IRB# 2000027787

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

Protocol Title: Preliminary Effectiveness of Remotely Monitored Blood Alcohol Concentration Device as Treatment Modality

Principal Investigator: Frank D. Buono, Ph.D.

Version Date: June 1, 2020

(*If applicable*) Clinicaltrials.gov Registration #: NCT04380116

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

APPROVED BY THE YALE UNIVERSITY IRB 6/9/2020

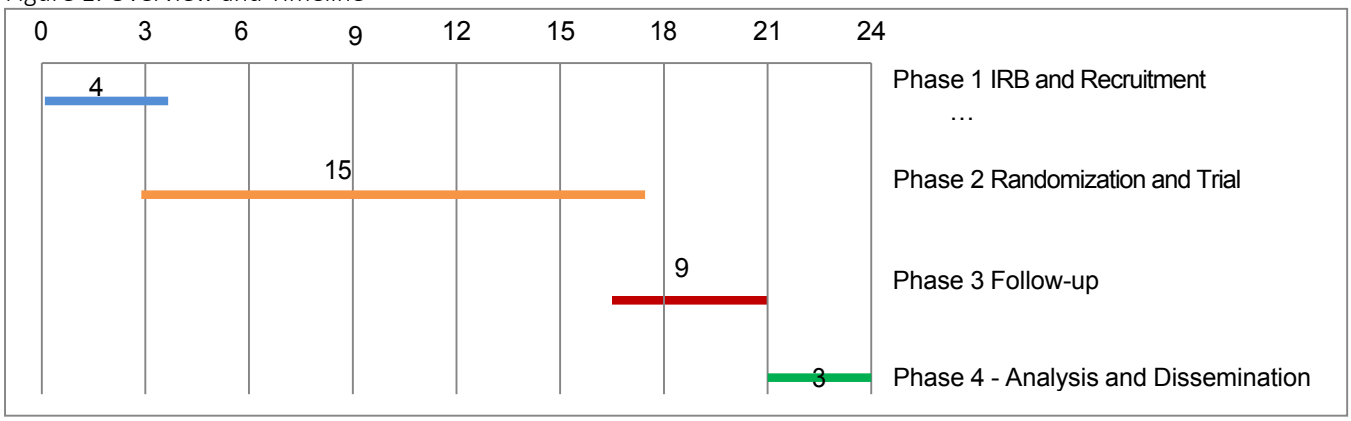
IRB# 2000027787

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   The purpose of the current study is to evaluate the usage and acceptability of the Soberlink's blood alcohol concentration (BAC) unit in collaboration with Aware treatment to assess increased sobriety within patients suffering from alcohol use disorder (AUD).
   The specific AIMS will be:
   1) To determine the effectiveness of Soberlink's ability to increase abstinence
   2) To evaluate the impact of Soberlink's device on the participant based on their quality of health and sobriety.
   3) To evaluate the extent to which need for higher levels of follow-up care and treatment is reduced for individuals who have had access to the Soberlink device.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   The duration of the time of the study will be two years to complete. This will include (as seen on Figure 1) time for IRB approval and recruitment, randomization and completion the study, follow-up and lastly analysis with dissemination.

Figure 1: Overview and Timeline



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.

Alcohol dependence (AD) has been characterized as a chronic disorder that presents an enduring vulnerability to relapse. Unfortunately, AD treatment is commonly delivered as a series of acute care sessions (Etheridge, Craddock, Dunteman, & Hubbard, 1995; McLellan, Lewis, O'Brien, & Kleber, 2000), which means that individuals seeking treatment often face the challenge of maintaining sobriety upon returning to the same environment where they had struggled with alcohol dependence previous to seeking treatment. Studies have shown that 40%–60% of patients treated for alcohol problems relapse within 3 months, and this rate increases to 70%–80% within 12 months (Bradizza, Stasiewicz, & Paas, 2006; McLellan et al., 2000; Witkiewitz & Marlatt, 2004). medical costs associated with alcohol use disorders (AD) are over $120 billion per year, until very recently, there has been relatively little involvement of physicians or other general healthcare providers in the treatment of AUDs (Sacks et al., 2015). By convention, most contemporary AUD treatment has been delivered outside mainstream healthcare by specialty "treatment programs" that are time-limited by insurance restrictions and highly structured to deliver a standardized "program" of care (McLellan et al., 2005; Foll et al., 2009).

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Outcome research has typically concentrated upon program "graduation" rates and "posttreatment" abstinence as standard measures of treatment "success" or "failure" (McLellan et al., 2005).There are conceptual (McKay and Hiller-Sturmhöfel, 2011; McLellan et al., 2014) and some methodological indications (Kim et al., 2011; Oslin et al., 2014) that ADs may be better managed using a chronic illness approach. However, for the reasons described above, there is not yet the evidence-base needed to guide a personalized, chronic care approach to the treatment of ADs, or even to guide the use of monitoring technology within that treatment approach. Previous research on the use of mobile phones for AD treatment include telephone-based monitoring of medication adherence (Stoner & Hendershot, 2012), behavioral self-control training to withstand cravings (Yu et al., 2012), and video-recording breathalyser tests to measure breath alcohol content (BrAC) combined with contingency management procedures (Alessi & Petry, 2013). Two recent studies used, the Addiction-Comprehensive Health Enhancement Support System (ACHESS) (Gustafson et al., 2014) and Location-Based Monitoring and Intervention for Alcohol Use Disorders (LBMI-A) (Dulin, Gonzalez, & Campbell, 2014) to monitor patients with AD. These two smartphone applications with composite functions have proven effective in reducing the incidence of hazardous drinking and promoting abstinence.

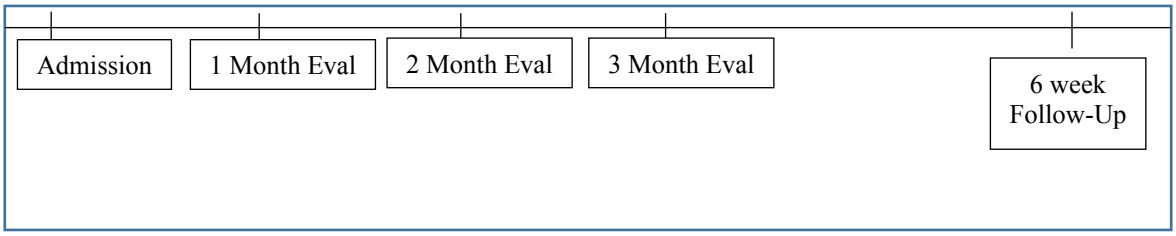
Soberlink is a comprehensive alcohol monitoring system designed to remotely monitor a person's Blood Alcohol Concentration (BAC). Combining a professional grade handheld breathalyzer with wireless connectivity, the technology includes real-time facial recognition, robust tamper detection and real-time alerting. The Soberlink System also provides professionals with a password protected, HIPAA compliant healthcare portal where they can set up a variety of advanced reporting tools. Soberlink is designed and assembled in the United States and is one of the few FDA 510(k) cleared medical devices in remote alcohol monitoring. The breathalyzer device uses fuel cell technology to detect BAC, is handheld, and includes an embedded camera. It uses wireless technology to send the data in real-time. The cloud-based monitoring system includes a scheduler that automatically tracks scheduled tests and sends reminders to the client for testing. Retesting is automatically scheduled if a positive test is received or if a client's identity cannot be verified. The device locks out for 15 minutes to ensure alcohol evaporates before the next test. Facial Recognition software ensures identity is approved or declined in real-time. Artificial intelligence is used to report on testing and Green, Yellow and Red visual icons are used in all reporting to identify events.

Aware Recovery Care (ARC) is an in-home addiction treatment program that provides highly intensive, rigorously monitored, 52 weeks of intensive outpatient care, based on a chronic disease model of care. This model was first used in 2012 and delivers a four-phased, year-long program treating substance use disorder. The approach implements principles of evidence-based practices including Motivational Interviewing, Cognitive Behavioral Therapy, and Dialectical Behavioral Therapy, in the home setting. Additionally, all families are offered education and the opportunity to participate in the treatment process. ARC works to transform the home environment into a healthy, healing environment for clients and families to recover. ARC supports clients in creating and maintaining both structure and recovery that is tailored to each individual's needs.

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.

Study Sites/Feasibility. The study will be conducted in at clinical office for Aware Recovery Center (North Haven, CT). The census of the facility on average recruits 38 new individuals a month and they currently have 300. This will be the first study, completed at this site, which is a randomized control treatment design.
Procedure:
(www.randomized.com). Individuals will be placed into one of two conditions (Soberlink+Aware; Named Group 1) or (Aware; Named Group 2). Both groups will be consented by either the principal investigator or the research assistants who will be present at all screenings and ensured that they understand their rights. Participants will be told they are allowed to leave or withdraw for the study without penalty or hindering the relationship between themselves and Aware Recovery.

Figure 2: Time Intervals for Assessments



Group 1
This group will include access to the Aware treatment (see 'Aware treatment' below), and access to the Soberlink device. A research assistant will train the participant and provide an orientation (see orientation to Soberlink below) for what will be taught. All participants will be complete screening and outcome assessments, along with using the Soberlink device for the first time. The participant's Soberlink device will be set up to test participants twice a day. Reminder emails (see attached reminder emails) will be sent out the day before, and the day of the 1 month, 2 month and 3-month surveys that will be completed online in the participant's home through a secure link sent directly to them. Subsequent phone calls will be made by the research assistant to the participant if they have missed their evaluation. Upon completion of the surveys, the participants in group 1 will be paid, and reminded of the subsequent follow-ups. The estimated time of the process will take 45 to 60 minutes to complete.

Orientation to Soberlink
Patients assigned to the Soberlink-Aware condition will receive a 30-minute orientation to the Soberlink, including an initial their first administration of the BAU. Participants will learn the following:

1. The Soberlink System consists of a wireless Breathalyzer that uses a professional grade fuel cell sensor to detect alcohol levels at an accuracy of +/-.005 BAC.
2. The device also has an embedded camera and uses Facial Recognition software to automatically identify the client at the end of the test.
3. The participant will have a set testing schedule that consists of a minimum of 2 tests per day. The participant will have a test window of 2 hours with a Late window of 1 hour.
4. When the participant blows into the Soberlink device, it will capture the BAC level while the embedded camera takes a photo of the participant during the test

The breathalyzer device uses fuel cell technology to detect BAC, is handheld, and includes an embedded camera. It uses wireless technology to send the data in real-time. The cloud-based monitoring system includes a scheduler that automatically tracks scheduled tests and sends reminders to the client for testing. Retesting is automatically scheduled if a positive test is received or if a client's identity cannot be verified. The device locks out for 15 minutes to ensure alcohol evaporates before the next test. Facial Recognition software ensures identity is

approved or declined in real-time. Artificial intelligence is used to report on testing and Green, Yellow and Red visual icons are used in all reporting to identify events.

All individuals in group 1 will be required to complete two BAC's per day. A testing window will be scheduled with each individual between 7am to 9am (morning BAC) and 8pm to 10pm (evening BAC). During the testing window, all individual in this group can provide the BAC at any time within the window, all tests performed outside the window will be recorded but counted as unscheduled test on the BAC spreadsheet. All participants can opt in to receive a text-reminder sent by Soberlink's automated server to remind the patient about their morning and evening BACs.

Individuals who miss two consecutive BAC's will be followed up by either Research Assistant or the PI. Individuals who miss four consecutive BAC's without contact of the PI or the research assistant will be temporarily hold unless the individual has expressed thoughts of leaving the study prematurely. Missing more than six consecutive BACs without communication will result in termination from the study by the PI. A pilot study contacted at Aware prior to the PI being involved demonstrated little reactivity or premature departure for those who had access to the Soberlink device.

Aware/Group 2 :

This group will not receive access or training to Soberlink device, however they will be recruited to complete the same set of surveys at the same time intervals (See Figure 2). Upon completion of the surveys, the participants in group 2 will be paid, and told reminded the subsequent follow-ups. Reminder emails (see attached reminder emails) will be sent out the day before, and the day of the 1 month, 2 month and 3 month evaluations. Subsequent phone calls will be made by the research assistant to the participant if they have missed their evaluation. The estimated time of the process will take under 30 minutes to complete.

Aware Treatment: Aware Recovery Care (ARC) is an in-home addiction treatment program that provides highly intensive, rigorously monitored, 52 weeks of intensive outpatient care, based on a chronic disease model of care. The approach implements principles of evidence-based practices including Motivational Interviewing, Cognitive Behavioral Therapy, and Dialectical Behavioral Therapy. Additionally, all families are offered education and the opportunity to participate in the treatment process. The client's individualized treatment team consists of a licensed professional (nurse or master's level clinician), two Certified Recovery Advisors (CRAs), and an LMFT. The clients care team is overseen by a master's level alcohol and drug counselor, an advanced practicing nurse, and an addiction psychiatrist. The licensed professional is responsible for leading the team, collaborating with external providers, communicating with family members and providing referrals to external providers as needed. The CRAs are lived-experience advisors, at least one of whom is both age and gendered match in order to provide a more intimate therapeutic relationship. CRAs are responsible for delivering a staged biopsychosocial curriculum. Familial involvement is another key component of this model, with education and frequent communication provided. All care teams include a Licensed Marriage and Family Therapist for 6 family therapy sessions, as well as 4 family education sessions delivered by a special trained family education facilitator.

Randomization. At the randomization visit, the research assistant will conduct assessments to evaluate alcohol use. Eligible patients will be assigned to one of the two groups using randomization sequence. The randomization sequence will allow for equal representation between two groups without bias on gender, age or ethnicity given all individuals will be categorized as single variable

Assessments:

We are planning to assess a broad range of subject characteristics, process measures and treatment outcomes over the 3-month trial and at the 6 week post treatment follow-up (See Table 1). Baseline assessments are designed to ensure that patients meet eligibility criteria and that important predictor variables such as cognitive impairment are assessed. Baseline measures include evaluation and understanding of the extent of the AUD issue from a several different vantages points. Primary outcome measures include reductions in days per week of use and negative BAU screens for alcohol. Monthly assessments will take approximately 30 minutes and monthly and follow-up's 45 minutes. Patients will be paid $10 for the baseline and monthly assessments, $25 for follow-up assessments (up to $65 total).

Table 1. List of Assessments

Screening & Baseline Assessments
a) Generalized Anxiety Disorder (GAD-7) will be used to assess for generalized anxiety
b) The Structured Clinical Interview for DSM-V (SCID) will be used to assess lifetime and current DSM- V substance use and Axis I and II psychiatric disorders[181] and screen patients for psychiatric eligibility.
c) Patient Health Questionnaire (PHQ-9) will be used for depression symptoms for the past 2 weeks.
d) Substance Use History will assess frequency, intensity and duration of use and route of administration of drugs.
e) Alcohol Abstinence Self-Efficacy Scale will evaluate the participant's beliefs of alcohol usage.
Outcome Measures.
a) Soberlink (BAC): sensor to detect alcohol levels at an accuracy of +/-.005 BAC. BAC is established by the manufacturer based on predetermined cut off points
b) The Time Line Follow Back (TLFB), administered by research administer onto a secure web-server. Will be used to collect self-reported frequency, quantity and route of administration of prescription opioids, cocaine, alcohol and other drugs use during the preceding 30 days, and use [185-187]
c) Quality of Life Scale is a self-directed survey that assess the quality of life of the individual.
d) Soberlink Use Survey is a self-directed survey that evaluates the effectiveness of the device.
e) The Drug Risk Response Test (DRRT) [189,190] is a role-playing assessment of coping responses to drug use risk situations, and takes 8-10 minutes to complete. The instrument is composed of six audio-taped scenarios. Patients are instructed to imagine that they are in the situation and provide a detailed account to how they would respond to that situation. Patient accounts are recorded and scored by trained evaluators. The instrument provides 4 measures: the number of coping responses, the number of activities per response, the quality of the best response and the quality of the overall response. The measure has been shown to predict days of drug abstinence
f) AUDIT C- is brief alcohol screen that reliably identifies patients who are hazardous drinkers or have active alcohol use disorders.

Data monitoring procedures involve an organizational structure of clearly defined tasks assigned to all research personnel involved in the conduct of this study. The organizational structure used to ensure quality of data in this project include: 1) extensive training and close supervision of research assistants in data collection;

2) direct entry of most data at time of collection; and 3) utilization of on-line error- checking procedures. The PI supervises data procedures. All error corrections are fully documented in the research records of the study. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research. Data entry and review in this study will be conducted using a web-based data collection and monitoring system. Another set of automatic email reports, sent on a weekly or less frequent basis, provides a set of designated recipients (e.g., the PI or Project Director) with information about study logistics, such as number of subjects enrolled, number of subjects active in the protocol, gender composition of the sample, percentage of missing data by each assessment instrument, or any other information necessary to monitor the progress of the project and the compliance with the protocol. A fully computerized system allows this type of monitoring without furnishing investigators with data that could influence the outcome of the study. The system meets the highest security and reliability standards. All connections to the systems are secured and encrypted using 128-bit strong encryption protocols and only authorized users are able to access the system.

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: Provide a detailed description of the types of human subjects who will be recruited into this study.
   We will recruit 110 individuals with alcohol use disorder as diagnosed by the DSM-5. They will be recruited at Aware Recovery Center in North Haven, CT.

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) are at least 21 years old, 2) currently enrolled at Aware In home treatment, and 3) Primary or secondary DSM-5 diagnosis of alcoholism use disorder (AUD).

   Exclusion Criteria: 1) Current suicide or homicide risk, 2) meet criteria for DSM-IV current psychotic disorder, or bipolar disorder, 3) does not have phone access with text message capabilities , 4) Unable to read or understand English, 5) Unable to complete the study because of anticipated incarceration or move, 6) Life-threatening or unstable medical problems, 7) No course of current or pending legal action, 8) Soberlink results being used for child custody or legal circumstance.

9. How will eligibility be determined, and by whom?
   Subjects will be interviewed by a trained and supervised research assistant to determine interest in participating in the study and eligibility. Participants will be interviewed at the Aware facility prior during the admission process, or via Zoom or telephone if the subject is unable to present to the clinic, using standardized psychological assessments or will complete similar standardized self-report forms. Eligibility will be evaluated by the research assistant and reviewed with the project director or PI prior to initiation

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
    The main risk associated with the study is the possibility that confidential information obtained during the study will be disclosed, given the social and legal sanctions associated with the use of psychoactive substances and psychiatric symptoms. Patient names and other identifying information do not appear on research records. Finally, we will clearly explain our mandated obligation to report incidents, as well as suspicion of child abuse or neglect, and risk of harm to self or others, and advise subjects that continued alcohol use alone does not require reporting to child protection services.

    Soberlink: All Soberlink results are sent directly from devices to Soberlink web portal where they are stored under specific password protected account, that only the PI and the research assistant will have access to. Soberlink uses Rackspace servers to host our sites which all use a Secure Sockets Layer (SSL) certificate and our public facing sites go beyond that and use an Extended Validation SSL (EVSSL or EV SSL) certificate. These Certs prevent online transaction fraud, EVSSL certificates help organizations gain consumer trust by providing secure transaction processes. All of the SSL Certificates use AES 256 encryption which is considered the industry standard.

    Rating Scales and Assessments: These are all noninvasive and should add no risk. The major disadvantage is the time it takes to complete them. Confidentiality of these results is specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the Principal Investigator.

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

Confidentiality with regard to collected materials will be maintained via a numbered reference system maintained by the principal investigator. Subjects' names will appear only on a consent form and "key" form kept in a secured cabinet by the PI, separate from the subject records. All collected materials will be kept in locked file cabinets in a secured office. Inclusion and exclusion criteria, and the use of trained clinical interviewers in the assessment phase of the study will help to avoid the acceptance of subjects into this study who have either insignificant substance abuse or significant psychiatric contraindications to both treatments in this study. In cases of psychological deterioration or worsening substance abuse, we will recommend to patients to contact their physician immediately and consider withdrawing from the study to receive more intensive treatments. When necessary subjects will be withdrawn from this study and research staff will assist patients with appropriate sites for treatment such as the care coordinator, their sponsor or the emergency room. In instances of suicidal or homicidal risk, appropriate authorities including their primary provider will be informed and necessary actions (seeking crisis/suicidality evaluations and possible hospitalization) taken. Soberlink have facial recognition to confirm its the correct participant testing, while also have internal sensors and algorithms that can detect if the participant is using an alternative air source (i.e. air pump) or sample is not consistent with human breath.

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? The risks associated with participating in this study can be categorized as minimal (i.e., risks are commensurate with everyday risks associated with drug abuse treatment and data have adequate protection for maintaining confidentiality).
    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? NA
        ii. What provisions are in place for management of interim results? NA
        iii. What will the multi-site process be for protocol modifications? NA

    The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency monthly, 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, 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 regular study meetings and/or via email as they are reviewed by the principal investigator. The protocol's research monitor, study sponsors, funding and regulatory agencies will be informed of serious 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.
A sample size of 110 would provide >80% power (α= .05) to detect a medium to large effect size (d= .65) and allow to fully evaluate gender differences. Greater power is provided by the repeated measures GEE and LMM analysis for the primary outcomes of BAC screen negative for alcohol drugs and days/month of self-reported illicit drug use. Sample size calculations for LMM are dependent on the number of repeated events, the retention rate, and the interclass correlation, in addition to the alpha level, the expected effect size, and the statistical power 198. The current randomized trial would provide estimates to guide a power analysis for a large Stage II study. Statistical procedures and models for analyzing data have been selected according to the research hypotheses being investigated and the types of data available. We will use α< .05, but will use appropriate corrections for multiple tests. Statistical analyses will be conducted on an intention-to-treat sample using SPSS. Using chi square and t-tests, we will first conduct preliminary analyses of the adequacy of the randomization procedure, the comparability of baseline measures for the two groups, and the possible need for covariates in the analyses of treatment outcome data.

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

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.
Write here

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.

Write here

B. DRUGS/BIOLOGICS ☒N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☐
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☐
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☐
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☐
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
Write here

3. **Source:** Identify the source of the drug or biologic to be used. *Write here*

a) Is the drug provided free of charge to subjects? ☐YES ☐NO
If yes, by whom? *Write here*

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Write here

Check applicable Investigational Drug Service utilized:

- ☐ YNHH IDS
- ☐ CMHC Pharmacy
- ☐ West Haven VA
- ☐ PET Center
- ☐ None
- ☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

5. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study. *Write here*
c) Address the greatest potential harm that may come to a participant as a result of receiving placebo. *Write here*
d) Describe the procedures that are in place to safeguard participants receiving placebo. *Write here*

6. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☐ NO If no, explain why this is acceptable. *Write here*

B. DEVICES ☐N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request; AND

Your request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. Background Information: Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
The Soberlink device has been FCC and FDA approved, and has been utilized in several all clinical trials evaluating the efficacy and durability of the device. It has demonstrated by Skipper et al (2014) as a pilot study, and by Koffarnus, et al 2017 as a randomized control study to evaluate the preliminary efficacy within adults with alcohol use disorder. The device utilizes face-id to recognize and document the individual who is providing a BAC, however all information is stored directly onto the Soberlink's secure server (see below for

security measures). Given that it has been approved by the FCC, all other risks have been minimalized based on research.

3. Source:
   a) Identify the source of the device to be used. Soberlink Cellular
   b) Is the device provided free of charge to subjects? ☒Yes ☐No

4. Investigational device accountability: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*
   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*
   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*
   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*
   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects: 110
   a. Targeted for enrollment at Yale for this protocol: 110
   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: Word of mouth		

* 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.
Clinicians at Aware Recovery Care (ARC) will inform potential participants through word of mouth about the research opportunity at ARC. Clinicians can direct them to the flyers or provide the contact information of the PI to set up a meeting. Flyers will be hung around the main facility and breakout rooms where potential participate congregate. The flyer provides name and telephone number of where the PI can be reached.

b. Describe how potential subjects are contacted. Patients will be enrolled at Aware Recovery Center a Connecticut community practice will be invited to participate as patient respondents. Patients will be recruited

through a flyer posted and word of mouth (through their clinician) at the Aware facility. Patients who call about information about the study will be screened based on inclusion criteria and ability to understand and read English. Individuals who meet the criteria will meet with the research assistant either in person, via Zoom, or via telephone to be evaluated for eligibility.

c. Who is recruiting potential subjects? Research Assistants and/or the PI of the study

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: It would be impracticable to obtain signed authorization prior to screening since the subjects will either call into the lab for screening or will be referred by the patient's clinician.

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: After seeing a flyer or being referred to the PI by the clinician, potential subject who call the PI/research team will be screened for eligibility over the phone or via Zoom. The waiver of written authorization allows for the collection of PHI. If the subject is found to be ineligible, the PHI will not be kept. It would be impractical for all participants to have a signed authorization prior to enrollment in the research study as some will be calling from an off-site location and asking them to physically sign something may not be possible. Not enrolling these subjects into this minimal risk study because they are unable to sign a form could negatively influence the analysis.

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.
   The process of consent will take place in person during the first study visit when possible. However, if the participant cannot meet with the research team due to one of the following: 1) not able to transport him/herself to the location, 2) autoimmune disease or 3) due to social distancing requirements, the consent process will take place remotely (see below),. All potential subjects interested in the study will be fully informed about all aspects of the study using the appropriate consent attachment (adult consent or parental consent with child assent) and invited to participate. The PI or a research assistant will meet with them to read through the informed consent document to ensure that they each understand the content and to answer any potential questions that may arise. Potential participants will be given a copy of the consent forms if they would like more time to decide if they wish to participate. Participants can request and keep a copy of the informed consent document. Participants will be informed that they are free to decline participation and withdraw from the study at any time and that neither action will adversely affect their relationship with study personnel or their clinic staff.

   If the consent is not completed in-person, a secure email will be sent to the individual with an attached specific Zoom (www.zoom.com) ID, and time to meet online. The participant will meet with the either the PI or RA to complete the consent. Signature of the consent will be conducted electronically through Zoom. Zoom has the capabilities to allow participants to electronically sign (e-sign) their names, through manually signing their name with their finger on the screen through an IPAD or through a mouse on a computer. Patients can retain copies of the signed consent through a secondary secure email sent directly to them by the PI or RA. Given that all clients at Aware have access to an online capability and have a secure registered email, there is no additional risks to the client.

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.
   For all participants, the PI or a research assistant will meet with them to read through the informed consent document. Each participant will be asked repeatedly throughout the consent whether they understand what is presented. In addition, subjects will be asked to provide a summary of their understanding of the consent. Participants will also be asked what questions they have about the study procedures, their rights and obligations and the expectations and obligations of the study staff. When it is clear that they understand the material, both the research staff and the participant will sign two consents and the participant will retain a copy for their records

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 subjects will not be included in this protocol.

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)*

☐ 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?
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?
  n/a

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? We will collect names, addresses, email addresses, phone numbers, birth date and admission, discharge dates, and psychiatric diagnosis.

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

   Data will be stored two in two servers: 1) Soberlink uses Rackspace servers to host our sites which all use a Secure Sockets Layer (SSL) certificate and all of the SSL Certificates use AES 256 encryption which is considered the industry standard. This server will collect, record and store all data regarding any data that is inputted from the Soberlink device. 2) All surveys will be stored through Qualtrics. Qualtrics is an approved vendor of Yale University, and will securely store, record and store all participants surveys.

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?

All survey information will be stored on a privately maintained, Yale approved vendor (Qualtrics) for all data collection. Specific native IPADs will be utilized for intake/admission only. All other survey's will be completed online in the participant's home through a secure link sent directly to them. Soberlink uses Rackspace servers to host our sites which all use a Secure Sockets Layer (SSL) certificate and our public facing sites go beyond that and use an Extended Validation SSL (EVSSL or EV SSL) certificate. These Certs prevent online transaction fraud, EVSSL certificates help organizations gain consumer trust by providing secure transaction processes. All of the SSL Certificates use AES 256 encryption which is considered the industry standard.

The PI and his research team will have access to coded information and will be responsible for all data collection and analysis. All information will be stored on Yale's secure server and will be encrypted. Information will not be uploaded to the sponsored server as identifiable data. Only aggregate information that does not consist of identifiers will be distributed to Soberlink, and Aware Recovery

Care. A copy of the de-identified information will be stored on a secure server at Yale. All data will be coded through in a password protected Microsoft Access file.

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. Files with identifiable data will be destroyed upon completion of the study in regulation with University Policy, non-PHI will be kept indefinitely for data analysis.

6. If appropriate, has a Certificate of Confidentiality been obtained? *N/A*

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 is no direct benefit to individuals. We hope individuals who are randomized into the Aware+Soberlink group will receive access to the Soberlink device to monitor their alcohol usage and give them a permanent product measurement. Those who are not randomized into the control group will still have access to the Aware Model. All individuals will have access to the Aware In-home treatment model. A five-phase step down model that provides access to continual care through an integrated team of medical, nursing, counselors and home health advisors coming to the patient's home.

The study will assist in evaluating the efficacy of the combined effect of Soberlink and Aware Model and given the limited risks of the current study the study would be categorized as minimal (risks are commensurate with everyday risks associated with alcohol abuse treatment as an adequate protection of confidentiality). This information is important in order to develop cost-effective treatments for alcohol dependence, which ultimately would be of great benefit to society. Given the anticipated benefits to subjects and to society, the low risks to subjects are reasonable.

Patients who are randomized to the Soberlink group will have receive the Soberlink device and four months of service for no charge (390 USD). Soberlink will purchase gift cards for the PI and PI/RA will distribute them to the participant.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   Patients are not restricted from seeking any ancillary treatment (i.e. Alcoholic Anonymous).

2. 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.

All patients in both groups (Soberlink+Aware and Aware) will be receive gift cards incentives of the following increments for completing assessments: Evaluations, Month 1, Month 2, Month 3will be 10USD. The six week follow-up appointment will be 25USD. The total compensation per person is 65USD.

3. 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.
   For this study there will be no direct costs associated with participation in the research. The study will not cover any costs that participants incur for their access to the internet or web browser. Patients will be responsible for their own coverage through this.

4. 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).

   N/A. The research is expected to involve only minimal risk.

   a. Will medical treatment be available if research-related injury occurs? *NA*

   b. Where and from whom may treatment be obtained? *NA*
   c. Are there any limits to the treatment being provided? *NA*
   d. Who will pay for this treatment? *NA*
   e. How will the medical treatment be accessed by subjects? *NA*

IRB# 2000027787

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.**

APPROVED BY THE YALE UNIVERSITY IRB 6/9/2020