zoom counseling session, the Zoom audio file will be saved using the participant's ID number on our secure server immediately after each session and deleted immediately after each session from Zoom. Audio recordings can be used to code fidelity to the manualized intervention and evaluate treatment process. Additional audio recordings will be collected via a handheld audio recorder for the qualitative exit interview completed by research staff at the Week 3 visit. Research staff will remind the participant of their consent to be audio recorded and ask permission to proceed prior to turning on the handheld audio recorder. The audio recorder saves files in an internal storage system. As soon as the session ends, research staff will upload the audio files to our secure server with only the participant's ID number. The original copy will be immediately deleted from the audio recorder. **Paper records.** Paper project data collection forms will include

locator forms so that participants can be contacted by study staff, project forms used by study staff to record information such as visit start and stop times, participant height and weight, etc., and project forms to record responses to interviews and questionnaires. Paper records will either include participant identifying information or participant ID numbers, but never both on the same paper record. Paper records containing participant identifying information will be stored separately from paper records identified by a participant ID number. The link for the paper records will be stored in a password-protected file on our secure departmental server and kept for the duration of the study and destroyed upon completion of the study. **Filemaker.** Filemaker is used to track subject enrollment and progress through the study protocol. Subjects are identified only by a subject ID #, which is assigned sequentially and contains no PHI. Scheduling of study visits as well as visit status is logged into Filemaker. Filemaker is also used for reporting of target and study completion totals. Users to the database are restricted based on project permissions, and login with username and password. The Filemaker database lives on a secure departmental server maintained by Brown CIS. **Metricwire**. When participants submit response data using the Metricwire Mobile App or sensor data is passively logged and the mobile device is connected to the internet, data are immediately synced to HIPAA-Compliant servers located in the United States and removed from the participant's mobile device. The data are encrypted end-to-end during transmission using TLS (1.2 &1.3) Protocol. Metricwire servers use an Encryption Token to verify that the data is coming from the correct source (authenticity) and that the data have not been modified in-transit (integrity). If an internet connection is not available, the data are temporarily stored on the participant's mobile device. The Metricwire Mobile Application stores response and sensor data in an encrypted format without any additional identifying information using AES-256 encryption keys. The data cannot be accessed using the Mobile Application Interfaces. When the Metricwire Mobile Application detects an internet connection, encrypted data are securely transmitted to Metricwire servers and removed from the device. App data are encrypted using AES 256 encryption. The Metricwire app can access only basic device features, such as OS Type & Version; Connectivity (Wifi vs Cell Network); App Permissions (Notifications, Location, etc); Battery Level, Charging & Disk Space; Localization Settings (Country/Language)

18. How will you protect the privacy of participants?

Access to private identifiable information collected in this study will be strictly limited to the PI and primary research staff. Participant data ad biospecimens will be identified using a unique participant ID number that is not related to personal identifiers. .

19. Does the study have or will you apply for a Certificate of Confidentiality (CoC)?

☒ **Yes** ☐ **No**

20. How will you maintain the confidentiality of participant data?

Links between personally identifiable information and participant IDs will be stored, secured, and destroyed upon completion of the study. Signed consent forms will be stored as described above and accessible only to the PI and trained research staff.

21. Who will have access to your identifiable study data / biospecimens?

☒ Brown PI and other Brown research team members (including advisor).

Describe how unauthorized access by others will be prevented.

Data will be stored in deidentified files on our secure departmental server that is managed by Brown CIS. The COBRE Clinical Lab Core data systems management coordinator and data analyst will ensure that digital data protection measures utilize the highest industry standards. Biological specimens collected in the course of the study will be marked with the participant's ID. Blood samples that are not sent to local HIPAA-compliant clinical laboratory for immediate analysis will be stored in a freezer in a protected lab space at 121 South Main Street or Brown-hosted biorepository.

☐ Data will be shared with research collaborators external to Brown.

Describe how you will securely share / transfer the data outside of Brown.

Click or tap here to enter text.

☐ Data will be shared with a data repository.

Describe how you will securely share / transfer the data outside of Brown.

Click or tap here to enter text.

PRINCIPAL INVESTIGATOR AGREEMENTS & RESPONSIBILITIES

A. Conduct of the Research

1. I accept responsibility for the ethical conduct of this research and protection of participants as set forth in the Belmont Report and all applicable federal and state regulations and requirements pertaining to human subjects research, including but not limited to the Department of Health and Human Services' Protection of Human Subjects (45 CFR 46), and the Food and Drug Administration's Protection of Human Subjects (21 CFR 50) and Institutional Review Boards (21 CFR 56).
2. I accept responsibility for ensuring that all members of the research team comply with all Brown policies and procedures pertaining to human subjects research.
3. I accept responsibility for ensuring that all members of the research team have or will complete the appropriate education and training to protect participants before any work begins with participants or identifiable information / biospecimens.

B. Ensuring and Maintaining Compliance

1. I will comply with relevant regulatory and institutional reporting requirements, including Brown University's *Reportable Events Policy*.
2. I will notify the Brown HRPP when I have completed all activities involving human subjects or identifiable participant information or identifiable biospecimens.
3. I will maintain approval, as applicable, with collaborative parties, including approvals from other countries or jurisdictions.
4. I will cooperate with any post-approval monitoring or auditing of study activities and/or study records as requested and/or required by the Brown ORI, the Brown IRB, funding entities, sponsors, and/or any federal or state regulatory agencies.

C. Study records, Reports and Documentation

1. I will comply by Brown's *Research Data and Research Materials Management, Sharing and Retention Policy*.
2. I will maintain all research protocol materials and consent materials for the duration of this study.
3. I will maintain research records for at least three years following the end of this research, or for a longer length of time if specified in applicable regulations or sponsor requirements. I will take measures to prevent accidental or premature destruction of these records.

By submitting this document, I certify that I have read and agree to uphold all of the Agreements and Responsibilities in this application.