DIGITAL INTERVENTIONS TO TREAT HAZARDOUS DRINKING

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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Effects of Stress on Emotion and Risky Drinking

Principal Investigator: Dongju Seo, PhD

(*If applicable*) Clinicaltrials.gov Registration #: Click or tap here to enter text.

SECTION I: RESEARCH PLAN

1. Statement of Purpose:

Studies have shown that stress is a major contributor to stress-related clinical disorders and to substance use problems including alcoholism (Perkins, 1999; Sebena, El Ansari, Stock, Orosova, & Mikolajczyk, 2012). Stress response involves increased arousals in the autonomic nervous system (ANS) (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). In particular, it is well documented that alcoholism is highly associated with stress and ANS disruption, suggesting that a strategy to address stress and ANS regulation may be helpful to reduce symptoms related to stress, mood, and addiction. For example, a breathing technique has shown to be effective in relieving stress-induced arousal. Studies have found that voluntarily regulated breathing practices normalize ANS system and improve sympatho-vagal balance, which resulted in reduction in psychiatric symptoms including anxiety, stressor-related symptoms, and addiction (Gerbarg & Brown, 2016). Relieving stress and arousal is particularly crucial in preventing alcohol addiction, as an inability to relax even during the neutrally relaxing state has been associated with high alcohol craving and early relapse in patients with alcoholism (Seo et al., 2013).

Overall purpose:
The current study will examine the effects of an intervention involving **P**roblem-focused target intervention, **S**tress management, and **B**reathing modulation (PSB intervention) on improving symptoms of mood and addiction related symptoms including mood, craving, and addictive behaviors. The purpose of the 4-week intervention is to test the efficacy of the 4-week intervention consisting of 8 sessions for those who are willing to invest a month of their time towards improving their symptoms and subsequent follow-up.

The specific aims are as follows:

Aim (4-week intervention): To examine the effects of the PSB intervention on mood and addiction related symptoms (emotional problems, craving, substance use) in individuals with either risky drinking problems or with high stress after the 4-week intervention (8 sessions) of two sessions per week. The effects will be examined before and after the 4- week intervention.

The effects of the 4-week intervention on daily mood, stress and substance use behaviors will also be examined during a 30 -day follow-up. Participants will be followed using a smartphone app to examine the effects of the PSB intervention on daily mood, stress and alcohol use behaviors in a real-life setting. And participant will receive an online evaluation assessment at the end of the 30-day follow-up period.

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.

   Study (4-week intervention): 2.5 months

   (2-3 weeks for 4-5 baseline intake sessions; 4 weeks for the telehealth intervention (8 session, twice weekly) with daily monitoring and intervention aids for assessing treatment progress via smartphone app survey; 1 post assessment; 30 days for daily follow-up via smartphone app; 1 post follow-up assessment)

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   Habitual alcohol abuse and stress-related mood disturbance are serious problems (Naimi et al., 2003; Wechsler et al., 2002). Studies have shown that stress is one of major contributors to mental health disorders including emotional disorders (e.g., depression, anxiety) or alcohol abuse problems (e.g., hazardous drinking) (Perkins, 1999; Sebena et al., 2012). Despite the significance of stress-related clinical disorders, challenges remain in implementing effective prevention and treatment approaches, as those with either high-risk drinking or high stress not only disregard their mood and substance-related problems, but also respond inadequately to currently available prevention or treatment programs.

   It is well documented that stress and alcohol abuse are associated with stress and ANS disruption including high stress sensitivity and negative emotion, increased basal heart rate (HR), sustained phasic HR acceleration, and reduced heart rate variability (Karpyak, Romanowicz, Schmidt, Lewis, & Bostwick, 2013; Sinha et al., 2009; Stormark, Laberg, Nordby, & Hugdahl, 1998; Vaschillo et al., 2008). In those with mood and drinking related problems, impaired autonomic regulation characterized by high heart rate and reduced heart rate variability (HRV; a primary index of ANS modulation) has been consistently reported (Ingjaldsson, Laberg, & Thayer, 2003; Quintana, Guastella, McGregor, Hickie, & Kemp, 2013; Shively et al., 2007; Thayer, Hall, Sollers, & Fischer, 2006).

   In particular, in times of national crisis, the prevalence of stress- and alcohol- related disorders increases substantially. Over the course of the ongoing COVID-19 pandemic, there has been a significance rise in mental health symptoms including high levels of emotional distress and alcohol/substance misuse, presenting unprecedented public health challenges (Callinan & MacLean, 2020; Rodriguez, Litt, & Stewart, 2020). Immediate clinical interventions are exigent to reach out to vulnerable individuals in high-risk areas to evaluate and treat those at risk for alcohol- and stress- related disorders.

   A strong association between stress and addiction suggests that a strategy to address stress and arousal should be included in mood and addiction related treatment or prevention strategies. For example, to relieve stress and ANS arousal, a breathing technique has shown to be effective. Studies have found that voluntarily regulated breathing practices normalize autonomic activity and improve sympatho-vagal balance, which resulted in reduction in psychiatric symptoms including anxiety disorders, trauma- and stressor-related disorders, and addiction (Gerbarg & Brown, 2016). Relieving ANS arousal is particularly crucial in preventing

alcohol addiction, as an inability to achieving a relaxing state has been associated with high alcohol craving and early relapse in AUD patients (Seo et al., 2013). In addition, stress reduction techniques including mindfulness have been useful in reducing stress and treating mood and addiction related problems (Kober, Brewer, Height, & Sinha, 2017). Taken together, these studies suggest that stress management and a method to relieve physiological arousal should be incorporated into prevention and treatment programs for stress and addiction related symptoms, emphasizing the need for the PSB intervention described above.

In addition, during the COVID-19, the infectious nature of the pandemic is a significant obstacle to treatment efforts. Telehealth interventions have emerged as an ideal tool to overcome this difficulty and treat problematic alcohol use by allowing rapid treatment access to those residing in high-risk zones.

To achieve these goals, the current study is intended to examine the efficacy of the PSB intervention on addiction symptoms in individuals (age 18-55) with either hazardous drinking or high stress using 4-week telehealth intervention as described in the Statement of Purpose. We will utilize an approach that allows a concurrent 4-week telehealth intervention using video communications and daily monitoring via a smartphone app.

4. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

   A total of 100 subjects will be recruited. Heavy drinkers will be defined as those who have risky drinking habits at levels to match heavy or binge drinking groups based on the NIAAA clinician guide (2005). COVID-19 related stress will be identified on the basis of two validated measures including the COVID Stress Scale (Taylor et al., 2020) and Perceived Stress Scale (Cohen et al., 1983). All study procedure will be conducted at the Yale Stress Center. The PI will work closely with a co-investigator, Dr. Sinha and the YSC clinical team. Dr. Sinha is the Chief of Psychology Section in Yale Psychiatry.

   In response to the current COVID-19 epidemic, the following study processes will be carried out. To limit exposure to COVID-19 and ensure the safety, we will mostly use virtual options, such as video communications (zoom, Skype for business, or Microsoft team etc. depending on participants' convenience), REDCap, or phone. An exception will be given to participants who do not have computers or electronic devices; these individuals will visit Yale Stress Center for experimental procedure.

   For the 4-week intervention, subjects will participate in the 4-week telehealth intervention (8 sessions, twice a week) for target intervention and subsequent smartphone app follow-up. During the 4-week period, the intervention group will visit Yale Stress Center twice a week for the PSB intervention. After the intervention, all participants will receive post-treatment assessment involving the examination of stress, mood, and alcohol use. The project will use prospective monitoring using smartphone app technology in the participants' natural environment during the 30 -days follow-up, during which we will monitor mood, stress, and alcohol intake daily. The intervention will be conducted via telehealth using Yale ITS approved video communications technology (e.g., Zoom, Skype for Business, or Microsoft Teams). After the 4-week intervention, all participants will undergo a post-intervention evaluation and followed for 30 days using a smartphone app. At the end of the 30-day survey period, they will have a remote session with a staff for post-study assessments and be remotely instructed on how to uninstall the app from their smartphone.

(a) Intake pre-intervention phases

Baseline Assessment (4-week intervention): Following screening using a Qualtrics prescreen survey or via phone, eligible subjects will be invited for a video session to obtain an informed eConsent (via REDcap) and an initial assessment to further determine eligibility via DSM-5 SCID interview. If the subject meets criteria, he/she will be scheduled for baseline sessions (2 hours each) to complete online assessments (via REDCap link) or in-person video interview. There will be 4-5 intake sessions depending on individual speed. All participants will work with specially trained research staff using standardized psychosocial assessments, self-report rating forms, and physical health questionnaires via remote sessions.

Assessments

All participants will be assessed across the following domains using psychometrically established measures.
The Structured Clinical Interview for DSM-V (SCID-I) will be used to ascertain DSM-5 Axis I and II psychiatric and substance abuse diagnoses (First, Williams, Karg, & Spitzer, 2015) and specifically to determine presence/absence of DSM-5 alcohol use disorder (AUD).
The Shipley Institute of Living Scale (SHIPLEY) (Shipley, 1940) has been widely used to assess cognitive functioning and impairment.

Assessment for Alcohol use and addiction:

Family history of alcoholism (FH) will be assessed using the Family Tree Questionnaire (Mann, Sobell, Sobell, & Pavan, 1985); (Vogel-Sprott, Chipperfield, & Hart, 1985) which provides a method to obtain drinking status and alcohol-related problems for all maternal and paternal first and second degree relatives above the age of 18.
The Time-Line Follow-Back Interview will also be used to assess alcohol, other drugs and nicotine use in the previous ninety days, during the study and during follow-up. This is a reliable experimenter-administered assessment (Sobell & Sobell, 1992), which uses a calendar prompt to facilitate recall of drug use during a targeted period, and has been well-validated in alcohol and drug abuse treatment studies (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000).
Smoking History Questionnaire (Brown et al., 2002): A smoking screening questionnaire consisting of items about current and past smoking habits will be used to obtain smoking history.
The Alcohol Use Disorders Identification Test (AUDIT) (Bohn et al., 1995) is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems.
The Quantity-Frequency Variability Index (CAHALAN) (Cahalan et al, 1969) measures alcohol consumption patterns over a specific time period.
The Alcohol Urge Questionnaire (AUQ); (Bohn, Krahn, & Staehler, 1995) is a reliable and valid 8-item self-report craving scale that can be used for repeated assessments. It has been found to be significantly associated with drinking measures and dependence severity.
The Cannabis Use Disorder Identification Test-Revised (CUDIT) will be used to quantify the severity of cannabis use over the past six months (S. J. Adamson et al., 2010).
The Marijuana Motives Questionnaire (MMQ) (Simons et al., 1998) is a self-report questionnaire that will be administered at baseline to assess reasons for using marijuana, including coping with stress.
The Marijuana Craving Questionnaire – Short Form (MjCQ-SF) (Heishman et al., 2009) will be administered weekly to assess craving for marijuana along four dimensions: compulsivity, emotionality, expectancy, and purposefulness.

Assessment for Emotional/Behavioral Problems associated with Addiction: The following assessments will be administered to assess stress, impulsivity, depression, trauma, and mood symptoms.
The Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983) is a 14-item self-report assessing the degree to which situations are appraised as threatening or demanding.
The Spielberger State/Trait Anxiety and Anger Questionnaires (Spielberger & . 1970) is a reliable and valid measure of both state and trait anxiety and anger.
The Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is regarded as a well-established, sensitive self-report measure of depression.
The Center for Epidemiologic Studies Depression Scale (CES-D) (Lewinsohn et al., 1997) a screening test for depression and depressive disorder.
The Emotion Regulation Scale (ERS, Gratz & Roemer, 2004) a 36-item questionnaire to provide a comprehensive measure of the difficulties in emotion regulation.
The Self-Control Scale -Brief (SCS-Brief) (Tangney, 2004) is a 13-item measure of self-control that measures processes that directly involve self-control such as breaking a habit or working toward long-term goals, rather than distal behavioral outcomes of self-control. The SCS-Brief will be administered at intake appointments.
The Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) is a questionnaire designed to assess the personality/behavioral construct of impulsiveness.
The Mindfulness Attention Awareness Scale (MAAS)(Brown & Ryan, 2003) is a 15-item scale designed to assess a receptive state of mindfulness and attention.
The Perseverative Thinking Questionnaire (Ehring et al., 2011) is a 15-item scale designed to measure the broad idea of repetitive negative thought. Intrusive thoughts are one of the symptoms of trauma.
The Zimbardo Time Perspective Inventory (ZTPI)(Zimbardo & Boyd, 1999) is a 56-item questionnaire that measures individual differences in time-orientation which has been associated with emotional problems.
The Multidimensional Personality Questionnaire (MPQ)(155 items; Patrick et al., 2002) provides for a comprehensive analysis of personality including Positive Emotionality, Negative Emotionality, and Constraint which embody affect and temperament constructs.
The Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994) assesses the severity of pain and its impact on functioning.
The Pain Catastrophizing Scale (PCS) (Sullivan, Bishop, & Pivik, 1995) measures the tendency to magnify the threat value of a pain stimulus and to feel helpless in the presence of pain.
The Externalizing Spectrum Inventory (Kruger et al., 2007) is 100-item questionnaire that indexes a range of correlated problem behaviors and traits in the domain of deficient impulse control such as alcohol or substance use problems.
The Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2008) is a survey toolkit to assess severity and intensity of suicidal ideation and behaviors. Suicidality can be one of the symptoms of major depressive disorder.
The Childhood Trauma Questionnaires (CTQ) (Bernstein et al., 1997): This is a 28-item test that measures 5 types of maltreatment-emotional, physical, sexual abuse, and emotional and physical neglect.
The Chronic Stress Checklist (CSC) adapted from the Cumulative Adversity Interview (adapted from (Turner & Lloyd, 2004). This measures chronic stress and adversity.
The Dutch Eating Behavior Questionnaire (DEBQ) (van Strien, 1986) measures eating styles that may contribute to or attenuate the development of obesity, through three scales that measure emotional, external and restrained eating. The DEBQ is administered to examine stress-driven eating behaviors
The Lifestyle and Behavior Survey, adapted from the Cornell Medical Index (Costa & McCrae, 1985; Perlmutter & Nyquist, 1990) and the NHANES is administered at intake.
The Social Media Questionnaire (SMQ) is a 5-item questionnaire given at intake to assess social media use.
The COPE Inventory (Carver et al., 1989) was developed to assess individuals' use of different coping strategies. The COPE is composed of fifteen subscales. This scale will be administered at intake.

The Cornell Medical Index (Abramson, 1966) measures current adverse physical and psychological health symptoms.

Additional surveys to assess the COVID-19 related stress

The COVID Stress Scales (CSS) (Taylor et al., 2020) is a 36-item designed to measure COVID-19 stress and anxiety symptoms including COVID danger and contamination fears, COVID fears about economic consequences, COVID xenophobia, COVID compulsive checking and reassurance seeking and COVID traumatic stress symptoms.

The Psychosocial Impact of COVID-19 (PIC) (Chung, 2020) is a 2-item assessing the level of difficulties and distress in people's lives over the past two weeks.

The Psychological Stress Associated with the COVID-19 Crisis questionnaire (PSACC) (M. Adamson, 2020) is a 37-item designed to measure the level of stress during the COVID-19 pandemic and characterize it according to location, gender, income, and other factor.

The UCLA Loneliness Scale (Version3) (Russell, 1996) is a 20-item measure that assesses how often a person feels disconnected from others.

The Interpersonal Support Evaluation List (ISEL) (Russell, 1996) is designed to measure perceptions of social support among individuals in the general population.

The COVID-19 Community Response Survey-Social Distancing Impacts (JHU-SDI) (Johns-Hopkins, 2020a) is designed to measure the impact of COVID-19 on people's lives due to a precautionary measure of social distancing.

The COVID-19 Community Response Survey-Substance Use (JHU-SU) (Johns-Hopkins, 2020b) is a 15-item designed to assess the use of substance after and during the COVID-19 pandemic.

(b) Target Intervention Combined with Breathing and Stress Management (PSB)

Subsequently, after the completion of the baseline assessment, all subjects will remotely participate in a 4-week digital intervention via video communications using platforms approved by Yale University IT services such as Zoom, Skype for Business, or Microsoft Teams. For 4 weeks, participants will attend 1.5 to 2 hours individual therapy sessions (8 sessions in total, twice a week) with Dr. Seo and her clinical team for prevention for alcohol use disorder using video communications. They will also be asked to use a smartphone app daily to assess treatment progress and learn coping skills (e.g., homework). At the end of the 4-week digital intervention, there will be post-treatment evaluations. Some components of the PSB intervention include:

(1) Problem-focused target intervention partially adapted from cognitive behavioral therapy and NIAAA-approved coping skills training strategies (Kadden et al., 2003).

(2) Breathing modulation to normalize ANS function including techniques partially adapted from resonance breathing (e.g, the Breath-Body-Mind (BBM) technique (Brown & Gerbarg, 2012)).

The content involves increasing knowledge on stress reactivity, emotional problems, and drinking habits, cultivating breathing and emotion and stress regulation strategies, including self-regulated breathing. Each session involves self-monitoring of current stressors and challenges to handling stressors (communication, emotional reactivity, drinking, substance use) and applying strategies of awareness, reflecting, goal setting as well as integrating healthy lifestyle and choices.

(c) Follow-up: real-world smartphone app

The method of daily monitoring has an advantage over traditional follow-up measures by overcoming recall bias and providing more accurate, real-time behavioral data in natural settings (Shiffman, Stone, & Hufford, 2008). This approach has been well supported in studies examining daily mood, stress and substance-use patterns (Runyan et al., 2013; Wray, Merrill, & Monti, 2014). We will provide smartphones to those who do not have. If it is lost or broken, we will provide another one. The app will only be shown to participants who will register the study. The app does not require a password to access once they register. However, no response will be stored in the phone, and all the data will be coded and transferred immediately. The MetricWire app is not commercial and research only app. This app is HIPPA compliant and passed Yale IRB and IT review previously.

The MetricWire app has previously been used in clinical research and is HIPAA compliant. All participants will complete a daily questionnaire during the study in the evening. Before the smartphone app phase, subjects will initially complete a face-to-face 15–20-minute training session where a research assistant will assist in installing an app on their smartphone devices which they will use to report their daily experiences. They will be given instructions on how to operate the smartphone app and a guide that they may take home with them that will outline the information covered in the training session. They will also be given contact information, should they have any problems or questions with the smartphone app over the course of the study. It will be explained that all data on the app is encrypted, and that the data is sent to a secure server where data is identified by subject ID only. Subjects will also be informed that we will be monitoring the upload of data from the smartphone app to the secure server to verify that everything is working correctly. Upon the completion of all study procedure, all participants will be debriefed about the study.

Data Management and Processing:

Data Management: Research data is collected using Yale University's REDCap system. REDCap is a secure HIPAA compliant web application for building and managing online surveys and databases, supported, and approved by Yale ITS. Research data is exported and stored on a secure shared virtual drive maintained by Yale ITS.

All subjective data are kept in locked cabinets at the Yale Stress Center (YSC), New Haven and are identified only by study ID. Data are de-identified and stored on the workstations at the Yale Stress Center, which are highly secure and HIPPA compliant. Access to YSC workstations is password-restricted and is only available to Dr. Seo and her research staff. All research data is kept in two places--one as a hardcopy in a locked file with records identified only by the participants' study number and the second in computerized databases protected by two-level password systems that are managed by Yale ITS. Upon completion of the study, all hardcopies will be destroyed. The only documents linking participants' names to their study numbers will be the consent forms. These will be stored in a separate locked file cabinet and may only be accessed by Dr. Seo (PI) and relevant study staff.

Safety planning in response to the COVID-19 epidemic

To limit exposure to COVID-19, one-on-one in-person meetings should be avoided as much as possible. Most of procedure will be conducted remotely. However, if one-on-one meetings must be held in person, the following guidelines will be carried out.

Before any study visits, research participants will be screened for COVID-19 symptoms by filling out the COVID-19 questionnaires prior to the study visit at Yale Stress Center (YSC) and at the time of the on-site study visit.

Participant will be asked to fill out YSC safety questionnaire for YSC visits. If study participants say "yes" to any of the COVID-19 related questions, their appointment will be moved to a later date, and they will be directed to the YNHH COVID-19 Support Call Center (203-688-1700 option 1).

The study site will be disinfected before and after each study visit based on CDC guideline. The measurements of temperature and oxygen saturation levels of research staff will be taken for both research personnel and study participants with a non-contact forehead thermometer and a pulse oximeter. If temperature is greater than 99.5 degrees Fahrenheit in subject, the research subjects and study staff will be asked to leave and seek medical attention. If oxygen saturation is below 95% in subject or research staff, participants will not be allowed to participate in research appointment, and research staff will be asked to leave and seek medical attention.

During in-person visits, both participants and research staff should maintain the required distancing (6 feet) and wear a mask. Anybody entering the study site should properly wash their hands with alcohol-based hand sanitizer (containing at least 60% alcohol) or soap and water in protecting against the spread of germs and viruses. In case participants do not have proper masks to wear, a mask and glove will be provided on-site study visits.

5. Genetic Testing N/A ☒
   - **A.** Describe
     - i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
     - ii. the plan for the collection of material or the conditions under which material will be received *Write here*
     - iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
     - iv. the methods to uphold confidentiality *Write here*

   - B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
   - C. Is widespread sharing of materials planned? *Write here*
   - D. When and under what conditions will materials be stripped of all identifiers? *Write here*
   - E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
     - i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
   - F. Describe the provisions for protection of participant privacy *Write here*
   - G. Describe the methods for the security of storage and sharing of materials *Write here*

6. Subject Population: heavy/binge drinkers

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled

in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☒ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

   Inclusion Criteria:
   (1) Aged 18-55 years;
   (2) Ability to read and write English;
   (3) Heavy/Binge Drinkers: Drinking at levels to match heavy or binge drinking groups (NIAAA Clinician Guide, 2005): **Heavy Drinkers (HD):** Regular alcohol use over the past year of, at least 8 standard drinks/wk for women and at least 15 drinks/wk for men. **Binge Drinkers (BD):** Binge drinking patterns (Women: 4 or more drinks; men: 5 or more drinks in one setting).
   (4) **COVID-19 related stress** will be identified on the basis of two validated measures including the COVID Stress Scale (Taylor et al., 2020) and Perceived Stress Scale.(Cohen et al., 1983). The PSS is a widely used measure of stress that provides standardized cut scores.

   Exclusion Criteria:
   (1) Meet current or past DSM-V criteria for Axis I psychiatric disorders including any substance use disorders except for mild alcohol use disorder (AUD), marijuana use disorder, tobacco use disorder, and opioid use disorder.
   (The current study targets alcoholism prevention in risky drinkers, and thus excludes those who already have moderate and severe AUD. However, many risky drinkers often have mild AUD, thus we include this. In addition, marijuana, tobacco, and opioid use disorders are included, given the high comorbidity found between marijuana/opioid use and heavy drinking in general population.)
   (2) Any significant current medical conditions;
   (3) Women: peri- and post-menopausal or pregnant women due to hormonal interactions with stress response;
   (4) Current use of psychotropic and other medications or illicit drugs.

9. How will **eligibility** be determined, and by whom? Write here
   Research staff will determine eligibility. Potential subjects will complete an initial telephone screening and then will be scheduled to meet using video communications with research staff to complete an intake appointment at the Yale Stress Center. Research staff will review the medical history of the participant to ensure all inclusion and exclusion criteria are met, under the supervision of Dr. Seo.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

    The potential risks to the subjects in the proposed study are listed below.

Behavioral assessments, questionnaires, and surveys are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality.
Past experience with these measures indicates that they are acceptable to subjects. Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only patients' code numbers will be recorded on the forms themselves to protect confidentiality. If the subject reports discomfort completing the questionnaires or the visual stimuli task, they are free to drop out at any time without penalty. Any subject that reports emotional discomfort during or after the completion of questionnaires will receive an individual counseling session by a trained clinical staff who is experienced in therapy. The screening of subjects using the inclusion and exclusion criteria, and the comprehensive physical and psychiatric evaluation will minimize the risk of including subjects who are otherwise inappropriate.

PSB Intervention
Participation in the study in completely voluntary. If a participant feels uncomfortable at any time during the intervention, counseling can be provided to address these concerns. Outpatient subjects are free to choose not to take part in this study and stop disclosing their health information at any time.

Smartphone app survey:
Subjects will respond to smartphone surveys as they go about their daily lives, which may occur in the presence of others. However, smartphones are widely used in public for many tasks by people in everyday life and the completion of the surveys will be brief and relatively discrete. Responses gathered on the smartphones will be encrypted and sent to a secure server. Confidentiality will be maintained to the degree permitted by the technology used. Data will be connected with subject ID only. The MetricWire smartphone app has been designed to be compliant with HIPAA regulations. This app is not commercial and research only app and passed Yale IRB and IT review previously. The app encrypts data on participants' phones and while data is wirelessly transferred. The app randomly generates a 24-digit identification code that contains numbers and letters and remains consistent for each subject throughout the smartphone assessment phase. This identification code will be linked by the research team with the numerical Subject ID that is assigned to subjects upon their initial laboratory visit. The data is monitored daily, and if any duplicate data or suspicious activity or pattern is detected in the participant's data, the research team will immediately contact the participant to ensure if a problem or issue has occurred. Also, all smartphones are required to be password protected in order to restrict access to the app other than the participants.

Confidentiality:
All data will be kept confidential except in cases of imminent danger to the participants. Such limits to confidentiality will be clearly explained to participants verbally and in the written consent forms. Confidentiality regarding collected materials will be maintained via a numbered reference system maintained by the investigators. Subjects' names will appear only on a consent form and a "key" form kept by the PI in locked filing cabinets. Only the PI (Dr. Seo), Dr. Sinha (co-investigator) and relevant research staff will have access to any forms specifying both participant name and subject number. All number-coded subjective data will be kept in locked offices with access only to investigators and research staff. In case we obtain eConsent, the completed PDFs will be downloaded and stored in a study folder that can only be accessed with a unique password in a 3-lock Yale ITS managed storage. The e-consent also records the IP address of the participant and displays this information in the file repository in order to help regulate potential duplicate forms from a single IP address. Furthermore, good clinical and research practice procedures and HIPAA regulations will be followed.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
    See above

12. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? minimal
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

    d. For multi-site studies for which the Yale PI serves as the lead investigator:
        i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
        ii. What provisions are in place for management of interim results? *Write here*
        iii. What will the multi-site process be for protocol modifications? *Write here*

Minimal Risk DSMP

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews quarterly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through weekly study meetings, and via email as they are reviewed by the principal investigator. The protocol's funding agency, National Institute on Alcohol Abuse and Alcoholism (NIAAA), and Yale Faculty Account, will be informed of Reportable Events adverse events within 5 days of the event becoming known to the principal investigator.

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Baseline screening, intake, self-report, and interview data will be collected using the web-based REDCap system that is fully supported by Yale and set up and well established at the Yale Stress Center. All rating data will be double-entered for verification. Quality control measures for out-of-range values and error checking programs are well established and will be implemented.

To test the efficacy of the PSB intervention in reducing stress, alcohol craving and use, all analyses will be conducted using the intent-to-treat sample and each hypothesis will be tested using General Linear models (GLMs) (Diggle, Heagerty, Liang, & Zeger, 2002) examining the main effects of Time (pre-/post-/Follow-up).

For smartphone data, alcohol use outcomes obtained from mobile app will be defined in both dichotomous and continuous manner (e.g., time to first drink or time to heavy drinking after the prevention; percent days abstinence and heavy drinking days (men: 5 or more; women: 4 or more) as continuous measures). Frequency, the total number of days of stress or alcohol use; and quantity, the average amount of alcohol use (number of drinks) or average levels of stress per occasion will also be computed. Multiple regression and mixed effects regression models (MRMs) will be used to evaluate the effects of prevention on prospective repeated assessments of stress, emotion, alcohol use, craving, and mood related data. Specific MRMs will model within person time varying and invariant data from daily stress and substance use patterns to assess group differences and examine whether behavioral changes after prevention predicts future stress and alcohol-related behaviors.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

B. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: 100
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: n/a

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☒ Web-based clinical trial registries	☐ Clinicaltrails.gov
☒ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:
a. Describe how potential subjects will be identified. *Write here*

Subjects will be recruited through flyers posted in the community, and advertisements on social media/internet sites. Potential subjects will complete an initial telephone screening or be asked to complete a Qualtrics prescreening survey and then will be scheduled to meet with research staff to complete an intake appointment at the Yale Stress Center.

For the COVID study, participants with COVID-19 stress, Participants will also be recruited from the regions that are most significantly affected by COVID-19 in the US (based on the Center for Disease Control and Prevention (CDC), www.cdc.gov) in addition to Connecticut area by placing targeted advertisements on social networking outlets (e.g., Craigslist, Facebook, and Twitter) or other local platforms.

b. Recruitment of participants will also be conducted through a dedicated Yale Stress Center (YSC) Recruitment Channel specializing in coordinating centralized recruitment of participants into center studies. This recruitment team that has a well-developed treatment referral network comprising a variety of treatment, social service and addiction referral sources in the Greater New Haven area.

   The YSC Recruitment Team provides coordinated centralized recruitment of participants into YSC affiliated studies typically through the placement of weekly advertisements in area newspapers, posting flyers in local areas. In addition, referrals from the Yale Substance Abuse Treatment facilities will also be a source of patients for study participation. Staff at these facilities will be given flyers detailing the study and encouraged to have their clients contact us for screening. This approach has allowed us to recruit subjects from a variety of race and socioeconomic backgrounds. Describe how potential subjects are contacted.

   Potential subjects will contact us via our toll-free phone number, which can be obtained from the study advertisements on social media/internet sites, or flyers posted in the community, and be screened by research staff.

c. Who is recruiting potential subjects? Research staff at the Yale Stress Center

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

   Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

   ☐Yes, all subjects
   ☐Yes, some of the subjects
   ☒No

   If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

   Choose one:

   ☐ For entire study
   ☒ For recruitment/screening purposes only
   ☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   Following the initial telephone screening, eligible participants will meet with a research assistant to obtain informed consent. The consent process can be done either in person or remotely via a REDCap eConsent if needed. The following procedure will be implemented for the eConsent procedure.

   First, the potential participants will receive a secure REDCap link to view the consent form and have a remote session with research staff. After reviewing the consent form, they will go over the study procedure and all aspects of the consent form with staff and have enough time for study Q & A and the risk involved before making decisions. If they agree to participate, they will be asked to sign their name using a mouse on an eConsent form. Then, they will select "Next Page" at the bottom and a read only copy of the consent will be generated that they can review, download, and/or print. Also, at the bottom of the page they will view "I certify that all the information in the document above is correct, and I understand that signing this form electronically is the equivalent of signing a physical document." Once this is selected, they will be able to submit the consent from. The completed PDFs will be downloaded and stored in a study folder that can only be accessed with a unique password in a 3-lock Yale ITS managed storage. The e-consent also records the IP address of the participant and displays this information in the file repository in order to help regulate potential duplicate forms from a single IP address.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   After the participant has read over the consent form, research staff will further explain the study, including the risks involved. Research staff will ask the potential subject how well they understood the consent, and answer questions they may have.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Non-English speaking individuals will not be recruited for this study.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only) telephone screen*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☒
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☒

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Results of the psychological assessments, self-reports, and data collected during pre-intervention, post-intervention, and interventions, will be collected and used for research. The proposed study will be conducted by specialized and trained research staff using standardized and psychosocial assessments. Data collected and analyzed in the study will be derived from two main sources: semi-structured clinical interviews and self-rating scales: psychiatric history, medical history, demographic self-reports of age, race, socioeconomic status, marital status, educational and occupational levels.

2. How will the research data be collected, recorded and stored?

   Research data will be collected on paper assessments and using Yale University's REDCap system. All research data is stored in two places--one as a hardcopy in a locked file, with records identified only by the participant's study number, and the second in computerized databases protected by two-level password systems on Yale encrypted desktop computers.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   Upon enrollment, all study subjects will be assigned a unique study number. The study number—and no personal identifiers—will be used as labels for study records, samples and any other related research documentation. All electronic and digital files will be stored on the secure Yale network, and the PC accessing the network will be password protected and encrypted. All paper files, such as consent forms, will be stored in a locked file cabinet in a locked office and access is limited to members of the study research team.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   Upon completion of study and data analysis, a professional information protection, storage, and disposal company will be retained to dispose of research files and informed consent documentation.

6. If appropriate, has a Certificate of Confidentiality been obtained? Yes, we obtained CoC.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There are some potential benefits of the proposed study. First, monitoring drinking, learning stress reduction and breathing modulation may be helpful to some subjects. Second, this study will evaluate the PSB as a potential alcoholism prevention program. If the efficacy of the PSB intervention is supported, our findings will identify an effective prevention strategy that can be delivered in the participants' community. Given these valuable benefits to the subjects and their community and the minimal risks of the study procedures, we believe that the study risks are reasonable in relation to the potential benefits.

Also, stress reduction and breathing methods may help participants self-regulate distress and emotion without over-reactivity. Thus, these skills may then allow participants to be particularly effective in implementing knowledge about regulating craving and drinking urge and to adopt healthier choices and habits.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   Subjects need not participate in this study to receive stress management or breathing training or substance use counseling.

   Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   For the 4-week intervention: participants will be compensated for their time taken for a series of study appointments and participations over the course of 2.5 months of the study period. The total amount that each participant may receive is up to $778 per participant for completing all aspects of the study (baseline assessments, 4-week digital interventions, 28-day daily monitoring, and a follow-up evaluation at the end of 30 days).

Baseline Assessments: Participants in the assessment and intervention groups will be paid up to $100 for screening, DSM-5 diagnosis, & 4-5 online baseline assessments ($20 per session).

4-week Period:
Intervention group
Participant will receive up to $488 for completing the study procedure related to 4-week intervention for treatment sessions, smartphone app surveys and post-treatment evaluation.

Sessions: Participants will receive up to $200 including $20 for per session (two sessions weekly; 8 sessions in total (8 x $20 = $160) and bonus. An additional $20 bonus will be rewarded for the completion of all 4 sessions every 2 weeks of treatment during the 4-week treatment period.

Smartphone surveys: They will also receive up to $248 for the completion of a 28-day daily smartphone app surveys including $3 for each daily intervention exercise (28 x $3 = $84), smartphone monitoring survey (28 x $3 = $84), and weekly bonus. They will receive an additional weekly bonus of $20 for completing 100% (14/14 surveys; submitted a total number of two surveys (daily evening surveys + daily intervention exercise) per week), $18 for completing at least 92.5% (13/14 surveys; submitted a total number of two surveys (daily evening surveys + daily intervention exercise) per week) or $16 for completing at least 86% (12/14 surveys; submitted a total number of two surveys (daily evening surveys + daily intervention exercise) per week) of the surveys in each week. Both the daily evening survey and daily intervention exercise must be completed for a day to count towards the weekly bonus.

At the end of treatment, they will also receive $40 for a post assessment at the end of 4-week intervention.

Follow-up evaluations: Participant will be compensated for their time up to $190 for 30-days follow-up after treatment. For daily monitoring follow-up assessments, they will be paid $3 for daily survey over 30 days (30 x $3 = $90). They will also receive additional $20 biweekly bonus for completing at least 100% (14 out of 14 surveys), $15 for 90% (13 out of 14 surveys), and $10 for 80% (12 out of 14 surveys) of every 14-day survey. Additionally, they will also receive $60 for a video session and completing online evaluation assessments at the end of the 30-day follow-up period.

Therefore, the total that the intervention group may be reimbursed for their time if they complete the study, attend all 8 treatment sessions and a 100% completion rate for the smartphone surveys, is $778.

2. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   All parts of the research process will be provided at no cost to the subjects.

3. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

While medical therapy will be offered for any physical injuries sustained as a consequence of participation in this research, the subject and their insurance carrier will be responsible for the cost of such treatment. Financial compensation for injury is not available.

a. Will medical treatment be available if research-related injury occurs? Medical therapy will be offered for any physical injuries sustained as a consequence of participation in this research.
b. Where and from whom may treatment be obtained? Any licensed facility / practitioner
c. Are there any limits to the treatment being provided? *No*
d. Who will pay for this treatment? The subject and their insurance carrier will be responsible for the cost of treatment. Financial compensation for injury is not available.
e. How will the medical treatment be accessed by subjects? Subjects will be encouraged to receive services through practitioners in any licensed facility where their insurance company may cover their medical expenses.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By

submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

References

Abramson, J. H. (1966). The cornell medical index as an epidemiological tool. *Am J Public Health Nations Health, 56*(2), 287-298 PMC1256865.

Adamson, M. (2020). *Psychological Stress Associated with the COVID-19 Crisis*. Stanford University. Retrieved from https://www.nlm.nih.gov/dr2/Psychological_Stress_Associated_with_the_COVID-19_Crisis_14.pdf

Adamson, S. J., Kay-Lambkin, F. J., Baker, A. L., Lewin, T. J., Thornton, L., Kelly, B. J., & Sellman, J. D. (2010). An improved brief measure of cannabis misuse: The Cannabis Use Disorders Identification Test-Revised (CUDIT-R). *Drug and Alcohol Dependence, 110*(1-2), 137-143. doi:10.1016/j.drugalcdep.2010.02.017

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of general psychiatry, 4*, 561-571.

Bernstein, D. P., Ahluvalia, T., Pogge, D., & Handelsman, L. (1997). Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *J Am Acad Child Adolesc Psychiatry, 36*(3), 340-348. doi:10.1097/00004583-199703000-00012

Bohn, M. J., Krahn, D. D., & Staehler, B. A. (1995). Development and initial validation of a measure of drinking urges in abstinent alcoholics. *Alcoholism, clinical and experimental research, 19*(3), 600-606.

Brown, R., & Gerbarg, P. (2012). *The Healing Power of the Breath: Simple Techniques to Reduce Stress, Anxiety, Enhance Concentration and Balance Your Emotions*. Boston, Massachusetts: Shambhala Publications, Inc.

Butler, S. F., Budman, S. H., Fernandez, K. C., Houle, B., Benoit, C., Katz, N., & Jamison, R. N. (2007). Development and validation of the Current Opioid Misuse Measure. *Pain, 130*(1-2), 144-156. doi:10.1016/j.pain.2007.01.014

Callinan, S., & MacLean, S. (2020). COVID-19 makes a stronger research focus on home drinking more important than ever. *Drug Alcohol Rev*. doi:10.1111/dar.13125

Chung, J. (2020). *Psychosocial Impact of COVID-19 Survey*. National Institute of Mental Health (NIMH). Retrieved from https://www.phenxtoolkit.org/toolkit_content/PDF/NIMH_DailyFunctioning.pdf

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore, 23*(2), 129-138.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav, 24*(4), 385-396 PMID6668417.

Costa, P. T., Jr., & McCrae, R. R. (1985). Hypochondriasis, neuroticism, and aging. When are somatic complaints unfounded? *Am Psychol, 40*(1), 19-28.

Diggle, P. J., Heagerty, P., Liang, K. Y., & Zeger, S. L. (2002). *Analysis of longitudinal data* (2nd ed.). New York: Oxford.

Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K., & Rutigliano, P. (2000). The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *Journal of consulting and clinical psychology, 68*(1), 134-144.

First, M., Williams, J., Karg, R., & Spitzer, R. (2015). *Structured Clinical Interview For DSM-5, Research Version*. Arlington, VA: American Psychiatric Association.

Gerbarg, P., & Brown, R. (2016). Neurobiology and neurophysiology of breath practices in psychiatric care. *Psychiatric times, 33*(11), 22-25.

Ingjaldsson, J. T., Laberg, J. C., & Thayer, J. F. (2003). Reduced heart rate variability in chronic alcohol abuse: relationship with negative mood, chronic thought suppression, and compulsive drinking. *Biol Psychiatry, 54*(12), 1427-1436. doi:S0006322302019261 [pii]

Johns-Hopkins, U. (2020a). *COVID-19 Community Response Survey: Social Distancing Impacts*. Bloomberg School of Public Health, Johns Hopkins University Retrieved from https://www.phenxtoolkit.org/toolkit_content/PDF/JHU_C4WARD_Social_Distancing.pdf

Johns-Hopkins, U. (2020b). *COVID-19 Community Response Survey: Substance Use*. Bloomberg School of Public Health, John Hopkins University. Retrieved from https://www.phenxtoolkit.org/toolkit_content/PDF/JHU_C4WARD_Substance_Use.pdf

Kabat-Zinn, J. (2013). *Full Catastrophe Living: Using the wisdom of your body and mind to face stress, pain, and illness*. New York, NY: Dell publishing, a division of Bantam.

Kadden, R., Carroll, K., Donovan, D., Coney, N., Monti, P., Abrams, D., . . . Hester, R. (2003). *Cognitive-behavioral coping skills therapy manual*. Rockwille, Maryland: National Institute on Alcohol Abuse and Alcoholism.

Karpyak, V. M., Romanowicz, M., Schmidt, J. E., Lewis, K. A., & Bostwick, J. M. (2013). Characteristics of Heart Rate Variability in Alcohol-Dependent Subjects and Nondependent Chronic Alcohol Users. *Alcohol Clin Exp Res*, PMID24117482. doi:10.1111/acer.12270

Kober, H., Brewer, J. A., Height, K. L., & Sinha, R. (2017). Neural stress reactivity relates to smoking outcomes and differentiates between mindfulness and cognitive-behavioral treatments. *Neuroimage, 151*, 4-13. doi:10.1016/j.neuroimage.2016.09.042

Kraemer, H. C., Wilson, G. T., Fairburn, C. G., & Agras, W. S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry, 59*(10), 877-883.

Mann, R. E., Sobell, L. C., Sobell, M. B., & Pavan, D. (1985). Reliability of a family tree questionnaire for assessing family history of alcohol problems. *Drug and alcohol dependence, 15*(1-2), 61-67.

Naimi, T. S., Brewer, R. D., Mokdad, A., Denny, C., Serdula, M. K., & Marks, J. S. (2003). Binge drinking among US adults. *JAMA, 289*(1), 70-75 PMID12503979.

Perkins, H. W. (1999). Stress-motivated drinking in collegiate and postcollegiate young adulthood: life course and gender patterns. *J Stud Alcohol, 60*(2), 219-227 PMID10091960.

Perlmutter, M., & Nyquist, L. (1990). Relationships between self-reported physical and mental health and intelligence performance across adulthood. *J Gerontol, 45*(4), P145-155.

Quintana, D. S., Guastella, A. J., McGregor, I. S., Hickie, I. B., & Kemp, A. H. (2013). Heart rate variability predicts alcohol craving in alcohol dependent outpatients: further evidence for HRV as a psychophysiological marker of self-regulation. *Drug Alcohol Depend, 132*(1-2), 395-398 PMID23601925. doi:S0376-8716(13)00084-7 [pii]
10.1016/j.drugalcdep.2013.02.025

Rodriguez, L. M., Litt, D. M., & Stewart, S. H. (2020). Drinking to cope with the pandemic: The unique associations of COVID-19-related perceived threat and psychological distress to drinking behaviors in American men and women. *Addict Behav, 110*, 106532. doi:10.1016/j.addbeh.2020.106532

Runyan, J. D., Steenbergh, T. A., Bainbridge, C., Daugherty, D. A., Oke, L., & Fry, B. N. (2013). A smartphone ecological momentary assessment/intervention "app" for collecting real-time data and promoting self-awareness. *PLoS One, 8*(8), e71325. doi:10.1371/journal.pone.0071325

Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. *J Pers Assess, 66*(1), 20-40. doi:10.1207/s15327752jpa6601_2

Sebena, R., El Ansari, W., Stock, C., Orosova, O., & Mikolajczyk, R. T. (2012). Are perceived stress, depressive symptoms and religiosity associated with alcohol consumption? A survey of freshmen university students across five European countries. *Subst Abuse Treat Prev Policy, 7*(1), 21 PMC3395565. doi:10.1186/1747-597X-7-21

Seo, D., Lacadie, C. M., Tuit, K., Hong, K. I., Constable, R. T., & Sinha, R. (2013). Disrupted Ventromedial Prefrontal Function, Alcohol Craving, and Subsequent Relapse Risk. *JAMA Psychiatry, 70*(7), 727-739. doi:1684869 [pii]
10.1001/jamapsychiatry.2013.762

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological Momentary Assessment. *Annual Review of Clinical Psychology, 4*(1), 1-32. doi:10.1146/annurev.clinpsy.3.022806.091415

Shively, C. A., Mietus, J. E., Grant, K. A., Goldberger, A. L., Bennett, A. J., & Willard, S. L. (2007). Effects of chronic moderate alcohol consumption and novel environment on heart rate variability in primates (Macaca fascicularis). *Psychopharmacology (Berl), 192*(2), 183-191. doi:10.1007/s00213-007-0709-z

Sinha, R., Fox, H. C., Hong, K. A., Bergquist, K., Bhagwagar, Z., & Siedlarz, K. M. (2009). Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. *Neuropsychopharmacology, 34*(5), 1198-1208 PMCID2734452. doi:npp200878 [pii]
10.1038/npp.2008.78

Sobell, L. C., & Sobell, M. B. (1992). Timeline Follow-back: A technique for assessing self-reported ethanol consumption. In L. Allen & R. Litten (Eds.), *Measuring Alcohol Consumption: Psychosocial and Biological Methods* (pp. 41-72). Totowa, NJ: Humana Press.

Spielberger, C., & ., G. R. (1970). *Test manual for the State-Trait Anxiety Inventory*. Palo Alto, CA Consulting Psychologists Press, Inc.

Stormark, K. M., Laberg, J. C., Nordby, H., & Hugdahl, K. (1998). Heart rate responses indicate locked-in attention in alcoholics immediately prior to drinking. *Addict Behav, 23*(2), 251-255 PMID9573428. doi:S0306-4603(97)00026-9 [pii]

Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The pain catastrophizing scale: development and validation. *Psychological assessment, 7*(4), 524.

Taylor, S., Landry, C. A., Paluszek, M. M., Fergus, T. A., McKay, D., & Asmundson, G. J. G. (2020). Development and initial validation of the COVID Stress Scales. *J Anxiety Disord, 72*, 102232. doi:10.1016/j.janxdis.2020.102232

Thayer, J. F., Ahs, F., Fredrikson, M., Sollers, J. J., 3rd, & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev, 36*(2), 747-756 PMID22178086. doi:S0149-7634(11)00207-7 [pii]
10.1016/j.neubiorev.2011.11.009

Thayer, J. F., Hall, M., Sollers, J. J., 3rd, & Fischer, J. E. (2006). Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. *Int J Psychophysiol, 59*(3), 244-250. doi:S0167-8760(05)00269-2 [pii]
10.1016/j.ijpsycho.2005.10.013

Turner, R. J., & Lloyd, D. A. (2004). Stress burden and the lifetime incidence of psychiatric disorder in young adults: racial and ethnic contrasts. *Arch Gen Psychiatry, 61*(5), 481-488. doi:10.1001/archpsyc.61.5.48161/5/481 [pii]

Vaschillo, E. G., Bates, M. E., Vaschillo, B., Lehrer, P., Udo, T., Mun, E. Y., & Ray, S. (2008). Heart rate variability response to alcohol, placebo, and emotional picture cue challenges: effects of 0.1-Hz stimulation. *Psychophysiology, 45*(5), 847-858 PMCID2964051. doi:PSYP673 [pii]
10.1111/j.1469-8986.2008.00673.x

Vogel-Sprott, M., Chipperfield, B., & Hart, D. M. (1985). Family history of problem drinking among young male social drinkers: reliability of the Family Tree Questionnaire. *Drug and alcohol dependence, 16*(3), 251-256.

Wechsler, H., Lee, J. E., Kuo, M., Seibring, M., Nelson, T. F., & Lee, H. (2002). Trends in college binge drinking during a period of increased prevention efforts. Findings from 4 Harvard School of Public Health College Alcohol Study surveys: 1993-2001. *J Am Coll Health, 50*(5), 203-217 PMID11990979
doi:10.1080/07448480209595713

Wray, T. B., Merrill, J. E., & Monti, P. M. (2014). Using Ecological Momentary Assessment (EMA) to Assess Situation-Level Predictors of Alcohol Use and Alcohol-Related Consequences. *Alcohol Res, 36*(1), 19-27.