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

Protocol Title: Guanfacine to Improve Substance Use Outcomes in Women
HIC#: 2000023100

Principal Investigator: Rajita Sinha PhD

Version Date: April 2018

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

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   We hypothesize that Guanfacine (GUA) (3mg/day) will reduce drug craving, improve cognitive flexibility and result in associated lower drug use in women with substance use disorder (SUD) in an outpatient clinical setting. This study proposes to extend our previous Phase I experimental work to address the following specific aims: (1) assess GUA's target engagement of drug craving and cognitive flexibility in a laboratory challenge session and in a 10-week outpatient clinical study, (2) demonstrate target validation by showing that reduced drug craving and improved cognitive flexibility will predict lower drug use outcomes during the 10-week clinical trial in SUD women, and finally, (3) evaluate data replication and scalability of GUA target effects across two clinical sites (Yale and SUNY-Stony Brook).

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

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.

   Growing basic evidence indicates that the alpha-2 adrenergic agonist, guanfacine (GUA) decreases drug-related striatal-limbic up-regulation and stress sensitization resulting in drug cue and stress-induced reinstatement in laboratory animals (Shaham and Hope, 2005), and also improves neurocognitive abilities such as attention, flexibility, working memory and decision making (Arnsten, 2009). In NIDA-supported medications development work (R01-DA027130, PI: Sinha), we identified in a 3-day inpatient laboratory controlled experiment that GUA at 3mg/day dose engaged target drug craving and cognitive flexibility processes, and more importantly, that GUA engaged these key processes in a sex-specific manner with

positive effects in women but not in men (Fox et al., 2012; Sinha et al., 2011). Preliminary data also showed that GUA 3 mg/day (bid dosing) vs. placebo led to higher cocaine-negative urines in an 8-week outpatient setting only in women and not men.

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.

   The current study will test **GUA (3 mg/day) vs Placebo (PBO) in a 10-week clinical trial across 2 sites** in a total of 100 SUD women.

   All participants will be titrated to steady-state medication levels over 2 weeks followed by a **7-week treatment period using a standard cognitive behavioral relapse prevention** with medication management and contingency management (CM) for treatment attendance. A 5-day taper will be implemented in week 10. All participants will also take part in **two laboratory challenge test sessions**: one at pre-treatment (pre-tx) and one during week 9 of treatment, to assess provoked drug craving and cognitive flexibility under stress, drug cue and neutral cue conditions in a randomized and counterbalanced order.

   Pre-treatment Intake Procedures: Following the initial telephone screening, eligible participants will meet with the research staff to obtain written informed consent. Subjects will complete 2-3 intake appointments, and during these appointments they will be consented, screened of substance use, and provide demographic and psychiatric data. Physical examinations, blood work, a urine test, and a breathalyzer test will also be completed. All subjects will meet with the study physician, and if deemed eligible, after discussion of risk and benefits, subjects will be randomized into the study.

   Randomization: Eligible subjects will then be randomized in a double blind manner to either placebo or 3 mg/day (bid dosing) of GUA balancing the patients on age, education, race, ADHD and severity of drug use.

   Medication Titration Period (wk 1-3): Following a 3-day abstinence period, a 2-week titration period, previously found to be safe and with only mild adverse effects (Fox et al., 2014; Fox et al., 2012; Milivojevic et al., 2017) will be initiated (see Table 1).

   Table 1: Dose Titration Schedule

B.I.D Dose (mg)	Day 1-3	Day 4-7	Day 8-11	Day 12-14	Week 3-9	Week 10 5 day taper
8AM	0	0.5	1.0	1.0	1.5	1.0 - 1.0 - 0.5 - 0.5 - 0
8PM	0.5	1.0	1.0	1.5	1.5	1.5 - 1.0 - 1.0 - 0.5 - 0

   Steady state period (wk 3-9 & medication taper (wk 10): Following titration, participants will continue taking medication as shown in Table 1 for seven weeks and with a 5-day taper in week 10 as used previously (Fox et al., 2012) and complete post treatment assessments. We have had no adverse events of medication

discontinuation using this taper schedule.

Discontinuation or dose adjustment due to side effects: While we anticipate subjects will tolerate study medication well, should participants experience side effects attributable to medication, titration will be stopped at the highest tolerable dose. Our previous studies indicated that 3mg/day was tolerable with adverse events rated as minimal or mild.

Medication compliance: Medication compliance will be assessed in multiple ways: 1) We will include 2X/daily cell/home phone prompts as a reminder to take study medication. This strategy has been successfully implemented in previous addiction trials (Kranzler et al., 2004); (Simpson et al., 2005). If a subject does not have a phone, a prepaid phone will be provided for the duration of the trial. 2) A riboflavin marker will be included in study medication and urines will be assessed by fluorescence at each study visit and quantitatively measured every other week. 3) We will assess GUA levels as in our previous study at week 3, 6 and 9. Importantly, we will explore the relationship between compliance and cocaine use outcomes.

Laboratory Challenge Component: An identical laboratory challenge session will be conducted in the initial week of outpatient treatment Week 0, prior to medication, and again in Week 9. Our standard imagery script development procedures will be used to develop the stress, drug cue and neutral relaxing imagery scripts. The stress imagery script will be based on participants' description of a recent personal event experienced as "most stressful", and determined as such by rating it above 8 on a 10-point stress scale. These may include breakup with a significant other, marital conflict or job-related stress. A drug cue script will be developed based on situations involving people places and things pertaining to drug use that led to wanting drug and eventual drug use (e.g., meeting drug using friend, going by a favorite bar, etc). The neutral script will be developed from a personal non-alcohol-related relaxing situation. A 5-minute 'script' of each scenario will be written using Scene Construction Questionnaires (Sinha, 2009) where verbal and non-verbal responses, and physiological and bodily sensations regarding the events will be obtained. A script is then written following standard format and content procedures and scripts are then recorded onto audiotape for guided imagery in the laboratory sessions (Sinha, 2009). On the morning of the day prior to the initial laboratory session, participants will be brought into the testing room to receive training in relaxation and imagery procedures, as well as familiarize themselves with the subjective rating forms. The 10-min relaxation training will comprise muscle relaxation procedures in order to help subjects reach a relaxed state prior to imagery exposure during the laboratory sessions.

The schedule of the laboratory challenge tests at pre-treatment in Week 0 and in week 8-9 is shown in Table 2 below. Each laboratory session will take place over 2-hours in one afternoon, and comprise exposure to 3, 5-minute personalized imagery conditions (stress, neutral, drug cue), presented in a randomized and counterbalanced order. In each case, all participants will be brought into the testing room at 2:45 PM. If needed, a smoke break will be given to control for nicotine withdrawal. An ambulatory EKG (Holter) monitor will be used to record vitals and heart rate variability (HRV). After 10 minutes relaxation, drug craving, anxiety, mood, HRV and saliva will be collected at -10 and -5 minutes prior to imagery exposure. Subjects will then be given headphones and asked to imagine the situation being described, 'as if' they were actively participating in it at that moment. The script will be presented for exactly 5 minutes. All measures will be collected again immediately following imagery (0) and at +15 and +30 minutes recovery. The Stroop task will be administered at baseline and following imagery only. All participants will have 10 minutes of relaxation in between each of the three imagery sessions. All saliva will be placed on ice immediately, prior to storing at -80. Relaxation instructions will be provided following exposure to all three imagery conditions in order to ameliorate any potential residual effects of stress. All staff and participants will be blind to the order of imagery presentation. Imagery script development, imagery training and relaxation techniques will be

conducted in the week prior to the laboratory sessions as per prior research (Sinha et al., 1999; Sinha et al., 2000; Sinha et al., 2003) (Fox et al., 2008; Fox et al., 2005; Sinha et al., 2006; Sinha et al., 2011) and our standardized imagery procedures manual (Sinha and Tuit, 2012).

Table 2. Laboratory Experimental Protocol (Eactly same for each of the two laboratory sessions).

2:45 PM	Subject arrived; urine and BAC check Psychophysiological setup
	Stress / Drug Cues (Condition 1)
3:00 PM	BASELINE PERIOD; on-line heart rate and anxiety ratings
3:05 PM	Craving and DES ratings; Cortisol samples
3:10 PM	IMAGE PERIOD; on-line heart rate and anxiety ratings
3:15 PM	Craving and DES ratings; Cortisol samples
3:20 PM	RECOVERY PERIOD; on-line heart rate and anxiety ratings
3:25 PM	Craving and DES ratings; Cortisol samples
3:30 PM	10-minute Relaxation Period
	Neutral Imagery Condition (Condition 2)
3:40 PM	Schedule as in condition 1
	Stress / Drug Cues (Condition 3)
4:20 PM	Schedule as in condition 1

Order of imagery conditions is counterbalanced across subjects.

Study Assessments: Assessments include the following:

1) Sample description and eligibility including sociodemographics; psychosocial, substance use, and medical history; psychiatric assessment using the:
i) Structured Clinical Interview of Diagnostics (SCID-I) for DSM-V,(First et al., 1995),
ii) Connors ADHD Assessment and Rating Scale (CAARS,(Conners, 1999)
iii) vitals
iv) CBC, blood chemistry
v) urinalysis
v) pregnancy testing;

2) Primary SUD outcomes assessed using the:
i) Substance Use Calendar (SUC) developed by Miller and Del Boca (Miller and Del Boca, 1994) and based on the Time-Line Follow-Back (Sobell and Sobell, 1992; Sobell et al., 1996) and urinalysis for objective drug use assessed 2X/weekly during the 10 week period (20 urines);

3) Secondary Outcome Measures assessing drug craving using the standard brief versions of the Drug Craving questionnaires for cocaine (Cocaine Craving Questionnaire: CCQ,(Tiffany et al., 1993), cannabis (Marijuana Craving Questionnaire: MCQ, (Heishman et al., 2009)), alcohol (Alcohol Urges Questionnaire: AUQ, (Bohn et al., 1995) and nicotine (Questionnaire of Smoking Urges: QSU(Tiffany et al., 1993); (Tiffany and Drobes, 1991). Drug abstinence symptoms using standardized cocaine selective severity assessment (CSSA, (Kampman et al., 1998), Clinical Alcohol Withdrawal Assessment-Revised (Sullivan et al., 1989); The Cannabis Withdrawal Scale (Allsop et al., 2011); and the Minnesota Nicotine Withdrawing Scale (MNWS; (Hughes et al., 1986). Other drug use and drug related problems will be measured using the SUC; urinalysis; breathalyzer; the Addiction

Severity Index (ASI; (McLellan et al., 1992)) and Treatment Services Review (McLellan et al., 1992); stress (Perceived Stress Scale; (Cohen et al., 1983)); anxiety (Hamilton Anxiety Rating Scale, Ham-A; (Hamilton, 1960)) and depressive symptoms (Hamilton Depression Rating Scale, Ham-D, (Hamilton, 1960)). cognitive flexibility will be assessed using the Stroop Color Word Test; (Golden, 1975),

4) Safety and Compliance Assessment using vital signs; the Systematic Assessment for Treatment Emergent Effects (SAFTEE; (Rabkin et al., 1992)) to assess adverse events; and medication compliance assessed using pills counts, riboflavin markers and plasma levels of GUA. Each of these instruments are widely used, state-of-the-art and have strong psychometric properties.

5) Predictor variables:
The Childhood Trauma Questionnaire (CTQ) (Bernstein, 1998) is a 28-item self-report inventory that provides a brief screening for histories of abuse and neglect. The CTQ will be administered at intake.

The Chronic Stress Checklist (CSC) adapted from the Cumulative Adversity Interview (Turner and Wheaton, 1995) will be administered at intake.

The Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983) is a 14 item self-report assessing the degree to which situations are appraised as threatening or demanding. The PSS will be administered at intake and weekly.

The Emotion Regulation Scale (ERS) (DERS) (Nock et al., 2008) is a 36-item questionnaire to provide a comprehensive measure of the difficulties in emotion regulation. The ERS (DERS) will be administered at intake and weekly.

6) Cognitive Control Testing for Executive Function:

The Shipley Institute of Living Scale (SHIPLEY) (Shipley, 1940) has been widely used to assess cognitive functioning and impairment. The Shipley will be administered at the intake.

CANTAB (Cambridge Cognition, Inc) Battery will be administered during intake appointments and includes cognitive tests of executive function.

7) Laboratory Challenge Assessments:

Craving: Participants will rate the intensity of their desire to use primary and secondary drug of choice at the current time using a 10-point visual analog scale (0= “not at all” and 10= "extremely high"). Visual analog scales will also be administered for cocaine, cannabis, alcohol and nicotine craving.

Anxiety: Participants will rate how *“anxious, nervous and jittery”* they feel at the current time using a 10-point visual analog scale anchored as above. *Mood*: Differential Emotion Scale (DES: (Izard, 1972)): comprises 30 emotional words. Participants rate on a 5-point scale the extent to which each word describes current feelings.

Cardiovascular: An ambulatory ECG (Holter) GE Seer and Seer Lite recorders (digital sampling 125 sps) will be used to measure HRV, and recordings will be scanned using a GE Mars Ambulatory ECG system (PC, version 7).

Saliva: Cortisol saliva samples will be collected using salivette tubes placed between their tongue and cheek for approximately 2–3 min until the swab is completely saturated. Samples will immediately be placed in ice subsequent to storage at -80 degrees. All samples will be assayed in duplicate at the Yale Core Laboratories.

Contingency management for treatment attendance and behavioral support:

Twice weekly treatment attendance will be reinforced using standard contingency management (CM) procedures, which are known to greatly increase study compliance and attendance (Petry and Simcic, 2002; Roll et al., 2006; Stitzer and Petry, 2006). CM will be provided in the form of a "fishbowl" containing 500 chips. Half of the chips have no monetary value but are imprinted with "good job," 219 chips have a value of $1, 30 chips have a value of $25, and 1 chip has a value of $100. Upon completion of all requirements for a given visit, patients will receive fishbowl draws. Attendance at both weekly visits earns the patient bonus draws for that week. Failure to attend a visit without prior approval or failure to complete all visit requirements results in no draws earned for that visit and loss of bonus draws for that week. Participants will initially earn three draws per visit in week one with draws increasing by one each week. The weekly bonus draws will remain constant at 5 draws. Patients who attend all required visits will have the opportunity to make 264 draws from the fishbowl, for estimated earnings of $725 over 3 months. Subjects will also participate in weekly (45 minute) manualized cognitive behavioral relapse prevention therapy (Carroll et al., 1991) integrated with Medication Management (MM), providing advice and support from medical practitioners concomitantly with dispensing medications, safety checking and compliance (Pettinati, 2004).

Relapse, c

5. Genetic Testing N/A ☒

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
   One hundred treatment seeking women with SUD (50 per site)

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:
i) 100 treatment seeking women
ii) Ages 18-55 years
iii) Body mass index (BMI) of 18-35

iv) Meet current DSM-V criteria for co-occurring SUDs, with primary DSM-V cocaine AND co-occurring cannabis or alcohol or nicotine use disorders;
v) Positive drug urine toxicology screens for primary addictive disorder during a 2-week intake assessment period
vi) Good health as verified by screening examination
vii) Able to read English and complete study evaluations
viii) Able to provide informed written and verbal consent

Exclusion Criteria:
i) Meet criteria for current SUD on other psychoactive substance, excluding cocaine, alcohol, nicotine or cannabis
ii) Meet criteria for physiological dependence on alcohol requiring medical detoxification
iii) Current use of opiates
iv) Regular use of anticonvulsants, sedatives/hypnotics, prescription analgesics, other anti-hypertensives, anti-arrythmics, antiretroviral medications, tricyclic antidepressants, naltrexone, disulfiram, and any other psychoactive medications with the exception of individuals stabilized on SSRIs
v) Psychotic or otherwise severely psychiatrically disabled (i.e., suicidal, homicidal, current mania)
vi) Significant underlying medical conditions which in the opinion of study physician would preclude patient from fully cooperating or be of potential harm during the course of the study
vii) Hypotensive women with sitting blood pressure below 100/50 mmHG
viii) Women who are pregnant, nursing or refuse to use a reliable form of birth control
ix) EKG evidence at baseline screening of any clinically significant conduction abnormalities, including a Bazlett's QT c>470 msec for women.

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 be scheduled to meet with research staff to complete a brief screening. The screening will include questions on substance use, psychiatric history, an EKG, blood work and a urine test. Subjects will meet with the study physician for a physical examination.

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

    1) Risk associated with taking the study drug, Guanfacine
    2) Risk of including subjects who are otherwise inappropriate
    3) The imagery procedure
    4) Increased risk for relapse
    5) Increased risk to subject privacy

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

    1) Risk associated with taking the study drug, Guanfacine
    Previous research established use of GUA in children with ADHD and tic disorders have used doses ranging from 1.5 to 4 mg/day (Hunt et al., 1995); (Scahill et al., 2001). Side effects that have occurred in clinical trials in adults with guanfacine include dry mouth, sedation, weakness, dizziness, impotence, and constipation. Hypotension and bradycardia may also occur. In the previous work with 3-week treatment of GUA (3mgs/day)

versus placebo, we found it to be safe and well tolerated. In the initial study (Fox et al., 2012), the most common side effects were mild tiredness and fatigue (guanfacine 24%; placebo: 8%) and headaches (guanfacine 18%; placebo 8%). All symptoms dissipated over time without further intervention. Side effects from a dose-ranging study comparing placebo, 2 and 3 mg/day of guanfacine (Fox et al., 2009) indicated mild symptoms which dissipated rapidly without intervention in 7/21 individuals in the placebo group (33.33%), 5/12 individuals in the guanfacine (2mg) group (41.7%) and 4/11 individuals in the guanfacine (3mg) group (36.4%). Furthermore, there were no significant blood pressure differences across medication and placbeo groups. Also, there were no significant sex differences in reported side effects. There is no evidence that guanfacine will pose a greater risk in the proposed study sample than those previously reported. Importantly, patients will be seen in person on a weekly basis when information on any potential side effects will be collected; in case of any concerns, the study physician will be alerted immediately.

2) Risk of including subjects who are otherwise inappropriate

The screening of subjects using the inclusion and exclusion criteria, and the comprehensive medical and psychiatric evaluation will minimize the risk of including subjects who are otherwise inappropriate. All subjects recruited will receive a comprehensive physical examination and laboratory blood work to ensure good physical health status. The physical examinations will be conducted by the study medical personnel, who will be aware of study entry criteria and will manage recruitment as well as physical and medical assessment for this study. Routine laboratory blood work (CBC, electrolytes, etc.) and blood samples for medication levels will be collected. Abnormal findings pertaining to physical health and blood chemistry will be evaluated further by the study physician and appropriate medical advice will be provided. These are routine medical procedures and should add no risks other than those normally associated with these procedures. However, the research staff, with advice from the study physician, will ensure that potential participants who may be excluded from research due to medical reasons or pregnancy, or who are in immediate need for medical or psychiatric attention, will be referred to primary care/psychiatric care facilities so they can receive the appropriate clinical care needed to address their condition. Breath screening and urine collections are performed primarily as safeguards to contamination of data and should add no risks other than those normally associated with these procedures. Pregnant women will be excluded from the study. Female subjects will be asked questions to assess the possibility of pregnancy, and if this information fails to establish that pregnancy is highly unlikely then a serum beta HCG pregnancy test will be done prior to participation.

3) The imagery procedure

Imagery exposure in the laboratory experiments involves reliving personalized stressful, drug cue and neutral relaxing events, while listening to the guided imagery scripts developed in a previous session. Although this can be particularly emotionally arousing during the sessions themselves, our previous experience has shown that there is very little anxiety that carries over after the session, thus posing minimal risk. It is, however, possible that some drug craving and low mood may linger for a prolonged period following the laboratory sessions and in order to reduce these symptoms the following safeguards will be taken: (a) Subjects will participate in relaxation procedures to return craving levels to baseline after the laboratory sessions. We have found that the relaxation procedures are particularly effective in reducing craving levels after alcohol/drug cue exposure. (b) To enhance response to relaxation procedures, subjects will also be trained on relaxation procedures prior to the laboratory sessions. (c) Any subject reporting residual craving or emotional discomfort after completion of laboratory sessions will receive an individual counseling session by the PI or her designee experienced in cognitive behavioral therapy to reduce cravings. The focus of this session will be coping with emotions and cravings.

4) Increased risk for relapse

In order to ensure that alcohol/substance abusing subjects are not at increased risk for relapse after completion of the lab experiments, the following safeguards will be taken:
(a) After completion of each lab session, subjects will be exposed to relaxation procedures to return craving levels to baseline. We have found that relaxation procedures are particularly effective in reducing craving levels after stress imagery (Sinha et al., 1999a.).
(b) To enhance their response to relaxation procedures, subjects will be trained on relaxation procedures in a session prior to the testing sessions.

5) Increased risk to subject privacy

To ensure private information regarding subjects is kept confidential, procedures outlined in the 'Confidentiality & Security of Data' section will be followed. Participants in this study will be free to drop out at any time without penalty. 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 in regard to collected materials will be maintained via a numbered reference system maintained by the investigators. Furthermore, good clinical and research practice procedures and HIPAA regulations will be followed.

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? Greater than minimal risk
    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

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or NIH have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with taking the study drug, Guanfacine as a minimal risk.
2. Given the now established safety and validity of the current study drug in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Dr. Rajita Sinha) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. *Please note* that adverse events are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

x All Co-Investigators listed on the protocol.
□ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
x National Institutes of Health
□ Food and Drug Administration (Physician-Sponsored IND #_____)
□ Medical Research Foundation (Grant_____)
□ Study Sponsor
□ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator (Dr. Rajita Sinha) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for <u>which the Yale PI serves as the lead investigator</u>:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? Dr. Schlager will serve as the medical monitor and oversee adverse event reports and all medical questions for both sites.
   ii. What provisions are in place for management of interim results? *Write here*

iii. What will the multi-site process be for protocol modifications? Any modifications made to the protocol for one site, will be duplicated and submitted to the second site.

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

Data Management: Data entry will be conducted using the Web-based REDCAP direct data entry system. Both sites are fully trained and running with REDCAP and have implemented this platform in clinical outcome studies with SUD samples. Utilizing the REDCAP system will allow data to be directly collected into the Yale managed web-based system across sites with no identifying information transmitted over the internet. Field validation (e.g. no out of range/invalid responses accepted) and form validation (e.g. logically impossible responses to different questions) are built into the REDCAP system and the study data manager will conduct weekly quality control and data management. After online reviews, the data are archived onto servers and password protected with only certain members of the team having appropriate level of data access. All quality control and management issues will be addressed immediately and also discussed in the across site weekly study meetings.

Data Analysis: Data analysis will be performed under the direction of Project PIs in consultation with Dr. Ralitza Geuorgueiva, the Yale biostatistician. Screening for data entry errors, outlier checks and assessment of missing data and testing of normality assumptions will be conducted. Transformations will be applied as necessary. We will compare the treatment groups on demographic and clinical variables using t-tests/chi-square analyses as appropriate. If any group differences are found, the specific variable will be entered as a covariate in all specific analyses. For the primary outcome, we will use significance level of 0.05. Significance levels for secondary outcomes will be adjusted using Bonferroni correction for number of analyses performed.

Adequacy of Sample Size: Sample size estimates are limited by the fact that there are no previous clinical outcome studies of GUA/PBO in SUD women. As shown in above, data from our previous work with GUA yielded highly significant sex X med group effects for target engagement measures of drug craving and Stroop improvements with moderate to high effect sizes (f's ranging from 0.39-1.22). Using the GUA/PBO preliminary data from the 8-week pilot trial, percent of negative cocaine urines were 40.18% versus 67.86% in PBO vs GUA for the whole group (large effect size d=0.76), with 53.12% versus 100% for PBO vs. GUA in women (d=1.0) and 35% vs 55% negative urines in placebo vs guanfacine in men (d=0.628). Thus, assuming power=0.80, and at $p<0.05$, α level of 0.05, sample size estimates indicate that we will need 40 subjects per cell (Medgroup) to assess GUA/PBO in clinical outcome hypotheses in Aim 2 and Aim 3. This sample size allows for detection of medium effect sizes (f=0.25, Cohen) with more than 80% power assuming α level of 0.05 for the main effect of medication group on the primary outcome variable. Assuming an α level of 0.01 to correct for multiple tests for the secondary outcome measures we can detect effects in the medium range (f=0.28) with 80% power for all the main effects for secondary outcome variables. Including a 20% attrition rate, we propose an N=50 per group for a total N of 100 (50 per site).

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

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	☒
2. 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).	☒
3. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

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.

In a previous medication development project (R01-DA27132, PI: Sinha), we conducted a human laboratory study to assess GUA dosing and its effects on provoked craving, anxiety stress physiology and cognitive flexibility. Men and women with Cocaine Use Disorder and co-occurring substance abuse (non opiates), were admitted on an inpatient treatment unit and treated with GUA or placebo (PBO) using a 14-day titration in a randomized double blind manner (Fox and Sinha, 2014). Guanfacine at 2 mgs/day versus placebo was able to lower peripheral sympathetic arousal and drug cue-induced craving but did not address stress-induced drug craving in 42 SUD men and women (25). Basal attenuation in norepinephrine ($p<.05$), heart rate ($p=.001$), and blood pressure (SBP: $p<.02$; DBP: $p=.01$) was seen in men and women given GUA, compared with the placebo group.

In preparation for the proposed study, Dr. Sinha compared guanfacine (3mg/day) versus placebo in a randomized, double blind laboratory study of SUD men (N=29) and women (N=13). After the 14-day dosing titration period and at the full 3mgs/day dose, participants were exposed to 3, 10-minute personalized guided imagery procedures (i) stress, (ii) drug cue, (iii) combined stress / cue, one per day, across three consecutive days in a randomized and counterbalanced order (Fox et al., 2014); (Fox and Sinha, 2014). Guanfacine was found to be safe and well tolerated in both men and women. Drug Group X Sex X Time-point interactions were observed for cocaine craving, alcohol craving and anxiety indicating attenuation of Drug craving (cocaine, nicotine and alcohol) as well as anxiety was observed in guanfacine compared with the placebo group immediately following all three provocation conditions, but only in the women not the men. A Drug Group X Sex interaction for negative mood, again indicated a decrease in negative affect following all three imagery conditions and time-points in the SUD

women on GUA but not men (106). Guanfacine also attenuated basal heart rate in males and females, but to a greater extent in females and decreased stress-induced heart rate in SUD women only. In contrast, a main effect of Drug Group for nicotine craving showed that guanfacine was able to reduce craving in both men and women administered guanfacine compared with placebo. Dr. Sinha also assessed the Stroop task at baseline and immediately following exposure to all three provoked imagery conditions (stress, stress/cue, cue/cue). Findings indicated that GUA (3mgs/day) improved stress and cue- provoked Stroop performance relative to placebo but only in women and not in men.

In the previous work with 3-week treatment of GUA (3mgs/day) versus placebo discussed above, Dr. Sinha found it to be safe and well tolerated. In the initial study (25), the most common side effects were mild tiredness and fatigue (guanfacine 24%; placebo: 8%) and headaches (guanfacine 18%; placebo 8%). All symptoms dissipated over time without further intervention. Side effects from a dose-ranging study comparing placebo, 2 and 3 mg/day of guanfacine (26) (106) indicated mild symptoms which dissipated rapidly without intervention in 7/21 individuals in the placebo group (33.33%), 5/12 individuals in the guanfacine (2mg) group (41.7%) and 4/11 individuals in the guanfacine (3mg) group (36.4%). Furthermore, there were no significant blood pressure differences across medication and placebo groups. Also, there were no significant sex differences in reported side effects.

In preparation for this proposal, Dr. Sinha conducted a randomized, double-blind, 8-week pilot study of GUA (3mgs/day) with treatment seeking CUD men and women (n=7: 5M/2F) vs placebo (n=7: 4M/3F). Using the same 16-day titration schedule used previously and proposed in the current project, GUA plasma levels were assessed as at weeks 4 and 8 in the outpatient study as well as in the inpatient study described above. GUA levels obtained in the outpatient pilot were comparable to levels to those from the inpatient study described above. These data suggest that generic GUA with bid dosing was acceptable, and patients showed high medication compliance in the outpatient setting.

Together, data indicates guanfacine 3 mg/day to be safe and tolerable with regard to assessing target engagement and validation across multiple sites in SUD women.

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

GUA pills will be obtained from Watson Pharmaceuticals by the Investigational Drug Service (IDS) at Yale-New Haven Hospital (YNHH). The research pharmacist will make up identical active and placebo capsules for medication administration for both sites. Medications will be shipped to Stony Brook from Yale for randomization and dispensing at the Stony Brook site. Medication administration will occur at 8am and 8pm each day to standardize the time of administration.

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom? IDS at YNHH

1. **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.
Yale research staff will pick up the prepared capsule blister packs from IDS and disperse to subjects at their outpatient appointments.

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.

2. 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.
No other available FDA medications for co-occurring SUDs in women, thus use of placebo is justified.

b) State the maximum total length of time a participant may receive placebo while on the study.
10 weeks

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
No known risks

d) Describe the procedures that are in place to safeguard participants receiving placebo.
n/a

3. 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

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: 50
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: 100

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.
Participants for the Yale site will be recruited for this study via on-line, posting flyers in the area, and via the Yale Stress Center Recruitment Network. The Network includes large primary care facilities such as the Adult Primary Care Clinic at Yale-New Haven Hospital (5000 patients/yr), Fair Haven Community Health Center and Greater New Haven area addiction treatment facilities and one of the largest family and child guidance services centers in New Haven (Clifford Beers Clinic) especially useful for recruitment of women, as established previously through our Stress and Addiction Women's Health and Addiction Center (P50-DA016556).

Dr. Fox at SUNY Stony Brook has established recruitment of SUD samples specifically women for her research through the Stony Brook Hospital system's secure Cerner Millennium electronic health records (EHR) system, the Emergency Room (ER) and Psychiatric ER departments, and the New York state supported Addictions Treatment Facilities for the Long Island region, in an addition to posting on-line ads and posting flyers in the area.

b. Describe how potential subjects are contacted.
Potential subjects will contact us via our toll free phone number and be screened by research staff as detailed in HIC protocol 911006003: Telephone Screening and Repository for Stress and Lifestyle Behaviors (Trialdb).

c. Who is recruiting potential subjects? Research staff at the Yale Stress Center (HIC 911006003).

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: We are collecting PHI as part of a phone screen.

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: *Write here*

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 conducted as part of the Yale Stress Center telephone screening protocol (HIC protocol 0911006003), eligible participants will meet with a research assistant to obtain informed consent.

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. Subjects who are under the influence of alcohol will not be consented at that time.

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 ☒

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? *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 physical examination, psychological assessments, self-reports, and data collected during the lab sessions will be collected and used for research. The proposed study will be conducted by specialized and trained research staff using standardized biophysiological and psychosocial assessments. Data collected and analyzed in the study will be derived from three main sources (1) semi-structured clinical interviews and self-rating scales: psychiatric history, medical history, levels of alcohol and substance use and demographic self-reports of age, race, socioeconomic status, marital status, educational and occupational levels. (2) Biophysiological data: includes heart rate, blood pressure, saliva and plasma HPA axis markers (cortisol and ACTH). Additionally, health checks prior to enrollment will comprise a physical examination and blood work. (3) Urine and breathalyzer data: will be used to confirm alcohol and substance use. It will be collected at intake and during weekly appointments.

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?

   As this study will be NIH funded, we expect that a CoC will be issued as outlined in the new NIH policy.

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.)

All patients will receive free empirically validated cognitive behavioral relapse prevention and medical management. However, because they will be in an experimental protocol with a medication that may not have direct benefits to the individual participant, subjects will be offered payment for completions of research assessments during the 10-week trial. Subjects will also receive vouchers for treatment attendance in the 10-week trial. Monitoring substance use, as

well as providing referrals and inpatient treatment may be helpful to those at risk in the short-term. In addition, the potential long-term benefits of the proposed research to the participants and to their community are great. Identifying some of the mechanisms underlying relapse in salient sub-populations of individuals with substance use disorders will assist in the development of customized, efficacious remedies. These could potentially include a broad range of medications and behavioral therapies.

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 treatment for SUD.

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.

   Participants will receive $25 compensation for all the screening visits, $5 a week for returning unused study medication, and $25 at weeks 4, 8 and 10. Subjects will be compensated $2 per day for completing the daily MetricWire smartphone app surveys, and a $6 bonus for completing all 7 surveys for the week. Subjects will also receive vouchers for treatment attendance. The fishbowl contingency management procedure described above will be used to enhance treatment retention. Participants can earn a total of 264 draws during the course of the study, for estimated earnings of $725. If needed, subjects will also receive bus passes and parking validation stickers to help cover transportation costs to attend appointments.

   Screening visits: ($25)
   Returned medication: 10 x $5 ($50)
   $25 bonus at weeks 4, 8, and 10: ($75)
   MetricWire: 10 x $20: ($200)
   CM fishbowl: max ($725)
   Total: $1075

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

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).

   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?

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.**

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