Enhancing the Effects of Adolescent Alcohol Treatment with Atomoxetine

Funding Source: National Institute on Alcohol Abuse and Alcoholism (NIAAA)
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Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CRF Part 46, 21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 312)
- International Conference on Harmonisation (ICH) E6

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

Protocol Synopsis

Name of Sponsor/Company: National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Name of Investigational Product: Atomoxetine HCl, oral administration, 40mg to 80mg QD

Name of Active Ingredient: Atomoxetine

Protocol Number: ATOM-000

Study Title: Enhancing the Effects of Adolescent Alcohol Treatment with Atomoxetine

Principal Investigator: Robert Miranda Jr., PhD, ABPP

Study Centers: 1 site in the United States (Brown University)

Study Period: Estimated date first subject enrolled: 03/01/2021; Last completed: 03/31/2022

Phase of Development: 2

Primary Objectives

The first primary objective of this study is to evaluate the feasibility, acceptability, and tolerability of atomoxetine (40 mg/day for 3 days then 80 mg/day thereafter) as compared to placebo for 6 weeks plus a psychosocial platform comprised of motivational enhancement therapy and cognitive behavioral therapy (MET-CBT; "*Path 180*") among adolescents (ages 14 to 20 years) with alcohol use disorder as confirmed by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™).

The second primary objective is to leverage a human laboratory paradigm (H-LAB) to evaluate the effects of atomoxetine on an intermediate phenotype (alcohol craving) associated with alcohol use and outcomes in clinical trials. We hypothesize that atomoxetine, as compared to placebo, will decrease the likelihood of craving in the human laboratory during *in vivo* alcohol cue reactivity.

Methodology

This proof-of-concept study is a double-blind, randomized, placebo-controlled, parallel group, single-site clinical trial. After obtaining consent/parent permission/assent, potential subjects and, if younger than 18 years, their parent(s) will complete a medical history and psychiatric diagnosis interview (about the adolescent) to screen for eligibility. Youth will also complete a physical examination, vital signs, drinking history by the timeline follow-back (TLFB) method, alcohol breathalyzer test, Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-AR), prior/current medication use, urine toxicology screen, clinical chemistry, and the Columbia Suicide Severity Rating Scale (CSSR-S). Females of child-bearing potential will have a pregnancy test.

If eligible for the study, 50 subjects will be randomized in an approximate 1:1 ratio (targeting 21 subjects per group – 42 subjects total) to either atomoxetine or placebo for 6 weeks.

Atomoxetine will be dosed at 40 mg/day for three days then increased to the maintenance dose of 80 mg (active) taken orally once daily (QD) for an additional 5.5 weeks. Subjects randomized to the placebo condition will be given an equal number of visually matched capsules.

At the randomization/baseline visit and after 4 weeks of investigational product administration (i.e., Study Week 5), subjects will undergo a human laboratory paradigm (i.e., alcohol cue reactivity assessment).

Number of Subjects (Planned): 50 (targeting 21 subjects per group – 42 subjects total)

Main Inclusion/Exclusion Criteria: Subjects will be male and female adolescents, ages 14 to 20 years old, who meet DSM-5 criteria for alcohol use disorder. They must be seeking to reduce their alcohol use.

Investigational Product, Dosage and Mode of Administration: Dose titration and maintenance will occur as scheduled below. Atomoxetine will be self-administered by subjects once daily after eating and with a full glass of water beginning on Study Week 1, Day 1 and continuing through Study Week 6, Day 7. The first dose will be taken in the study clinic whenever possible. Subjects will be provided with water and a snack to take with first dose. Dose will be titrated, as tolerated, to a target dose of 80 mg once per day of atomoxetine. Capsules should be swallowed whole and should not be cut, crushed, or chewed. Capsules should be taken with food and water.

Schedule of Administration of Investigational Product

Study Period	Time Period	AM Dose (# of capsules)	PM Dose (# of capsules)
Titration	Study Week 1, Day 1 – 3	40 mg (1)	None
Maintenance	Study Week 1, Day 4 – Week 6, Day 7	40 mg (2)	None

Reference Therapy, Dosage and Mode of Administration: Identically over encapsulated placebo tablets will be dispensed according to the same schedule as the atomoxetine capsules.

Table of Contents

List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUD	Alcohol use disorder
AUQ	Alcohol Urge Questionnaire
BAC	Blood alcohol concentration
BrAC	Breath alcohol content
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CSQ-8	Client Satisfaction Questionnaire – 8
CLIA	Clinical Laboratory Improvement Act
CIWA-AR	Clinical Institute Withdrawal Assessment for Alcohol-revised
CrCl	Creatinine clearance
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case Report Form
CTCAE	Common terminology criteria for adverse events
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSMB	Data and Safety Monitoring Board
EOS	End of study
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIPAA	Health Insurance Portability Accountability Act
H-LAB	Human Laboratory Paradigm (i.e., alcohol cue reactivity assessment)
hr	Hour
ICH	International Conference on Harmonization
IRB	Institutional Review Board
K-SADS	Schedule for Affective Disorders for School-Age Children
L	Liter
MAOI	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MET-CBT	Motivational Enhancement and Cognitive Behavioral Therapy
mg	Milligram

Abbreviation	Definition
µg	Microgram
min	Minutes
mITT	Modified intention-to-treat
mL	Milliliter
mm	Millimeter
NIAAA	National Institutes on Alcohol Abuse and Alcoholism
oz	Ounce
PI	Principal Investigator
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDU	Standard drinking unit
SOC	System Organ Class
SNRI	Serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
THC	Tetrahydrocannabinol
TLFB	Timeline/follow-back interview
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
WHO	World Health Organization

Introductory Statement

1.1 Alcohol Use Disorder

Alcohol use disorder (AUD) affects nearly one-third of adults in the United States during their lifetime (1). Excessive alcohol use causes myriad acute and long-term medical, psychological, and social problems (2) and carries an economic burden of $249 billion each year (3). Although advances in pharmacotherapy have improved treatment options for adults who struggle to reduce their alcohol use, treatment options for youth are limited.

Adolescent alcohol use is a leading public health concern. The harmful effects of underage drinking are irrefutable and include premature death and possible irreversible damage to the developing brain (4, 5). In addition, adolescence is a critical period in the pathogenesis of AUD; an estimated 3 to 15% of youth develops AUD before age 18 (6, 7). Clinical trials have tested psychosocial interventions with youth, including family treatments, cognitive behavior therapy (CBT), and motivational enhancement therapy (MET) that yield only modest short-term benefit (8-11). Our group has contributed substantially to this body of work (12-17).

One potential way to improve treatments is to augment psychosocial interventions with pharmacotherapy. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has mounted a concerted effort to identify medications that reduce drinking for nearly three decades. Although this effort improved treatment for adults, no medication is indicated for adolescent use and randomized controlled trials with teenagers are almost nonexistent. This gap raises key questions about if and how medications could benefit youth. Optimizing treatment options for youth requires closing this important gap, and FDA guidelines require that all applications for new pharmacotherapies include data from pediatric populations.

1.2 Human Laboratory Studies

Human laboratory studies of acute responses to alcohol, alcohol cues, or other experimental manipulations have progressed in important ways and hold potential to advance our understanding of how medications exert beneficial effects on drinking outcomes (18). These studies may help identify important individual difference factors affecting alcohol response, such as personality traits, drinking characteristics, and genotype, and aid in our understanding of the variability in cue and craving states, and provide additional information relevant to the design of clinical studies to assess the effectiveness of pharmacological agents.

The study to be conducted in this protocol utilizes an alcohol cue reactivity paradigm to attempt to recreate in the human laboratory risk conditions for relapse like those experienced by individuals with AUD in their natural environment. Alcohol cue reactivity, which involves systematic exposure to *in vivo* alcohol cues and simulates high-risk situations for relapse, is one of the most widely studied laboratory paradigms in the context of AUD (19, 20). Exposure to alcohol cues reliably elicits responses presumed to relate to the motivational processes that underlie drinking (21), and it is sensitive to medication effects among treatment seeking and non-treatment seeking adults and adolescents.

Impact on individual variability. Reactivity to alcohol and other drug cues varies from person to person, with some individuals showing little or no increase in target variables (e.g., craving) from the baseline or neutral cue trials to alcohol/drug cue trials (22-25). Some researchers have operationalized "responders" as individuals who show any change (22, 23, 26-28), whereas others have specified an exact minimum change (e.g., > 1-point increase in average craving) (25, 29, 30). Potential sources of variability include sex (31), genetic factors (32, 33), personality (26, 34), and substance use factors, such as lifetime alcohol

use indices and parental drinking problems (35), and these individual differences may moderate the effects of medications on alcohol cue reactivity (36-38).

Reproducibility. A highly cited meta-analysis of cue reactivity studies reported robust effects for self-reported craving in response to cues and a somewhat smaller, albeit still meaningful, effect size for physiological responses to cues (39). The autonomic profile of cue reactivity is fairly similar across drugs of abuse (40) and is often characterized by increases in heart rate and sweat gland activity and decreases in peripheral temperature. These physiological reactions are sensitive to medication effects (22, 41, 42).

Sensitivity to detect differences between experimental medication and placebo. The alcohol cue reactivity paradigm reliably detects significant medication-placebo differences for most, but not all, medications studied. Studies show that cue-induced craving is blunted by a variety of medications, such as naltrexone (22, 41, 43-47), gabapentin (48), mifepristone (49), prazosin (50), d-cycloserine (51), and olanzapine (52), as well as combinations of these medications (53). Some studies of these and other medications, however, did not find these effects (36, 54-56). Nonetheless, cue reactivity effects are generally consistent with decreases in craving observed in clinical trials of these medications (49, 57-61). It is noteworthy that certain medications that reduce drinking, namely topiramate and acamprosate, consistently fail to show medication-placebo differences in cue reactivity (62-65), and thus require other paradigms to characterize medication-placebo effects on clinically meaningful phenotypes.

Predictability of clinical trial success. Craving and other indices of cue reactivity are associated with relapse (66-68) and, as such, they are considered clinically relevant endophenotypes predictive of alcohol use outcomes (69). Craving is a strong predictor of drinking in the laboratory (46, 70, 71) and the natural environment (27, 54, 72-80), and medications (e.g., gabapentin, naltrexone) that decrease cue-elicited craving in the laboratory typically also reduce craving and drinking in clinical trials (43, 49, 58, 81). Indeed, human studies and animal models suggest that individuals for whom drug cues attain incentive motivational value or incentive salience are most likely to exhibit relapse (40, 82, 83). Although few studies have directly examined whether cue reactivity measured in the laboratory prospectively predicts clinical trial success, mounting evidence suggests it may be a powerful tool for understanding how interventions work and for identifying promising new treatment options for addiction (66, 84-91). Craving in response to alcohol or affective cues is predictive of subsequent drinking outcomes, including relapse (54, 75-80, 92); albeit others did not find this association. (93). Researchers have also examined the association between physiological cue reactivity and relapse and findings are mixed (94). Yet many studies show physiological reactivity (e.g., heart rate) predicts relapse (68, 77, 95-97).

1.3 Rationale for Atomoxetine

Atomoxetine is safe with adolescents and does not adversely interact with alcohol. It is a highly selective norepinephrine reuptake inhibitor that is FDA-approved to treat attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. Unlike other ADHD pharmacotherapies, atomoxetine is not a stimulant and has no abuse potential (98-102). Pooled data from four trials showed it is equally well tolerated by heavy drinkers, non-heavy drinkers, and non-drinkers (103).

Atomoxetine targets brain mechanisms implicated in the pathogenesis of AUD, namely the norepinephrine system (104, 105). Norepinephrine innervates key limbic areas that govern arousal, reinforcement, and stress. Dysfunction in norepinephrine underlies problems with maintaining attentional homeostasis (106) and behavioral responses to stress (104, 107, 108), two key contributors to alcohol misuse. Although it does not appear to increase intracellular dopamine in regions involved in reward and reinforcement (e.g., nucleus accumbens), it increases extracellular dopamine in regions that drive craving and compulsive drug seeking (e.g., prefrontal cortex) (109).

There is strong preclinical evidence that altering the norepinephrine system reduces alcohol use and reinforcement. Selective pharmacological and neurotoxin-specific disruption of norepinephrine function reduces voluntary alcohol intake in rats (110, 111), and selective depletion of norepinephrine in the medial prefrontal cortex of high alcohol-consuming mice decreases alcohol consumption (112). Similarly, mice unable to synthesize norepinephrine because of dopamine-beta hydroxylase show reduced preference for alcohol (113). In addition, propranolol, a hypertensive and migraine medication that blocks the effects of norepinephrine on both β_1- and β_2-adrenergic receptors, suppresses progressive ratio operant alcohol-reinforced responding in alcohol-dependent and non-dependent rats (114). These findings further support the idea that manipulation of the norepinephrine system suppresses both the appetitive and consummatory reinforcing properties of alcohol.

These preclinical findings were supported by a rigorous double blind, placebo-controlled 12-week randomized controlled trial with 147 adults with comorbid AUD and ADHD (115). Individuals randomized to atomoxetine (mean dose = 90 ± 17.6 mg/day) had 26% fewer heavy drinking days compared to placebo. Reductions in ADHD symptoms were correlated with decreases in alcohol craving, and this association was more pronounced in the atomoxetine group (116). Two additional smaller and less scientifically rigorous studies also examined atomoxetine effects, including one with adolescents. In an open-label trial (N = 14) of adjunctive atomoxetine (41.9 ± 13.7 mg/day) to drug abuse treatment as usual, adult patients had longer durations of abstinence and reengaged in treatment more quickly following relapse when taking atomoxetine as compared to their past maximum period of abstinence (117). Patients also reported a significantly better quality of life and higher treatment efficacy scores after taking atomoxetine. There was no difference between patients with and without ADHD in terms of treatment responsiveness. Alcohol was the primary substance of abuse for 8 patients; the onset of dependence occurred on average during adolescence. In an additional trial, 70 adolescents, ages 13 to 19 years, with comorbid ADHD and substance use disorders were randomized to atomoxetine (weight-adjusted up to 100 mg/day) or placebo plus psychotherapy for 12 weeks (118). Youth were not selected for a specific substance use disorder and thus varied in their type of substance use disorder (i.e., cannabis, nicotine, and alcohol use disorders). Although atomoxetine was well tolerated, substance use was a single aggregate outcome (no alcohol-specific outcomes reported; only 7 teens randomized to atomoxetine had AUD), and there was no effect of atomoxetine on ADHD symptoms or substance use.

Atomoxetine enhances executive function in patients with ADHD and healthy controls, especially in improving response inhibition (119) and researchers hypothesize that these effects may attenuate factors that confer liability for AUD and maintain pathological drinking habits (117). From this perspective, atomoxetine may not only affect drinking by blunting craving or altering the reinforcing properties of alcohol use, as observed in preclinical and clinical studies, but also by improving executive function. Attention, working memory, and decision-making are core facets of executive function and key to regulating behavior (120-122). Disruption of brain regions that govern executive function are strongly related to compulsive alcohol use and drug taking as well as problems associated with use (123, 124). Studies consistently show bidirectional relations of executive function and substance use, such that lower levels of executive function confers increased risk for developing addictions (125) and substance use produces acute (126) and long term (127) decreases in executive function. Indeed, impaired executive function is related to drinking in adults (128) and adolescents (129), and improved executive function via cognitive training is related to reduced alcohol use one-month post treatment, especially for those with strong automatic impulses to drink (130). Enhancing executive function may also improve outcomes of behavioral therapy by facilitating skill acquisition and durability of skill uptake.

Possible adverse effects of atomoxetine are considered mild given the dose (80 mg/day) and titration period proposed; participants randomized to atomoxetine will take one 40 mg capsule for the first 3 days, followed by one 80 mg capsule each day for the remainder of the active medication phase of the study. The FDA approved atomoxetine for treating children (ages 6 and older), adolescents, and adults with ADHD. As such, side effect data for atomoxetine comes from clinical trials research on children (ages 6 and older), adolescents, and adults with ADHD. The most common adverse reactions to atomoxetine, defined as ≥ 5% and at least twice the incidence of placebo patients, in child and adolescent trails are nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence. In adult clinical trials, the most common adverse reactions are constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation.

As indicated by the FDA, pooled analyses of 12 short-term (6 to 18 weeks) placebo-controlled trials of atomoxetine with a total of 2,200 children and adolescents, including 11 trials for ADHD and 1 for enuresis, showed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (*N* = 5/1357 patients), compared to none in the placebo condition (*N* = 851 patients). No suicides occurred in these trials. Notably, all suicidal ideation reactions in these trials occurred in children 12 and younger. We will be excluding youths younger than age 14 years. Studies with adults with ADHD or major depressive disorder have not revealed an increased risk of suicidal ideation among patients prescribed atomoxetine.

1.4 General Investigative Plan

This proof-of-concept study is a double-blind, randomized, placebo-controlled, parallel group, single-site clinical trial. After obtaining consent/parent permission/assent, potential subjects and, if younger than 18 years, their parent(s) will complete a medical history and psychiatric diagnosis interview (about the adolescent) to screen for eligibility. Youth will also complete a physical examination, vital signs, drinking history by the timeline follow-back (TLFB) method, alcohol breathalyzer test, Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-AR), prior/current medication use, urine toxicology screen, clinical chemistry, and the Columbia Suicide Severity Rating Scale (CSSR-S). Females of child-bearing potential will have a pregnancy test.

If eligible for the study, 50 subjects will be randomized in an approximate 1:1 ratio (targeting 21 subjects per group – 42 subjects total who complete the protocol) to either atomoxetine or placebo for 6 weeks.

Atomoxetine will be dosed at 40 mg/day for three days then increased to the maintenance dose of 80 mg (active) taken orally once daily (QD) for an additional 5.5 weeks. Subjects randomized to the placebo condition will be given an equal number of visually matched capsules.

As shown in Figure 1, subjects will be seen in the clinic (or remotely) at the screening appointment, the randomization/baseline session, and at weekly visits during the study. At the randomization/baseline visit and after 4 weeks of investigational product administration (i.e., Study Week 5), subjects will undergo a human laboratory paradigm (i.e., alcohol cue reactivity assessment).

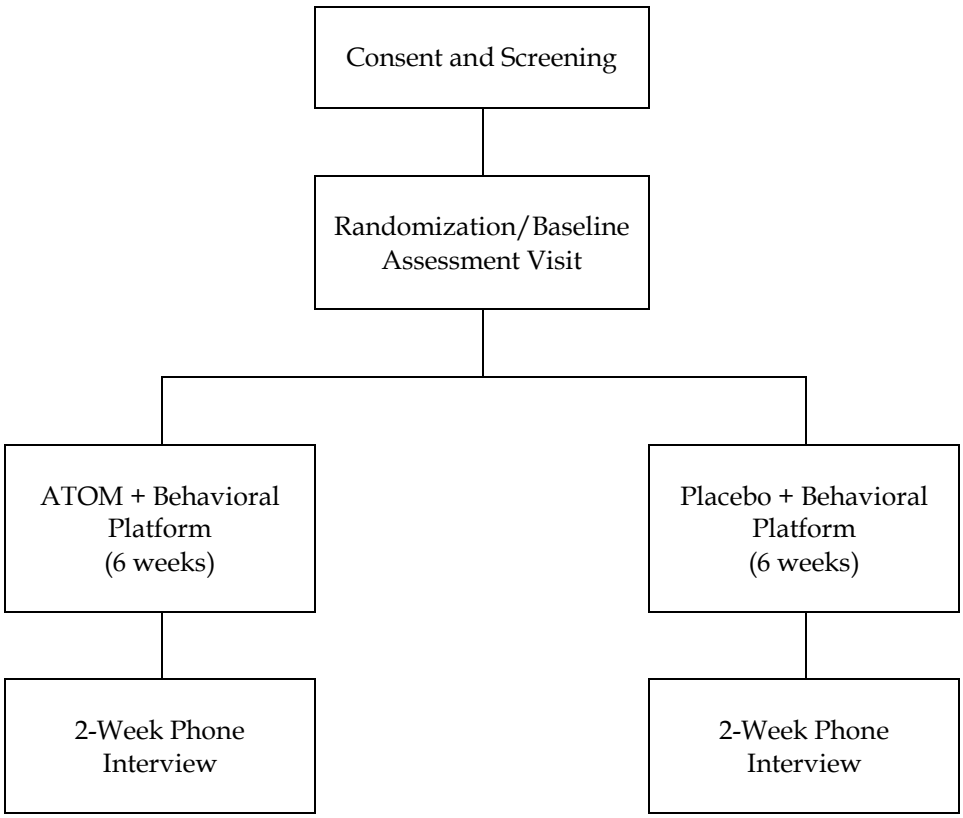

Figure 1: Overview of Study Chronology

Study Objectives

2.1 Primary Objectives

- **Evaluate the feasibility, acceptability, and tolerability of atomoxetine (40 mg/day for 3 days then 80 mg/day thereafter) plus MET-CBT (i.e., "Path 180") for 6 weeks among adolescents with AUD as confirmed by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™).**

- **Apply our H-LAB paradigm to evaluate the effects of atomoxetine on intermediate phenotypes associated with alcohol use and outcomes in clinical trials.** We hypothesize that atomoxetine, as compared to placebo, will reduce the likelihood of craving in the human laboratory during *in vivo* alcohol cue reactivity.

Study Interventions

3.1 Investigational Products: Atomoxetine and Placebo

Atomoxetine (40 mg/day for 3 days then 80 mg/day thereafter) will be over encapsulated and supplied by a contracted pharmacy, along with identical matching placebo capsules. Capsules in identical blister packaging configurations will be prepared in kits for each subject containing one blister card with 7 days of drug/placebo for each week of drug/placebo administration + 2 extra blister cards (with enough drug/placebo for one week if a subject loses or misplaces an entire blister card or is late for an appointment and needs an additional blister card until the next appointment is scheduled).

3.2 Investigational Product Acquisition

All compounding and packaging of study medications is done at a compounding pharmacy. The pharmacy is licensed with the Rhode Island Board of Pharmacy and registered with the DEA. They adhere to the U.S. Pharmacopeial Convention (USP) 795 standards for compounding non-sterile preparations. All work is conducted in conformity with all applicable federal, state and local laws and regulations. They are certified HIPAA compliant and a member of the International Academy of Compounding Pharmacists. They utilize all the latest compounding equipment and techniques. They utilize Air Science PurAir powder containment hoods. These are HEPA/ULPA-filtered hoods that eliminate any chemical powders from being in the work environment. The pharmacy employs Registered Pharmacists and technicians.

3.3 Investigational Product Storage and Stability

Kits will be stored at room temperature (within the range of 59°F to 86°F) in a secured area at the clinical site. Our facility, the Brown University Center for Alcohol and Addiction Studies (CAAS), is restricted to authorized personnel, with a security guard stationed 24/7 at the building's entrance. CAAS has a secure alarmed and monitored room for onsite drug storage, dispensing and record keeping. This area is DEA approved for the storage and monitoring of controlled substances. Only authorized personnel have access to the room. Our facilities have adequate lighting, ventilation, temperature, sanitation, humidity, space, and security for suitable storage. Storage areas are secure from unauthorized entry, clean, sanitary, and orderly. Each incoming shipment of medication from the compounding pharmacy is carefully inspected for identity and possible damage of the drug products. All medications are stored at appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the United States Pharmacopeia/National Formulary (USP/NF).

Outdated, damaged, and otherwise unused medication is stored in a separate secure location and container from other medications; the pharmacy disposes of all outdated, damaged, and otherwise unused medication. We develop and maintain study medication logs where we record all transactions regarding the receipt and distribution or other disposition of medications. These records include the source of the medications, and the identity and quantity of the medications received, distributed, and returned to the pharmacy.

3.4 Investigational Product Dispensing

One blister card containing 7 days of drug/placebo and 1 additional (emergency) blister card containing 7 days of drug/placebo will be distributed after randomization (and on or prior to Study Week 1, Day 1). Each week the subject will receive a new blister card with enough medication for 7 days of drug/placebo. The extra blister card will be collected at the end of the study or at the next clinic visit if drug/placebo was used during the week prior. A second emergency blister card will be dispensed if the subject returns the first used emergency blister card prior to the end of the study.

3.5 Investigational Product Accountability

The principal investigator, Dr. Robert Miranda Jr., or designated study personnel will maintain a log of the receipt of all investigational products and record of dispensing of all investigational products to the subject. Investigational product for each subject will be inventoried and accounted for throughout the trial. The principal investigator or his staff will count the capsules remaining at the end of the study and record the capsules count on the appropriate drug accountability form. Subject compliance with investigational product will be assessed by comparing unused capsule count to dispensing logs and dosing records (number of capsules dispensed, number of capsules prescribed, versus the number returned). Subjects will also be asked to account for any missing capsules. If the blister card is not returned, the subject will be asked to report daily drug self-administration.

3.6 Investigational Product Administration

A licensed individual (i.e., study physician, nurse practitioner) or their designee will ensure the appropriate study medication packets will be dispensed to the appropriate study subject (i.e. perform a drug utilization review on all study medication prior to it being given to a study subject).

One blister card containing 7 days of drug/placebo and 1 additional (emergency) blister card containing 7 days of drug/placebo will be distributed after randomization (and prior to Study Week 1, Day 1). Each week the subject will receive a new blister card with enough medication for 7 days of drug/placebo. The extra blister card will be collected at the end of the study or at the next clinic visit if drug/placebo was used during the week prior. A second emergency blister card will be dispensed if the subject returns the first used emergency blister card prior to the end of the study.

Atomoxetine will be self-administered by subjects once daily after eating and with a full glass of water beginning on Study Week 1, Day 1 and continuing through Study Week 6, Day 7. The first dose will be taken in the study clinic whenever possible. Subjects will be provided with water and a snack to take with first dose. Dose will be titrated, as tolerated, to a target dose of 80 mg once per day of atomoxetine. Dose titration and maintenance will occur as shown in **Table 1**. Capsules should be swallowed whole and should not be cut, crushed, or chewed.

Table 1: Schedule of Administration of Investigational Project

Study Period	Time Period	AM Dose (# of capsules)	PM Dose (# of capsules)
Titration	Study Week 1, Day 1 – 3	40 mg (1)	None
Maintenance	Study Week 1, Day 4 – Week 6, Day 7	40 mg (2)	None

Missed Doses: If a subject misses more than one dose of investigational product, s/he will be instructed to re-start taking the investigational product at the dosage level that s/he was taking before stopping. If one dose of investigational product is missed, s/he should take it immediately unless it is close to the time for the next dose. In that case the subject should skip taking the missed dose of investigational product and wait until the usual time to take their next dose of investigational product. The subject should not double up doses.

Dose Reduction and Discontinuation. For problematic nausea (or other mild-moderate AEs), the dose may be reduced. If the adverse event (AE) resolves at the lower dose, another attempt to increase the dose to the target is permissible at the designated study physician's discretion.

3.7 Psychosocial/Behavioral Platform

The psychosocial/behavioral platform, *Path 180*, consists of a series of seven computerized alcohol intervention modules. This sophisticated interactive alcohol intervention was adapted from *Take Control* (131), a proven adult program co-developed by Megan Ryan (NIAAA) and Dr. Eric Devine (Boston University School of Medicine). *Take Control* is derived from a self-help approach developed by the NIAAA that provides evidence-based, field-tested information for individuals with alcohol problems, and suggestions for making changes in their drinking. The NIAAA material is available in a NIAAA booklet entitled "Rethinking Drinking" and on an NIAAA website http://rethinkingdrinking.niaaa.nih.gov.

Path 180 is adapted from *Take Control* and modeled after work by Drs. Robert Miranda and Peter Monti and colleagues (132) and implemented in the principal investigator's prior research (133). Seven sessions of motivational enhancement (MET) and cognitive behavioral therapy (CBT) were selected based on the positive relationship between intervention duration and successful treatment outcomes. Many adolescents are ambivalent about changing their alcohol use, consequently MET is often necessary to help challenge cognitive distortions regarding personal use and improve treatment readiness. CBT is grounded in social cognitive learning theory and targets common maladaptive beliefs and behaviors associated with alcohol misuse, including cognitive distortions, poor coping and communication skills, and maladaptive problem solving.

Subjects will view a single module of *Path 180* at each clinic visit starting at the baseline/randomization visit on Week 1, Day 1. If a visit is missed, missed modules will be reviewed at the next visit. As part of *Path 180,* subjects complete worksheets, which they take home with them (after study staff make photocopies for the subject's reference at future sessions). Paper versions of the actual modules, however, are not to be given to the subject to take home and must remain at the laboratory.

Delivering these materials in a computerized method in this trial mitigates COVID-19-related risks associated with face-to-face counseling sessions and has the advantage of standardizing the amount of educational material received by the subject. Subject viewing of the *Path 180* Modules will be recorded on a CRF.

3.8 Concomitant Medications

For study inclusion, subjects cannot have taken any psychotropic medication in the **30 days prior to the date of randomization**.

Pharmaceutical treatments approved for treatment of AUD or treatments known to be used off-label or experimentally for treatment of AUD are prohibited during the study. The following drugs approved for the treatment of AUD are also prohibited (in the 30 days prior to randomization):

- Oral naltrexone (Revia, Depade)
- Depot naltrexone (Vivitrol)
- Disulfiram (Antabuse)
- Acamprosate (Campral)
- Nalmefene (Selincro)

Subjects will be instructed to check with study staff before taking any new medications or stopping current medications. Subjects will be informed that starting any new medication without consulting study staff could pose health risks and/or result in their discontinuation from the study drug.

Management of investigational products and concomitant medications during the study (i.e., post-randomization) is at the discretion of a designated study physician. The principal investigator or designee may consult with the medical monitor if there are questions.

Study Procedures

4.1 Recruitment of Subjects

Subject recruitment methods will include standard tactics (i.e., flyers, newspaper advertisements, social media advertisements, radio advertisements, and television advertisements). The Brown University Institutional Review Board (IRB) will approve all advertising materials used for subject recruitment.

Interested youth that see our social media ads will be provided a link to a brief online (Qualtrics) survey to determine whether they are tentatively eligible based on our IRB-approved subject selection criteria. Specifically, in our IRB-approved social media advertisements, interested youth will click on the ad, which will link them to the brief online survey. If tentatively eligible, youth will be asked to provide their contact information so that study staff can reach out to them and conduct further screening.

Interested candidates responding to recruitment materials either initially by telephone or after providing their contact information on the online survey, will be asked to complete a standardized telephone interview that includes questions about their drinking behavior, health status, interest in participation, and availability for the entire trial. Study staff will ask these questions without revealing the entry criteria for the study. Candidates who report drinking and other information consistent with the entry criteria and appear to be available and interested in the study will meet with the principal investigator or designated investigational staff, ideally within 14 days after the initial inquiry, to start the informed consent/assent and assessment process. If interested volunteers contact us by email, a telephone appointment will be scheduled and the email will be deleted as soon as possible to decrease risks associated with a breach of confidentiality. Phone messages will also be deleted as soon as possible. Interested volunteers can also leave their name and phone number and/or email address with study staff, so that we can contact them.

Research assistants and if applicable, any other staff, will be charged with monitoring recruitment inquires. Research staff will contact potential subjects via text, email, or phone call to schedule a telephone interview. All staff will be trained, first with mock sessions and subsequently supervised, in administration of the telephone interview and responding to extensive questions regarding the study.

4.2 Informed Consent, Assent, and Parent Permission

Informed Consent Process. At the in-person screening visit, candidates and their parent(s)/legal guardian(s) (if younger than 18 years) — herein referred to as 'parent' — will meet with the principal investigator or his designee and receive an explanation of the study purpose and requirements. Potential subjects must have breath alcohol content (BrAC) of 0.000 measured by breathalyzer when signing the form (tested before review and signing of document). Repeat measurements of BrAC are permitted at the discretion of the investigator. If still interested after receiving an explanation of the study, the candidate and his/her parent(s) (if < 18 years) will be given the opportunity to review, inquire about, and sign the study informed consent, assent, or parent permission form approved by the Brown University IRB. The purpose and procedures of the study will be fully explained orally and in writing in a manner that is understandable and appropriate for all youth and parents. The informed consent/assent/parent permission process will be carried out in a manner and location that ensures privacy; provides adequate information about the study in language understandable to the potential subject and their parent(s) (i.e., we will require all potential subjects and, if younger than 18 years, their parents to understand English); ensures the potential subject and parents of youth younger than age 18 years comprehends the information provided (i.e., embedded comprehension questions throughout the informed consent/assent/parent permission documents and process); affords adequate opportunity for the potential subject and, if applicable, their parent(s) to consider all options; adequately addresses all of the questions from the potential subject and, if applicable, their parent(s); and obtains the potential subject's voluntary agreement to participate.

Parents of youth younger than 18 years will provide informed written parent permission. Parents will be informed that the purpose of the study is to test if and how a medication, in combination with counseling, helps to decrease alcohol use among adolescents who want to reduce their drinking. Our assent process considers each minor's level of understanding of the research protocol, including potential risks, actively conveys respect for their autonomy and rights in the context of clinical research, and requires all minors to voluntarily agree to participate in the study. It will be made clear that all information obtained during assessments is confidential and that parents will not have access to adolescents' responses, except if youth endorse intent to harm themselves or others. Subjects and if applicable their parent(s) will be given a copy of the signed informed consent/assent/parent permission form(s). Parents of individuals 18 years of age and older will not be involved in the study.

Facilitate Understanding. Throughout the consent/assent/parent permission forms and during consent review with potential subjects and if applicable their parent(s) there are embedded questions to facilitate understanding. These embedded questions highlight the most essential aspects of the study. Potential subjects and parents (if applicable) will be reminded and encouraged to ask questions, not only during the consent process but throughout the study. Potential subjects and parents (if applicable) will be given a copy of the consent/assent/parent permission form to review at their discretion. Subjects and parents (if applicable) will be required to understand simple English and thus, translators will not be required.

Documentation. A form will be maintained after each consented subject. This form will include the subject's first name, date/time consented, version of consent form consented, and whether they were randomized or not. Assent and parent permission forms will be similarly completed when appropriate. These forms will be kept away from subject data and with locator forms.

Additional Considerations. We will obtain assent from minors; for details, see above (*Informed Consent Process*).

4.3 Selection and Withdrawal of Subjects

4.3.1 Inclusion Criteria

The study physician will make all medical eligibility and termination decisions. To be eligible, the subject must:

1. Be 14 to 20 years old, inclusive; we will exclude children < 14 due to diversity across adolescence and youths > 20 because our focus is teenagers
2. Self-report consuming alcohol ≥ 2 days/week on average in the past 28 days
3. Meet the DSM-5 criteria for AUD
4. Be interested in reducing alcohol use
5. Be able to verbalize an understanding of the consent/assent form, able to provide written informed consent/assent, verbalize willingness to complete study procedures, able to understand written and oral instructions in English and able to complete the questionnaires required by the protocol.
6. Have parent permission, if younger than 18 years
7. Be able to take oral medication and be willing to adhere to the medication regimen
8. Complete all assessments required at screening and baseline.
9. Agree to the schedule of visits, verbally acknowledge that s/he will be able to attend each scheduled visit, participate in phone visits and that s/he does not have any already scheduled events or a job that may substantially interfere with study participation.
10. Not anticipate any significant problems with transportation arrangements or available time to travel to the study site over the next 2 months.
11. Agree (if the subject is female and of childbearing potential) to use at least one reliable method of birth control, unless she is surgically sterile, partner is surgically sterile or she is postmenopausal. Examples of reliable methods include (but may not be limited to):
    a. oral contraceptives
    b. contraceptive sponge
    c. contraceptive skin patch
    d. diaphragm or condom
    e. intrauterine contraceptive system
    f. levonorgestrel implant
    g. medroxyprogesterone acetate contraceptive injection
    h. complete abstinence from sexual intercourse
    i. hormonal vaginal contraceptive ring
    j. surgically sterile
    k. postmenopausal

l. partner is surgically sterile

4.3.2 Exclusion Criteria

To be eligible, the subject must not:

1. Be currently receiving AUD treatment

   NOTE: Current psychotherapy for other reasons will be considered on a case-by-case basis. Psychotherapy for a disorder that may be related to the subject's use of alcohol will be exclusionary. However, shorter term focused behavioral therapy for defined problems for non-alcohol related problems may be acceptable.
2. Have significant alcohol withdrawal symptoms (score > 10) on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-AR)
3. Have a coexisting moderate to severe substance use disorder other than cannabis and nicotine, as defined by DSM-5 criteria
4. Have a urine toxicology screen positive performed during screening or baseline for any of the following substances:
   a. benzodiazepines
   b. cocaine
   c. opiates
   d. amphetamines
   e. buprenorphine
   f. methadone
   g. barbiturates
   h. oxycodone
   i. 3, 4-methylenedioxy-methamphetamine (MDMA, also known as ecstasy)
   j. methamphetamines

   NOTE: Testing for tetrahydrocannabinol (THC) will be included in the urine drug test; however, subjects who test positive for THC are still eligible to participate in the study. The results for THC will be recorded for information only.
5. Have been treated with a pharmacotherapy for AUD or a carbonic anhydrase inhibitor within 30 days prior to randomization
6. Compelled to alcohol treatment by the justice system or has probation or parole requirements that might interfere with study participation
7. Have a history of liver disease or have clinically significant abnormal laboratory values, including elevation of liver enzymes (AST, ALT) 5-fold above the upper limit of normal (ULN).
8. Have a history of renal impairment or renal stones
9. Have a history of narrow angle glaucoma or pheochromocytoma
10. Have a history of heart problems or defects, abnormal blood pressure

11. Have a history of progressive neurodegenerative disorder, or clinically significant neurological disorders
12. Have clinically significant physical abnormalities per physical exam
13. Be pregnant or nursing, if female
14. Have taken prescribed psychotropic medication use in the past 30 days
15. Have any of the following, based on DSM-5 criteria as assessed using the K-SADS:
    a. Current or lifetime diagnosis of psychotic disorders
    b. Current bipolar disorder
    c. Current major depressive episode

    NOTE: Subjects diagnosed with psychiatric disorders not specifically excluded above may be included at the discretion of the principal investigator as long as the concurrent treatment for the comorbid psychiatric condition does not compromise the study integrity by virtue of its type, duration, or intensity.

16. Have any of the following:
    a. Attempted suicide ever
    b. Current (past year) suicidality risk in accordance with DSM-5 criteria as assessed using the K-SADS (see note below about assessment of subjects at low risk)
    c. Current (since screening K-SADS) suicidality risk as indicated during the conduct of the C-SSRS with concurrence after a study physician's evaluation if the response to C-SSRS questions 1 or 2 is "yes"

    NOTE: The K-SADS suicidality module is inadequate to fully determine the potential suicidal risk of an individual, any subject who endorses any item should be evaluated further by a study clinician using the C-SSRS who should document whether the subject is appropriate for study inclusion based on his/her clinical judgment of the potential suicide risk of the subject. Likewise, if the subject responds "yes" to either the first two questions on the screening C-SSRS performed on the day of randomization as a final eligibility check, the subject should also evaluated by a study clinician for current suicidality risk, who should document the subject's suitability for study inclusion.

17. Have a known sensitivity to atomoxetine
18. Have a history of prior treatment with atomoxetine
19. Have a serious or unstable medical illness or any potentially life-threatening or progressive medical condition other than addiction that may compromise subject safety or study conduct

4.4 Eligibility Screening Assessments

After the subject signs informed consent/assent form and, if younger than 18 years, their parent signs the parent permission form, screening may begin. After providing written informed consent, subjects complete the Screening Visit for initial evaluation of eligibility.

Prohibitions and Restrictions. Potential subjects must be willing/able to adhere to the following prohibitions and restrictions to be eligible for the H-LAB session:

- Refrain from consuming alcohol during the H-LAB alcohol cue exposure trials.
- Refrain from smoking during the H-LAB session except for designated smoke breaks (approximately 1-1.5 hours prior to lab session).

Subjects will be instructed not to take atomoxetine prescribed from a doctor outside of the study during their time in the study and that they should report any new medications they are taking at each visit or telephone contract.

The above assessments can be performed in any order except that it is recommended to perform all self-report and vital sign assessments prior to the blood draw assessments. If any of the assessments reveals that the subject is not eligible for the study, screening can be immediately terminated. Clinical chemistry tests may be repeated at the discretion of the study physician if the first assessment yields values outside normal laboratory limits. The eligibility checklist will be reviewed, and if the subject is still eligible after the assessments are completed at the first screening visit (or additional screening visits), the subject will be scheduled for Randomization/Baseline Visit, where final eligibility will be determined. Hypertensive subjects will be referred to their primary care physician for additional assessment and possible treatment.

4.5 Randomization/Baseline Visit(s) and Final Eligibility Assessments

If the subject is eligible after performing all the initial screening assessments, s/he will be scheduled to start the study and will come to the clinic for a final eligibility check and physical exam approximately 1 week after the initial screening visit.

An eligibility checklist will be completed and reviewed by a study investigator and/or his designee.

NOTE: The Randomization/Baseline Visit may be conducted over additional days/appointments if necessary.

4.6 Measures Taken to Minimize/Avoid Bias

4.6.1 Randomization

If eligible for the study, subjects will be randomized in an approximate 1:1 ratio ($N = 50$; targeting 21 subjects per group – 42 subjects total) to either atomoxetine or placebo for 6 weeks. Urn randomization will ensure approximately equal representation of males and females.

If the subject is randomized and is never dispensed study drug, then the subject will be considered a randomization failure and an additional subject will be randomized with the next randomization sequence at the time s/he is randomized. Likewise, if the subject was randomized and then is determined to not be eligible for the study and never received study drug, then another subject will be randomized such that the total numbers of subjects who were eligible, randomized, and dispensed study drug meet the enrollment goals. In the case of a subject who was eligible, randomized, and dispensed study drug but did not return for follow-up visits, this subject will not be replaced. Any subject who received study drug but was later determined to be ineligible will likewise not be replaced. The reason(s) that a subject was considered a randomization failure or screen failure will be documented in source documents and case report forms (CRFs).

4.6.2 Blinding

Atomoxetine and placebo capsules will be identically matched in appearance and the blister cards labeled not to reveal the drug identity. The principal investigator or designated study physician will make the decision to unblind the identity of the investigational product if the study blind needs to be broken to

make medical decisions regarding subject treatment. If it is determined that unblinding is necessary to assess AEs or SAEs for expedited reporting, the Data and Safety Monitoring (DSMB) may request unblinding of a subject. The principal investigator will notify the medical monitor.

4.6.3 Interventions on Study Week 1, Day 1 (Baseline Visit)

After the subject is randomized, s/he will receive the first blister pack of study drug. Project staff will explain the dosing plan to the subject.

Every study subject will be provided with a **wallet card** and instructed to carry this card that identifies the potential investigational products that s/he could be taking during the study. The card will provide the name and 24-hour phone number of the investigator (study physician) who can be contacted in the event of an emergency. The card will also instruct the non-study physician rendering emergency care to contact the study physician and inform him/her about the care.

Visits may be scheduled and conducted on any day of the week. Visits can be conducted outside of the scheduled study week, but only based upon subject request (e.g., for reasons related to patient non-compliance with the study schedule) and with prior approval from the principal investigator. Each subject will receive a visit schedule to take home for future reference.

4.6.4 Study Week 1 Telephone Contact

On Study Week 1, Day 3 subjects will be called for a safety assessment including alcohol withdrawal symptoms and given a reminder their dose will increase Study Week 1, Day 4.

4.6.5 Maintenance Phase

During the six-week active treatment phase of the study (Study Weeks 1 to 6), subjects will be seen in person at our offices or remotely, as needed and appropriate, each week. Reminder phone calls, text messages, and/or emails will be sent prior to each visit.

Note that the maintenance phase begins 4 days after study drug administration (Week 1 Day 1). The Week 1 visit needs to be completed between Week 1 Day 3 and Week 1 Day 7 (inclusive).

An alcohol breathalyzer will be administered at each visit, prior to any study assessments, to determine if the subject meets the BrAC requirement of a BrAC ≤ 0.00 before proceeding with assessments. A urine drug test will be performed at each visit. At each of the clinic visits, subjects will meet with one or more study staff members who will assess for possible adverse events since the last visit, take vital signs, inquire about other medication use and assess drinking by TLFB. Pregnancy test and birth control methods (if female) will be assessed.

A new supply of investigational product will be given and the blister cards from the previous period will be collected and a capsule count will be performed for accountability. Blister cards with unused capsules will be returned to the subject. The dosing schedule will be reviewed. The subject will be instructed to bring the blister cards with them to the next visit so the project staff can perform drug accountability (capsule counts). The subject will also be instructed to contact project staff if they are experiencing any intolerable adverse events and/or are contemplating drug discontinuation.

Additional in-clinic visits are permitted under the protocol, if needed, due to the following circumstances: (a) the subject has concerns either about the medication or their drinking and wishes to be seen at a time other than their next scheduled in-clinic visit, (b) the subject has missed a visit and wishes to resume regular participation before their next scheduled visit, (c) the subject has reported some change in health, functioning, or circumstances that necessitates a visit to conduct safety assessments and evaluate the risk

of continued participation in the trial, (d) clinical laboratory measurements need to be repeated, or (e) a study physician or principal investigator deems it necessary.

Subjects desiring additional counseling or professional therapy for non-crisis psychiatric matters (e.g., family or relationship problems, transient school issues) will neither be discouraged from such activity nor asked to postpone until their study participation is concluded. Subjects who initiate outside psychotherapy during the study will not be withdrawn. Subjects may (or may not) be withdrawn if they start new medications, at the discretion of the study physician, if there are any safety concerns.

During the Study Week 5 clinic visit, subjects will complete a second H-LAB paradigm session, which will follow the same procedures as the pretreatment baseline assessment session.

4.6.6 Telephone Assessments

A brief telephone interview (approximately 10 minutes) will occur if a subject misses a clinic visit but agrees to check-in by telephone to assess AEs, concomitant medication use and the emergence of withdrawal symptoms, to encourage the subject to continue taking investigational products, to verify that the subject is taking the prescribed dose, and to remind the subject of the next scheduled visit and dose increases. A summary of the telephone script follows:

1. ***AEs:*** An open-ended question will be asked as follows: "How have you been feeling since your last clinic visit or phone contact?" If the subject reports a new AE, the resolution of an AE, or a change in the severity of an AE, ask additional questions to determine the severity and dates of occurrence or resolution.
2. ***CIWA-AR:*** Subjects will be assessed for the emergence of withdrawal symptoms using the CIWA-AR. The subject may be asked about changes in drinking status after responses to the CIWA-AR interview indicate significant withdrawal.
3. ***Concomitant Medications:*** Ask the following question: "Have you taken any new medications since you were last seen in the clinic or since our last call? If the subject responds affirmatively, record the name of the medication, the daily dose, route of administration, and reason used. If the medication is contraindicated for the study, then notify a study physician, nurse practitioner, or physician assistant for follow-up with the subject.
4. ***Drug Compliance:*** Verification that the subject is taking the prescribed dose and a reminder to take investigational product and to return the blister card(s) with untaken capsules at the next visit will be made. During the Study Week 1 telephone contact, the subject will be reminded of the drug escalation schedule.
5. ***Reminders:*** Remind the subject of their next scheduled clinic visit, and adjust the date within the visit week if they have a conflict.

4.7 Human Laboratory Paradigm Testing (H-LAB)

During the Randomization/Baseline Visit (prior to taking the study medication) and in Study Week 5, subjects will be seen in-person in the clinic for the human laboratory paradigm testing. The human lab session will last for approximately 45 minutes. Laboratory sessions should occur in the late afternoon if possible. The subject must have BAC = 0.00 prior to starting the H-LAB session. Whenever possible, to ensure that subjects take the capsule on the day of cue reactivity, subjects should either self-report taking their study medication earlier that day or take their study medication while observed by study staff just

before the cue reactivity session. If the subject, for whatever reason, cannot take their study medication that day, they can be rescheduled to complete the cue reactivity paradigm.

After confirmation of eligibility for the H-LAB paradigm, subjects who use nicotine will have the opportunity to use it approximately 1 hour prior to starting the H-LAB paradigm. All subjects will be asked (but not required) to drink 4 oz of water and a restroom break prior to the lab session will be provided. Upon completion of clinical assessments, subjects will be escorted to a comfortable chair in a lighting-controlled, sound-attenuated room for alcohol exposure.

Subjects will be presented with either their *most commonly consumed* alcoholic beverage (e.g. vodka, lager beer) or bottled water. The alcohol or water beverage is presented in the subject's preferred mode of consumption (e.g., small tumbler for vodka, Pilsner glass for beer). Specific alcohol brand preferences are accommodated whenever possible, including choices of mixers (e.g., vodka will be poured into a glass along with orange juice if the favorite drink were a screwdriver).

The H-LAB paradigm will follow our standardized procedures. Audio-recorded instructions ensure standardization within and across subjects. After attaching the physiological monitor (i.e., blood pressure cuff), the session begins with a 3-minute relaxation period that involves subjects sitting quietly and doing nothing. Then a 3-minute water trial begins, in which subjects hold and smell a glass of water as a standard procedure to control for the effects of simple exposure to any potable liquid, including all aspects of stimuli and movement except the nature of the beverage. A second 3-minute relaxation period follows the water trial. Next, subjects hold and smell a glass of their most desired or commonly consumed alcoholic beverage for two consecutive 3-minute alcohol trials. Order of water and alcohol trials is not counterbalanced due to known carryover effects. The water is accompanied by a commercially labeled water bottle and alcohol by the bottle or can from which it was poured and prepared as the teen usually drinks it. Across water and alcohol trials, subjects sniff the beverage for 5 seconds each time a tone sounds: 13 tones sound at variable intervals during each 3-minute block to ensure that all youth receive the same olfactory exposure. Observation via one way window ensures compliance. Subjects rate their alcohol craving after each 3-minute trial.

After every 3 minutes of exposure, each subject will rate his/her urge to drink alcohol using a visual analogue scale (VAS). The primary efficacy endpoint in the H-LAB is the "strength" of alcohol craving measured on a visual analogue scale (VAS; Item 1 below).

Following the H-LAB paradigm, subjects will receive a 7-day supply of the blinded study medication, and the dosing schedule will be reviewed. The subject will be instructed to bring the blister cards with them to the next visit so the project staff can perform drug accountability (capsule counts). The subject will also be instructed to contact project staff if they are experiencing any intolerable adverse events.

4.8 Final Clinic Visit (End of Study Visit)

The final in-clinic assessment will occur at the end of (or immediately following) the active treatment phase, **typically Study Week 6, Day 7**. This visit should occur after the subject takes the last dose of study drug. Subjects will complete the Client Satisfaction Questionnaire - 8 (134), an instrument used to assess patients' satisfaction with psychiatric treatment (135, 136). If a subject withdraws from the study early for any reason, the subject will be asked to return to the clinic for the conduct of the final clinic visit assessments.

4.9 Telephone Follow-up Assessments

Subjects will be contacted by telephone for a follow-up interview 2 weeks after the final in-clinic visit. During this 2-week follow-up interview, the subject will be asked about any ongoing AEs that they may have been experiencing at the last clinic visit and any newly emerged medical conditions/AEs since that visit. To prompt reporting of new AEs, the subject will also be asked about any ongoing or new medication use.

4.10 Conducting Sessions Remotely

Study visits may be conducted remotely, when necessary. By limiting in-person contact, allowing remote sessions may effectively decrease COVID-19-related risks. At the study physician's discretion, the physical exam may be conducted via the Brown University HIPAA-compliant Zoom platform (either in an adjacent room or remotely). Research staff still need to collect vital signs, weight, a urine toxicology drug screen, and a urine pregnancy best (if biological sex at birth is female) in person (prior to the physical exam). Blood chemistry and related tests must be done at a local laboratory.

For weekly visits, Zoom video conferencing will be used to conduct the session for those items amenable to remote collection. Extra medication will be mailed from participants to the laboratory via pre-paid postal mail. When remote sessions are held, biospecimen collection will not be done. Even so, to capture biospecimens on a regular basis, no two consecutive post-randomization weekly checkups may be done remotely unless approved beforehand by a study physician.

Dose-Adjustment Criteria

5.1 Safety Criteria for Dose Adjustment or Stopping Doses

The principal investigator or sub-investigator will follow the protocol to identify and intervene with subjects experiencing clinical deterioration during study participation. Criteria to determine when a subject requires a higher level of care and discontinuation from the trial intervention are detailed below.

5.2 Investigational Produce Dose Reduction

The daily dosage of investigational product may be reduced by the study physician for any AE determined, by the study physician, to compromise the subject's ability to maintain activities of daily living or if the subject reports undue discomfort. While at the target dose (80 mg/day), the dose may be reduced to 40 mg once daily. If the AE resolves at the lower dose, another attempt to increase the dose to the target dose is appropriate at the study physician's discretion.

5.3 Investigational Product Discontinuation

Subjects who are discontinued from investigational product should continue in the study and complete all assessments, including the follow-up assessments, as well as *Path 180*. If the subject discontinues the investigational product before Study Week 5 then they will not complete the H-LAB paradigm.

a. **Pregnancy.** Females who become pregnant during the medication phase of the study, Study Weeks 1 through 6, will be immediately discontinued from the investigational product. The investigator must report a pregnancy within 1 working day of the site being aware to the medical monitor.

b. **Physical Illness.** Subjects will need to be removed from investigational products if they have a serious illness or a disabling condition that precludes them from taking the investigational product.

c. **Adverse Events.** If the subject experiences any AEs that are considered study drug related and for which the investigator has determined that continuation of the study drug could be detrimental to the health of the subject, then drug will be reduced for 1 week, then discontinued, or immediately discontinued as described above.

5.4 Subject Withdrawal or Discontinuation Procedures

Each subject has the right to withdraw consent/assent and withdraw from the study at any time. Parents of minors younger than 18 years of age have the right to withdraw their permission for their child to participate in the study at any time. In addition, the investigator may find it necessary to discontinue a subject for any reason, including (but not limited to) the occurrence of an AE or noncompliance with the protocol.

If a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded and a pregnancy test (females only), vital signs, clinical chemistry, C-SSRS, TLFB and an assessment of AEs will be performed as soon as possible after discontinuation from the study.

5.5 Situations Requiring Discontinuation from the Study or Investigational Product

It is possible that there will be some subjects who cannot be safely managed in the clinical study even though investigational products have been discontinued. Examples are given below.

1. **Increased Drinking.** Subjects whose alcohol problems worsen and, in the opinion of the principal investigator, sub-investigators, or study nurses or physicians, require a more intense level of care than provided in the study may have the investigational product suspended and referred to more appropriate care.
2. **Psychiatric Crises.** Examples of psychiatric crises include but are not limited to the following:
   a. Acute psychosis (hallucinations, impaired reality testing, paranoid ideation, etc.) requiring medication and/or hospitalization or intensive outpatient intervention;
   b. Suicidal or homicidal ideation that results in a credible threat of violence directed at oneself or others;
   c. Hospitalization for psychiatric symptoms.

   Subjects requiring more intensive treatment resulting from acute psychosis or suicidal/homicidal behavior will be referred to local treatment centers, emergency departments, or hospitals as appropriate, but will not be provided with medication or psychotherapy by study staff.

Study Termination Criteria

The principal investigator may terminate the study for reasonable cause after providing written notice to the funding agency in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the DSMB terminates the study for safety reasons, the principal investigator will immediately notify the medical monitor, IRB, and funding agency.

Study Endpoints

6.1 Feasibility and Acceptability Endpoints

6.1.1 Primary Feasibility Endpoint

The number and percentage of subjects who completed the 6-week active medication phase will determine feasibility.

6.1.2 Primary Acceptability Endpoint

The Client Satisfaction Questionnaire (CSQ-8), which ranges in scores from 8 to 32 (higher scores indicate higher satisfaction), will determine acceptability. Treatment satisfaction will be considered acceptable if the number and percentage of subjects who rate their treatment experience in the "satisfactory" or "highly satisfactory" range on the CSQ-8 is ≥ 80%.

6.2 Secondary Outcome: Alcohol Craving Assessed in the H-LAB Paradigm

The secondary endpoint will be alcohol craving assessed during a laboratory alcohol-cue exposure paradigm, at week 5. During the paradigm, participants rated their alcohol craving immediately following exposure to water cues and again immediately following exposure to alcohol cues.

The primary measure of alcohol craving will be the number and percentage of participants who report any level of alcohol craving during a laboratory alcohol-cue exposure paradigm using the following single item: *How strong is your craving to drink alcohol?* Scores range from 0 (None) to 20 (Extremely Strong). Individuals who endorse any level of alcohol craving (e.g., > 1) are considered to experience craving. Individuals who do not report any alcohol craving (e.g., 0) will be regarded as non-craving.

Safety Monitoring Plan

Safety monitoring will be conducted throughout the study; therefore, safety concerns will be identified by continuous review of the data by the principal investigator, clinic staff, medical monitor, and study nurses and physicians.

The Brown University IRB, medical monitor, principal and sub-investigators, and study nurses and physicians will review any safety concerns throughout the trial. In addition, a DSMB will participate in this study.

Quality control is central to all aspects of the activities detailed in this proposal to ensure clinical data accuracy and integrity. Day-to-day oversight of data quality will be delegated to the principal investigator, Dr. Robert Miranda and/or his designee. With assistance from our core team, he will provide direction with the development of data collection forms, recruitment and tracking databases, data management tasks, and statistical analyses and interpretation. The principal investigator or his designee will oversee the production of standard labels/codebooks for all data collection activities. He or his designee will oversee the production of reports that will track indices of project success, which will be reviewed weekly or biweekly at meetings of our core team, where issues or concerns will be deliberated and corrective action plans put into place.

Our research team has substantial experience in the design and implementation of data management procedures that: (a) ensure the validity and integrity of data; (b) guarantee the accuracy and completeness of data during data collection, transmission, and analysis; and (c) maintain confidentiality and data security. These procedures are in accordance with FDA and ICH standards. All procedures involving human research subjects will be performed at the Brown CAAS. The principal investigator will be responsible for coordinating activities of the data safety and monitoring, including arranging weekly meetings and communications, and identifying and reviewing subject materials.

Medical Monitor: A medical monitor, Dr. Robert Swift, MD, PhD, has been appointed by the principal investigator. Dr. Swift will be available for making recommendations to the investigator on the severity of any SAEs and the relatedness to the study interventions. Dr. Swift will also be responsible for tracking and assessing trends in the AEs reported.

Data and Safety Monitoring Board: Although an independent DSMB is not required because this project is not a Phase III clinical trial, we will assemble a DSMB. The DSMB for this project will consist of senior researchers in the field who have expertise in adolescent or pharmacotherapy research or both, and will include at least one physician.

No member of this DSMB will be directly involved with the conduct of this study or have a conflict of interest with this study. The DSMB will meet at the onset of the study, at least once quarterly thereafter, and when 25%, 55%, and 85% of subjects have been enrolled. Ad hoc meetings may also be scheduled if the need arises (e.g., in the event of a study-related SAE). The DSMB will discuss study conduct and progress, subject safety, and, when appropriate, efficacy. Specifically, items to be reviewed include: interim/cumulative data for evidence of study-related adverse events, interim/cumulative data for evidence of efficacy when 85% of subjects have completed the protocol (if necessary), data quality, completeness and timeliness; adequacy of compliance with goals for recruitment and retention, including those related to females and minorities; adherence to the protocol; and factors external to the study, such as scientific or therapeutic developments that may impact subject safety or the ethics of the study.

The Board will be blinded to subjects' actual randomized group assignments but may request at any time that the blind be broken, if concerns arise from the blinded data. Ad hoc meetings will be convened if SAEs occur that are considered at least possibly related to the investigational product. At the end of each meeting, the DSMB will make a recommendation regarding trial continuation and will forward that recommendation to the principal investigator who will forward it to the Brown University IRB and the Program Official at the funding agency (i.e., NIAAA).

In addition, the investigative team will meet on a weekly or biweekly basis to evaluate the study's recruitment and retention procedures, to monitor any potential significant benefits or risks that may occur to warrant the early termination of the study and to monitor study progress.

Adverse Event Assessment

7.1 Adverse Events and Serious Adverse Events

The investigator and study project staff are responsible for the detection, documentation, classification, reporting, and follow up of events meeting the definition of an adverse event (AE) or serious adverse event (SAE).

7.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of an investigational product, whether related to the investigational product. Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in severity or frequency.

7.1.2 Serious Adverse Events and Serious Unexpected Adverse Events Definition

An SAE is any untoward medical occurrence that meets one of the following:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information included in the Product Label for the drug.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

7.1.3 Methods/Timing for Assessing, Recording, and Analyzing Safety Endpoints

AEs will be assessed at study visits starting after the first administration of investigational product until the final follow-up visit. However, SAEs will be collected from the time of informed consent onward. General symptoms will be collected via an open-ended question: "How have you been feeling since your last visit or the last time we spoke?"

AEs will be documented in the source records, and recorded on the CRFs using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the CRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess all AEs for seriousness, relationship to investigational product, and severity. When an event has not resolved by study closure, it will be documented on the AE CRF as "ongoing."

If a female has a positive or borderline pregnancy test after enrollment, the medical monitor will be contacted, and the pregnancy will be recorded as an AE. In accordance with standard clinical practice, results of pregnancy tests will not be disclosed to the subjects' parents unless the subject is age 15 or younger. Parents will be informed of this point during the parent permission process. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed. The outcome of the pregnancy will be reported to the medical monitor, funding agency, and the Brown IRB without delay within 24 hours of knowledge of the event if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution (the event either resolved or stabilized and is not expected to resolve in the near term). AEs will be reported up to 2 weeks following completion of, or termination from investigational product administration. At the follow-up telephone contact, AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

7.1.4 Classification of Adverse Event Intensity and Relationship to Investigational Product

For each recorded AE or SAE, a study physician must assess severity. For those AEs included in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 5.0), these severity criteria will apply. For those not listed in the CTCAE, the following criteria will be used:

Mild:	An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.
Moderate:	An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention.
Severe:	An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required, and typically requires intensive therapeutic intervention.
Life-threatening	An event that puts the subject into imminent risk of death without intervention.

Clinical chemistry severity and blood pressure increases will be graded in accordance with the CTCAE version 5.0.

The investigator must assess relationship to the investigational product based on the following criteria:

Unrelated:	The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.
Unlikely:	There is evidence of exposure to the investigational product but there is another more likely cause of the AE/SAE.
Possible:	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.
Probable:	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.
Definite:	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

7.1.6 Outcomes and Actions Taken

All unresolved AEs will be followed for a minimum of 14 days (unless the AE is an ongoing pregnancy which must be followed to conclusion) after the subject's End of Study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized prior to the 14-day period, or the subject is lost to follow-up.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.

For each recorded AE or SAE, the investigator must assess outcome at the time of last observation, as follows:

Fatal:	The subject died.
Resolved without Sequelae:	The AE or SAE has ended.
Resolved with Sequelae:	The AE or SAE has ended but changes are noted from baseline.
Unresolved – Ongoing:	The AE has not ended and is ongoing at the end of the reporting period (i.e., 14 days after the final Follow-up visit) and the investigator deems that further follow up is not medically required
Unknown – Lost to Follow-up:	Lost to follow-up after repeated unsuccessful attempts to contact the subject.

Actions taken with respect to investigational agents (discontinuation or not) will also be recorded. In addition, if the AE was treated (medications or other physical measures), this will also be recorded.

7.2 Reporting Serious Adverse Events

7.2.1 24-hour Reporting Requirements (Initial Report)

Any SAE, including death due to any cause, which occurs to any subject from the time of admission through discharge whether related to the investigational product, must be reported ***within 24 hours*** of knowledge of the event to the medical monitor or alternate.

The following information must be provided with the initial report of an SAE:

- Name of person reporting the SAE/unexpected AE
- Subject's ID number
- Name of the principal investigator and institution
- Date the subject signed informed consent
- Date first dose of investigational product was ingested
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of investigational product prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to investigational product (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the investigational product, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-Day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the medical monitor/alternate within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- AE CRF pages
- Copies of source documents pertinent to the event (lab reports, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the medical monitor/alternate

These documents must be submitted by either email attachments or via overnight courier.

7.2.2 Reporting to the IRB

Unanticipated problems involving risk to subjects or others, SAEs related to participation in the study and all subject deaths should be promptly reported by phone, email, or fax to the Brown University IRB.

An FDA cleared, CLIA waived urine drug test card will be used to assess candidates for recent use of opiates (i.e., morphine test), cocaine, amphetamines, methamphetamine, tetrahydrocannabinol (THC), buprenorphine, methadone, benzodiazepines, oxycodone, barbiturates, and 3,4-methylenedioxy-methamphetamine (MDMA – also known as ecstacy). During screening subjects must be negative for all substances except THC. If positive for these drugs at other times during the study, the subject will not be removed from the study but should be asked about medication use and possibly re-evaluate their medical history for substance abuse.

Statistical Methods

8.1 Feasibility and Acceptability Endpoints

8.1.1 Primary Feasibility Endpoint

The number and percentage of subjects who completed the 6-week active medication phase will determine feasibility (target ≥ 70%).

8.1.2 Primary Acceptability Endpoint

The Client Satisfaction Questionnaire (CSQ-8), which ranges in scores from 8 to 32 (higher scores indicate higher satisfaction), will determine acceptability. Treatment satisfaction will be considered acceptable if the number and percentage of subjects who rate their treatment experience in the "satisfactory" or "highly satisfactory" range on the CSQ-8 is ≥ 80%.

8.2 Secondary Outcome: Alcohol Craving Assessed in the H-LAB Paradigm

The secondary endpoint will be alcohol craving assessed during a laboratory alcohol-cue exposure paradigm, at study week 5. During the paradigm, participants rated their alcohol craving immediately following exposure to water cues and again immediately following exposure to alcohol cues. The primary outcome measure will be is the number and percentage of participants who report any level of alcohol craving during a laboratory alcohol-cue exposure paradigm (following exposure to alcohol cues) using the following single item: *How strong is your craving to drink alcohol?* Scores range from 0 (None) to 20 (Extremely Strong). Individuals who endorse any level of alcohol craving (e.g., > 1) are considered to

experience craving. Individuals who do not report any alcohol craving (e.g., 0) will be regarded as non-craving. Using generalized estimating equations, we compared the likelihood of alcohol craving as a function of medication condition.

Quality Control and Quality Assurance

This study will be conducted under International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use; the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor's representatives (clinical monitors). The Project Coordinator or Project Director will review source documents and CRFs for accuracy and completeness. Any discrepancies will be resolved with the investigator, as appropriate.

Audits and Inspections

Authorized representatives of the Sponsor and the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines, and any applicable regulatory requirements.

The principal investigator will notify the Brown University IRB and the sponsor, NIAAA, if contacted by a regulatory agency about an inspection.

Ethics

9.1 Ethics Review

The study will be conducted under a protocol reviewed by the local IRB; the study is to be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 Code of Federal Regulations (CFR) Part 50 and the Belmont Principles.

9.1.1 Review/Approval of Study Protocol

Written approval from the appropriate IRB before study initiation. Progress reports will be submitted to the IRB by the principal investigator at the frequency requested by the Brown University IRB (i.e., at least annually).

9.1.2 Protocol Modifications/Amendments

All necessary protocol changes will be submitted in writing as protocol amendments to the Brown University IRB by the principal investigator for approval prior to implementation.

9.1.3 Protocol Deviation Reporting Procedures

All subject-specific deviations from the protocol will be documented. The principal investigator or his designee(s) will be responsible for identifying and reporting all deviations, which are occurrences involving a procedure that did not follow the study protocol. Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study is considered a major deviation and will be reported immediately to the Brown University IRB.

9.2 Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guideline and the Code of Federal Regulations (CFR).

9.2.1 Confidentiality

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the IRB, the sponsor, or regulatory agencies. We obtained a Certificate of Confidentiality from NIH.

9.2.2 Compensation for Participation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of gift cards or ClinCard.

9.2.3 Written Informed Consent, Assent, and Parent Permission

The informed consent/assent/parent permission process and documents were reviewed and approved by the Brown University IRB. The consent/assent/parent permission documents contain a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR Part 50.

A written informed consent/assent/parent permission document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles, and HIPAA Authorization will be signed by the subject and when applicable his or her parent before any study-related procedures are initiated for each subject.

All potential subjects for the study and when applicable their parents will be given a current copy of the appropriate informed consent, assent, and/or parent permission form(s) to read. All aspects of the study and informed consent/assent/parent permission will be explained in lay language to the subject and when applicable his or her parent(s) by either the investigator or a medically trained designee. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation.

All study subjects and when applicable their parents will be given a copy of the signed informed consent/assent/parent permission form.

9.2.4 Delegation of Responsibilities and Adequate Resources

The principal investigator will have adequate time to conduct the study properly and have an adequate number of qualified staff to assist with the conduct of the study.

The term "investigator" used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. The principal investigator may delegate responsibilities to other study personnel. The principal investigator shall delegate tasks only to individuals qualified by education, training, and experience to perform the delegated tasks. The principal investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The principal investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the study site.

Data Handling and Record Keeping

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, laboratory results, data recorded in automated instruments, and pharmacy records, etc. Data will be transcribed from source documentation into paper CRFs. Only questionnaire data will be entered directly onto CRF (i.e., without prior written or electronic record of data). The transcribed data will be consistent with the source documents or the discrepancies will be explained.

10.1 Subject Identification and Confidentiality

Subjects will be identified on CRFs by a unique subject number. No personal identifier will be used in any publication or communication used to support this research study. The subject number will be used if it becomes necessary to identify data specific to a single subject. The IRB is eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied or electronic medical and research records.

10.2 Retention of Records

The investigator is responsible for creating and/or maintaining all study documentation required by ICH E6 section 8, as well as any other documentation defined in the protocol. Investigators are required to retain a copy of all regulatory documents and records that support the data for this study for 3 years following study completion. If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.

10.3 Trial Registration

The principal investigator registered the trial on the National Library of Medicine's Clinical Trials Registry on the world wide web at http://www.clinicaltrials.gov prior study subject recruitment.

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