Effects of Pioglitazone on Stress Reactivity and Alcohol Craving

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ABSTRACT

Alcohol use disorder (AUD) is significant public health concern. Stress is a central component in modern theories of alcohol use, and stress is intimately related to drinking for many individuals. There are a number of approved medications for AUD, but the majority of individuals do not respond to these medications and no medications address the role of stress. The current proposal looks affect alcohol use by targeting stress-related systems in the body through peroxisome proliferator-activated receptors (PPARs), which may effect stress reactivity, stress-induced alcohol craving, and alcohol use. Pioglitazone (Actos) targets PPARγ and is FDA-approved for treating individuals with diabetes and metabolic disorders. Promising results from both human trials and animal research suggest that pioglitazone holds great promising for addressing AUD, including preliminary data from our own research. The current proposal will attempt to expand on our preliminary findings targeting alcohol use among treatment-seeking individuals with AUD and elevated stress and/or anxiety with the following specific aims: 1) to assess if pioglitazone decreases stress reactivity and stress-induced craving in a human laboratory model; and 2) to assess if pioglitazone changes weekly psychometric reports of stress/anxiety, craving, and alcohol consumption. Notable strengths of the current proposal include: 1) targeting individuals with elevated stress/anxiety and AUD; 2) biological assessment of stress reactivity (heart rate, blood pressure, salivary cortisol); 3) a multi-dimensional assessment of alcohol craving incorporating relatively novel behavioral economic measures (i.e., alcohol demand, delay discounting); and 4) inclusion of powerful Bayesian statistical tools that are well suited for smaller samples, such as the current proposal.

INTRODUCTION TO THE REVISED PROPOSAL

We thank the Reviewers for their thoughtful comments regarding the initial grant submission. Overall enthusiasm for the initial application was strong, with Reviewers highlighting the strength of the research team and sound study design. Below, we provide responses to the major Reviewers' concerns. Relatively minor concerns have been addressed within the proposal. We believe that the application has been substantially strengthened as a result of addressing these concerns.

The study would be improved by targeting individuals with elevated stress/anxiety that drink to cope. Response: As suggested, the revised proposal now targets individuals with elevated stress/anxiety (as done in our initial feasibility study, see **Preliminary Data**) as well as those who report drinking to cope with stress/anxiety as measured by the Drinking Motives Questionnaire - Revised (DMQ-R)[1,2]. Additionally, the revised statistical analyses will directly examine the relationship between changes in stress/anxiety and alcohol use, as affected by pioglitazone.

Transdermal alcohol concentration (TAC) as measured by SCRAMx has limitations. Response: Reviewers' comments were mixed regarding the SCRAMx. However, we acknowledge limitations of the system and have removed the SCRAMx in the revised submission. Removal of SCRAMx has also allowed us to address concerns regarding the trial duration, which has now been increased from 4 weeks to 8 weeks, and fits well within the scope of an R21 project and budget.

Outcome measures related to alcohol consumption need to be operationalized and justified and the role of behavioral economic measures (delay discounting, alcohol demand) needs to be clarified. The revised submission now defines alcohol-related dependent measures as heavy drinking days in the past week (as highlighted by the Reviewers) and average drinks/day for the past week. Abstinence will be verified using ethyl glucuronide (ETG) test strips. The revised submission now clarifies that delay discounting and alcohol demand using a purchasing task will be assessed at weekly clinic visits to examine changes in craving and alcohol reward value, whereas a brief assessment of alcohol demand will examine changes in craving during the human laboratory model of stress reactivity. Previous studies have demonstrated that demand assessments are sensitive to experimental manipulations, including acute laboratory stress inducers[3].

The PI has very limited experience in human laboratory models, clinical alcohol studies, and limited leadership on extramural projects. Response: Dr. Yoon's biosketch has been edited to highlight his recent work in human laboratory model studies and studies involving pharmacotherapies that target stress/anxiety systems for substance use disorders. We agree that Dr. Yoon has relatively little experience with clinical alcohol studies and limited leadership on extramural projects, but he does have extensive and broad experience in addictions research for a variety of drugs of abuse as well as in implementing the behavioral economic measures proposed in the current study. He also has related experience in assessing medications for drug addiction that target stress related systems[4].

The current proposal is also supported by a number of experienced researcher. Dr. Lane (Co-I) is the Vice Chair for Research in the Department of Psychiatry and Behavioral Sciences and Director of Research at UTHealth Harris County Psychiatric Center (HCPC). He has conducted numerous human laboratory studies, including among individuals with AUD[5,6]. Dr. Weaver (Co-I) is the Medical Director of the Center for Neurobehavioral Research on Addiction (CNRA) and is experienced in addictions research and will provide medical guidance and ensure participant safety over the course of the study. He has an extensive history serving on a number of NIH-funded studies for alcohol and has published broadly on treatments and interventions for alcohol use disorders (AUD)[7–12]. Drs. Haass-Koffler (Consultant) and Vujanovic (Consultant) both have extensive experience in studies evaluating stress/anxiety and AUD[13–24]. They have provided valuable input in developing this resubmission and will continue to lend their expert guidance over the course of the study. Dr. Suchting is an experienced biostatistician with expertise in Bayesian statistics, a unique strength of the current proposal. He also has expertise in analyzing medication effect data in addictions, including those that effect stress-related systems[4].

Importantly, Dr. Yoon recently completed a pilot study supporting the current proposal (see **Preliminary Data**). Treatment-seeking individuals with elevated baseline stress/anxiety and AUD (N = 4) were administered pioglitazone (45 mg) in a single-blind manner for 4 weeks and completed stress-reactivity assessments at baseline and study week 4. All participants completed the study and systematic decreases in stress reactivity, self-reported stress/anxiety, alcohol craving, and alcohol use were observed. We hope this information provides Reviewers with additional confidence in the PI and study team with regard to the success of the current R21 proposal.

SPECIFIC AIMS

Alcohol use disorder (AUD) is a public health problem associated with significant health, social, and economic costs to society. Alcohol and stress/anxiety are intimately related. Alcohol activates the hypothalamic-pituitary-adrenocortical (HPA)-axis and stress can increase the reward value of drinking. As time progresses, excessive drinking results in a number of behavioral changes marked by increased compulsive drinking, stress reactivity, and neuro-inflammation[25]. FDA-approved pharmacotherapies for AUD (e.g., naltrexone, acamprosate, disulfiram) are effective in less than one-third of treated individuals[26]. *Importantly, none of the currently approved medications for AUD directly addresses stress reactivity, underscoring the need to develop novel pharmacotherapies targeting stress-related processes associated with AUD.*

Peroxisome proliferator-activated receptors (PPARs) are promising therapeutic targets for addiction that exhibit both anti-inflammatory and neuro-protective responses in the brain[27,28]. Building on a strong and growing body of pre-clinical findings, recent trials in humans have shown promising effects for opioids and nicotine[29,30]. In regards to alcohol, the PPARγ agonist pioglitazone *1) significantly reduced free-access alcohol consumption;and, 2) attenuated alcohol consumption and withdrawal symptoms following stress exposure in rats bred to highly prefer alcohol*[31,32]. We recently conducted a single-blind pilot study in treatment-seeking individuals with AUD and elevated baseline stress/anxiety that demonstrated feasibility and showed promising decreases in stress reactivity, stress/anxiety, alcohol craving, and alcohol consumption following 4 weeks of pioglitazone (see **Preliminary Data**).

The current proposal will build on our pilot study and utilize a double-blind, mixed-model design with a between-groups factor of dose (pioglitazone vs. placebo) and a within-subjects factor of time. Eligible participants will consist of treatment-seeking individuals with AUD who score high on screening measures of stress/anxiety and stress-related drinking. Study medication (pioglitazone or placebo) will be administered for 8 weeks. Relapse risk outcomes will be assessed using both a human laboratory paradigm of stress reactivity and stress-induced craving (Specific Aim 1) and real-life measures of stress/anxiety, craving, and alcohol consumption (Specific Aim 2).

Strengths of the current proposal include: 1) targeting individuals with elevated stress/anxiety and AUD; 2) biological assessment of stress reactivity (heart rate, blood pressure, salivary cortisol); 3) a multi-dimensional assessment of alcohol craving incorporating relatively novel behavioral economic measures (i.e., alcohol demand, delay discounting); and 4) inclusion of powerful Bayesian statistical tools that are well suited for smaller samples, such as the current proposal.

We propose the following Specific Aims:

Specific Aim 1: To examine the effects of pioglitazone on stress-induced relapse risk in a laboratory model.

Hypothesis 1a: Participants receiving pioglitazone will show decreased stress reactivity (heart rate, blood pressure, salivary cortisol) compared to those receiving placebo.

Hypothesis 1b: Participants receiving pioglitazone will show decreased alcohol craving (subjective, alcohol demand) compared to those receiving placebo.

Specific Aim 2: To examine the effects of pioglitazone on drinking, stress/anxiety, and alcohol craving in the natural environment.

Hypothesis 2a: Participants receiving pioglitazone will show greater reductions in weekly psychometric measures of stress/anxiety compared to those receiving placebo.

Hypothesis 2b: Participants receiving pioglitazone will show greater reductions in weekly psychometric measures of alcohol craving compared to those receiving placebo.

Hypothesis 2c: Participants receiving pioglitazone will show greater reductions in past week alcohol use (heavy drinking days, average drinks/day) compared to those receiving placebo.

There is increasing attention and preclinical evidence supporting the potential role of the PPARγ system as a novel target in the treatment of AUD. From a translational perspective, this R21 project is timely and likely to advance our understanding of stress as a mechanism of action of pioglitazone effects. Additionally, this project will establish the feasibility of a paradigm for assessing medication effects under naturalistic and standardized laboratory conditions, thus setting the stage for subsequent R01 projects.

SIGNIFICANCE

Public Health Impact of AUD. AUD is 1) the 4th leading cause of death in the US (~88,000 deaths/year), decreasing lifespan by ~30 years; 2) a tremendous economic burden on society (~$249 billion/year), with the majority of these costs due to binge drinking; and 3) associated with a host of short- and long-term negative consequences including violence, legal problems, morbidity, and family problems[33–35].

AUD and the Central Role of Stress. Stress can enhance alcohol reward during initial stages of drinking[36,37]. However, persistent excessive drinking acts as a chronic stressor that 1) shifts brain systems beyond normal homeostatic limits into a state of allostasis; 2) which in turn alters physiological and brain motivational systems central for regulating alcohol use; and 3) has a negative impact on autoimmune and inflammatory responses that can in turn influence alcohol use[38–42]. Therefore, initial drinking is under relatively greater control of positive reinforcing effects of alcohol and impulsive characteristics of the individual. However, over time, drinking takes on more compulsive characteristics as it becomes maintained by negative reinforcement due to increased withdrawal symptoms, stress-related anxiety, alcohol craving, and decreased stress-resiliency and cognitive deficits from neuro-inflammatory damage[38,43,44]. Despite the profound negative impact of stress on AUD, *none of the currently approved medications for AUD directly target stress or stress-related consequences associated with AUD, underscoring the need for pharmacological interventions that target novel biological systems.*

Targeting Stress-Reactivity and AUD through the PPAR System. PPARs are proteins that act as ligand-activated transcription factors, which are central to their anti-inflammatory actions[45]. Several PPAR isoforms (α, δ/β, γ) have been identified, all of which are present in the CNS with relatively high activity[46–48]. PPARγ agonists can modulate genes linked to synaptic transmission and neuronal function in stress-related brain regions such as the amygdala and hippocampus[49,50]. A growing number of pre-clinical studies have observed promising effects of PPAR agonists on various aspects of drug use (e.g., discrimination, self-administration, reinstatement, sensitization) for several drugs of abuse including alcohol[28]. In alcohol-related human studies, expression of PPARδ and PGC-1α, the coactivator of PPARγ, is altered in brains of individuals with AUD[51]. Associations between single nucleotide polymorphisms (SNPs) and several PPAR genes related to PPARα and PPARγ have been found for AUD and alcohol withdrawal using human genome wide association study (GWAS) data from the Collaborative Study on the Genetics of Alcoholism (COGA)[52].

Currently, only the PPARγ isoform can be targeted in humans. PPARγ is highly expressed in a number of brain regions associated with drug reward[53] and stress response[31,32]. Activation of PPARγ mediates neuroprotective responses against inflammatory damage, which can attenuate drug affects. Pioglitazone (Actos) is a PPARγ agonist and currently FDA-approved for the treatment of diabetes and metabolic disorders. Recent human addiction studies have shown pioglitazone to reduce heroin craving and anxiety[29] as well as nicotine craving[30]. In regards to pioglitazone's potential to address stress-related alcohol use, two preclinical studies indicate that *pioglitazone 1) significantly reduced alcohol drinking in rats; and 2) attenuated stress-induced alcohol drinking and alcohol withdrawal symptoms in rats bred to highly prefer alcohol, but did not affect cue-induced alcohol drinking*. Naltrexone did attenuate cue-induced alcohol drinking, but had no effect on stress-induced alcohol drinking, suggesting a unique role for pioglitazone. More recently, our group collected preliminary data suggesting attenuation of stress-induced reactivity and weekly psychometric measures of stress/anxiety, alcohol craving, and alcohol use among individuals with AUD following 4 weeks of treatment with pioglitazone (see **Preliminary Data**). Currently, there is one registered study (NCT03864146) assessing the effects of pioglitazone on alcohol use among Veterans, but that study does not appear to be targeting individuals with stress/anxiety in addition to AUD.

Multi-Dimensional Assessment of Relapse Risk. Drug craving often serves as a proxy of motivation to consume drug. Self-report craving measures are ubiquitous in addictions research but have limitations that have likely result in equivocal results[54]. We hope to mitigate these potential limitations by incorporating behavioral economic measures (i.e., alcohol demand, delay discounting) that are closely tied to drug use and a broader framework of drug addiction. Both delay discounting and drug demand have been associated with virtually every aspect of drug use (e.g., initiation, severity, relapse risk, etc.), and multiple meta-analyses have cemented the utility of these measures in addictions research[55–58]. These measures are not correlated, supporting a multi-dimensional model in which these measures represent distinct aspects of motivation to use alcohol[54,59–61]. Dr. Yoon (PI) is an expert in utilizing behavioral economic measures in both human laboratory and clinical research involving individuals with SUDs.

Bayesian Statistical Methods in Addictions Research. The current proposal will incorporate Bayesian analytical methods in addition to traditional frequentist methods utilizing significance testing. Null hypothesis statistical testing under frequentist inference values a rigid focus on dichotomous evaluations of evidence (i.e., exhibiting a *p* value greater or less than a pre-defined alph . In comparison, Bayesian

approaches avoid these issues by directly evaluating the probability that an alternative hypothesis exists, given the current data and prior evidence for the alternative hypothesis[63]. The primary limitation of Bayesian methods is that they require relatively greater computational power, which has been largely mitigated with advances in computer technology. Subsequently, Bayesian methods have been increasingly utilized in clinical research. Dr. Suchting (Co-I) is an expert in implementing Bayesian methods in addictions research.

INNOVATION

The current proposal has a number of innovative features. First, we are targeting a relatively novel biological mechanism that has potential to expand treatment options, particularly for those in which stress-related process are a central component of their AUD. Second, we are utilizing a multi-dimensional assessment of relapse risk that includes stress-related biomarkers, traditional measures of alcohol craving, and behavioral economic measures. Third, this study will assess change in stress reactivity and stress-induced alcohol craving within a human laboratory model as well as changes in stress/anxiety, alcohol craving, and past 7-day alcohol consumption (heavy drinking days, average drinks/day) in the natural environment. Fourth, the current proposal utilizes Bayesian statistical methods, which can be particularly useful in evaluating treatment effects in relatively small studies, necessitated here by the scope and intent of the NIH R21 mechanism.

APPROACH

Preliminary Data. Our group has experience safely administering pioglitazone at doses matching the current proposal among treatment-seeking individuals with cocaine use disorder (CUD). In a post hoc analysis, our group observed decreased alcohol use among individuals with concurrent CUD + AUD receiving pioglitazone vs. placebo in a study assessing cocaine craving and white matter integrity among individuals with primary CUD[64]. Directly related to current proposal, Dr. Yoon (PI) recently completed a pilot study assessing the effects of 4 weeks of pioglitazone (45 mg) administered in a single-blind manner among treatment-seeking individuals with AUD and elevated baseline levels of stress/anxiety (N = 4). **Figure 1** below shows changes in laboratory stress reactivity measures following a cold-pressor challenge to the stress axis (left panel) and weekly psychometric measures of stress/anxiety, craving, depressive symptoms, and alcohol consumption (right panel). All participants completed the study with no missed visits. Notably, decreases in all variables of interest were systematically observed over 4 weeks, *with 3 of 4 participants reporting no drinking by week 4*. Accordingly, these preliminary data support both feasibility and potential utility of pioglitazone for attenuating stress reactivity and alcohol use.

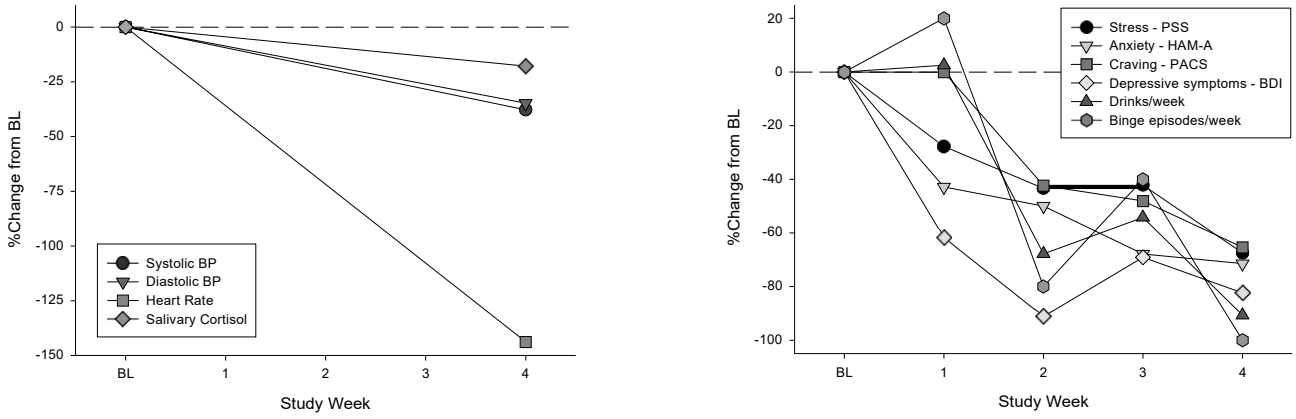

Figure 1. Changes in stress reactivity (left panel) and weekly measures of stress/anxiety, alcohol craving, depressive symptoms, and alcohol consumption (right panel).

Overall Study Design. To accomplish the project aims, we will utilize a double-blind, mixed-model design with a between-groups factor of dose (pioglitazone vs. placebo) and a within-subjects factor of time. We will utilize urn-randomization based on gender and severity of alcohol use (AUDIT). A summary of the study timeline, procedures, and assessments is shown in **Table 1** below.

Table 1. Outline of Study Timeline, Procedures, and Assessments

Study Week / **Procedures and Assessments**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
			IRB	NU	BE	: HS	C-M	S-18	-092
Consent and Baseline Screening			IRB	APP	OV	AL I	T	: 10	11/2

SCID, ASI, KMSK, TLFB, CIWAA, AUDIT	X								
Receive Study Medication (Pioglitazone or Placebo)	X	X	X	X	X	X	X	X	X
Assess Medication Compliance and Adverse Events		X	X	X	X	X	X	X	X
Brief Counseling		X	X	X	X	X	X	X	X
Human Laboratory Assessments (**Specific Aim 1**)									
Stress-Reactivity Assessment (Salivary Cortisol, HR, BP, self-report)	X				X				X
Alcohol craving (self-report, brief alcohol demand)	X				X				X
Weekly Assessments (**Specific Aim 2**)									
Alcohol Use and Craving (TLFB, BrAC, ETG, PACS, DMQ-R)	X	X	X	X	X	X	X	X	X
Stress and Anxiety (HAM-A, PSS, PCL-5)	X	X	X	X	X	X	X	X	X
Delay Discounting, Alcohol Demand (purchasing task)	X				X				X

SCID - Structured Clinical Interview for DSM-5**, ASI** - Addiction Severity Index[65]; **KMSK** - Kreek-McHugh-Schluger-Kellogg scale[66]; **TLFB** - Timeline Followback[67]; **CIWAA** - Clinical Institute Withdrawal Assessment for Alcohol[68]; **AUDIT** – Alcohol Use Identification Test[69]; **BrAC** – Breath Alcohol Concentration; **ETG** – Ethyl Glucuronide; **PACS** – Pennsylvania Alcohol Craving Scale[70]; **DMQ-R** – Drinking Motives Questionnaire Revised[1,2]. **HR** – Heart Rate; **BP** – Blood Pressure; **HAM-A** – Hamilton Anxiety Rating Scale[71]; **PSS** – Perceived Stress Scale[72]; **PCL-5** - PTSD Checklist for DSM-5[73]**.**

Recruitment. Recruitment strategies will include local advertising in print media, public service announcements on radio, and referrals to CNRA in the Houston metropolitan area. Additionally, we will utilize the University of Houston SONA system, which provides students credit for participating in various research studies. Access to SONA is made possible with the inclusion of Dr. Vujanovic (Consultant). We will also recruit from the Department of Psychiatry Recruitment Registry: HSC-MS-23-0768.

Participants. We will enroll 60 participants to reach a target of ***N* = 50** completers (25/group). Participants will consist of otherwise healthy treatment-seeking individuals with AUD exhibiting elevated baseline stress/anxiety. All participants will meet the following inclusion and exclusion criteria:

Inclusion criteria. Be treatment-seeking individuals diagnosed with AUD (DSM-5); be at least 18 years old and fluent in English; past month excessive alcohol use (>7 drinks/week for woman, >14 drinks/week for men, >3 drinks/occasion for women>4 drinks/occasion for men)[35]; exhibit baseline measures of either 1) 8-23 on HAM-A indicative of mild to moderate anxiety, 2) 14-26 on PSS Score indicative of moderate stress, or 3) ≥2 on DMQ-R questions related to drinking indicating that individuals drink at least "some of the time" to cope; and exhibit increased stress reactivity (increased physiological response and/or self-report) at the baseline stress reactivity assessment.

Exclusion criteria. Exhibit severe scores on the HAM-A, PSS, or PTSD checklist (PCL-5) – may be enrolled at the discretion of the admitting physician (Dr. Weaver); physical dependence on alcohol (CIWAA > 10); greater than mild substance use disorder on drugs other than alcohol, nicotine, and marijuana; contraindications for taking pioglitazone; medical conditions (e.g., congestive heart failure, clinically significant edema, clinically significant liver disease, hypoglycemia, diabetes, history of bladder cancer) contraindicating pioglitazone pharmacotherapy or taking contraindicated medications (e.g., CYP2C8 inhibitors or inducers, antihyperglycemic medications); be pregnant, nursing, or planning on becoming pregnant during the course of the study; females will need to agree to use of barrier methods of contraception due to pioglitazone's effects on plasma concentrations of oral contraceptives; have any other illness, condition, or use of medications, which in the opinion of the PI and/or admitting physician would preclude safe and/or successful completion of the study.

Baseline Screening. Participants will receive a comprehensive medical and psychiatric evaluation including a medical-history questionnaire, physical examination, laboratory chemistries (e.g., blood chemistry screen, complete blood count, urinalysis and serum pregnancy test), and ECG. Clinicians will conduct the **SCID**, the **ASI**[65], the **KMSK**[66] assessment of lifetime substance use interview, and **TLFB**[67]. Alcohol dependence will be assessed using the SCID and the **CIWA-A**[74]. A CIWA-A score > 10 will be exclusionary.

Alcohol-Related Measures. Assessment of alcohol use will include self-report **(TLFB)** and **BrAC** (Alco-Sensor FST, Intoximeters, Inc., Saint Louis, MO). The TLFB will be used to assessed the occurrence of heavy drinking days (>3 drinks/occasion for women>4 drinks/occasion for men)[35] in the past 7 days and average drinks/day for the past 7 days. Severity of alcohol use will be assessed using the **AUDIT**[69]. **Alcohol craving** will be assessed using a 4-item questionnaire[75] during the stress reactivity assessment and the **PACS** at weekly clinic visits. Motivations for drinking will be assessed using the **DMQ-R**[1], with demonstrated utility in the general[2,76,77] as well as clinical[78,79] populations. The DMQ-R consists of 20 questions assessing motivations for drinking that are rated on a 1 "almost never/never" to 6 "almost always/always" scale. **ETG** will

be assessed using dipcards with a 300 ng/ml cutoff. ETG dipcards show good agreement with traditional immunoassays[80–82].

Behavioral Economic Measures. During the stress reactivity assessment, alcohol demand will be assessed via the **Brief Assessment of Alcohol Demand** (BAAD)[59]. The BAAD is a 3-item questionnaire measuring the three most common indices of alcohol demand. A recent meta-analysis has demonstrated demand measures to be sensitive to acute experimental manipulations, include small but significant increases for stress[83]. Global changes in alcohol demand and delay discounting will be assessed at baseline and Weeks 4 and 8 using a purchasing task and computerized **delay discounting** task developed by Dr. Yoon (PI)[84–94]. In addition to the standard money now vs. later choices, the delay discounting task will present choices between alcohol now vs. money later, which more closely models alcohol-related decision making and has also been demonstrated by Dr. Yoon to be sensitive to weekly changes in drug use status for cigarettes[87].

Stress and Anxiety Measures. Stress and anxiety levels will be assessed using the **HAM-A**[71], **PSS**[72], and the **PCL-5**[73]. Established norms will be used for the HAM-A and PSS to assess mild to moderate stress and anxiety and screen out for cases in which laboratory induced stress may be too aversive. The PCL-5 will be administered at baseline and Weeks 4 and 8.

Study Medication and Compliance. Pioglitazone (Actos®, Takeda Pharmaceuticals U.S.A., Inc.) is FDA-approved for the treatment of diabetes mellitus type 2; has anti-inflammatory, neuroprotective, antioxidative, and anti-excitotoxic properties[95]; and extensive research has shown it to be safe and well tolerated in human patient populations[96,97]. The medication schedule is based on previous work from our group showing that a daily dose of 45mg (maximum suggested dose) was associated with acceptable levels of tolerability, safety, and compliance in a study assessing the effects of pioglitazone on individuals with CUD and AUD[64]. We will follow recommended adult initial dosing at 30 mg/d to reach a maintenance dose of 45 mg/d by the end of Week 1, which is within standard titration parameters as per the investigator's brochure.

One week's supply of the study medication will be dispensed. Cell-phone assisted remote observation of medication adherence (CAROMA) will be used to assess compliance. Riboflavin will be added to medication capsules and urine ultraviolet fluorescent tests will be conducted at weekly clinic visits to also assess compliance. Participants will receive $10 at each clinic visit based on self-report, CAROMA, and riboflavin measures all being consistent with medication compliance. For safety purposes, blood will be drawn every 2 weeks for liver function testing as is standard for other Pioglitazone protocols at the CNRA.

Assessment of Stress Reactivity. At baseline and Weeks 4 and 8, stress reactivity will be assessed using a modified cold-pressor task (CPT). The CPT is widely used as a stress-inducer in human laboratory studies and elicits moderate activation of the sympathetic nervous system and limited activation of the HPA-axis, which are two major stress systems in the body[98–101]. HPA-axis activation during the CPT can be increased by incorporating a social evaluative component. These will include 1) a study member dressed in a white labcoat and taking notes on a clipboard; and 2) a webcam and monitor showing the participant's face. Participants will be informed that their facial expressions will be assessed during the CPT. The addition of these social components during the CPT has been demonstrated to selectively activate the HPA-axis and significantly increase salivary cortisol levels[100]. During the CPT, participants will submerge their dominant arm in an ice-water bath for up to 2 minutes. Physiological measures of stress reactivity will include HR, BP, and salivary cortisol consistent with previous studies from our group[102,103]. HR and BP will be will be assessed using standard laboratory equipment. Saliva samples will be collected in swabs using the Cortisol-Salivette® system (Sarstedt) and measured using the Cortisol ELISA Kit (Enzo Life Sciences), per manufacture instructions, detailed in Suchting et al (2019)[4]. Alcohol craving will be assessed using a 4-item questionnaire[75] as well as the BAAD. Stress will be assessed using a single-item VAS question.

Table 2. Time Course for Assessing Stress-Induced Relapse Risk

Time (pm)	Study Procedures
3:00	Assess Craving, BAAD, Stress, Cortisol, HR, BP
3:15	Cold Pressor Task
3:20	Assess Craving, BAAD, Stress, HR, BP
3:45	Assess Craving, BAAD, Stress, Cortisol, HR, BP

Brief Counseling. At baseline, all participants will receive the NIAAA booklet "Rethinking Drinking: Alcohol and Your Health" providing research-based information related to alcohol use (RethinkingDrinking.niaaa.nih.gov). Study therapists will go over the booklet with the participant at the initial visit and at subsequent weekly visits using motivational interviewing techniques. At each visit, participants will also be assessed for recent alcohol use (self-report, ETG, BrAC), alcohol craving (PACS), and stress/anxiety (HAM-A, PSS). At the end of the study, referrals to local alcohol treatment services will be provided as needed.

Participant Payment & Compensation. Participants will receive $50 for completing the baseline screening, $25/visit for attending study visits (9 visits), $25/assessment for completing stress reactivity

assessments (3 assessments), $10/week for medication compliance (8 weeks), and $100 for completing the study ($530 total). Participants will also receive $5 compensation for busfare/parking at each study visit.

DATA ANALYTIC STRATEGY

Descriptive Statistics & Confounding Variables Descriptive statistics will evaluate measures of central tendency (continuous) and frequencies (categorical) for study-related variables. General variable relationships will be evaluated using correlation analyses. Preliminary analyses will inspect relationships between sample characteristics (e.g., demographics), predictor variables (e.g., inflammatory markers), and specified outcome variables (e.g., resilience measures) via traditional statistical tests (e.g., chi-square, Mann-Whitney-Wilcoxon, Kruskal-Wallis, and *t*-tests). Sample characteristic variables demonstrating a relationship with both the predictor and outcome variables in a given model will meet criteria as a potential confounder[104,105] and included as a covariate in such models for hypothesis testing and explored as potential moderators of treatment group effects on experimental outcomes.

Inferential Paradigm Following recommendations in the literature[106–108], analyses will utilize parallel frequentist and Bayesian statistical inference. Frequentist results yield the probability of the data (or data more extreme), given the null hypothesis, whereas Bayesian results directly yield the probability of an alternative hypothesis[109]. If possible, Bayesian analyses will incorporate informative priors as they develop in the literature; otherwise, weakly informative priors will be incorporated as a default. Sensitivity analyses using optimistic and pessimistic, skeptical priors will evaluate prior assumptions[110]. Assessing the convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will use diagnostic evidence including effective sample size and scale reduction factors. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Statistical analyses will use the most up-to-date stable release version of the R statistical computing environment[111] using packages rstan[111] and brms[112].

Statistical Modeling Analyses will primarily use generalized linear modeling (GLM). Continuous, count, and dichotomous outcome variables will utilize normal, Poisson/negative binomial, and binomial distribution families respectively, with identity, log, and logit link functions as appropriate. Evaluation of distributional assumptions will use residual plots, formal statistical tests, and posterior predictive checking. Violations of assumptions will be addressed via transformation, robust estimation, stratification, and/or coefficient scaling where appropriate.

Missingness & Multiple Comparisons Missing data will be addressed via maximum likelihood, explicit modeling of missingness, and/or imputation where appropriate. Each approach is robust to ignorable missingness (i.e. MCAR and MAR). Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions. While Bayesian analyses are not influenced by traditional concerns of multiplicity, for the frequentist analyses, all primary outcome variables (those specified by name in the hypothesis statements below) will be evaluated at the $\alpha = 0.05$ statistical significance level. Secondary analyses will examine additional predictor and outcome variables (e.g., other inflammatory markers collected by assays); these and any otherwise *post hoc* analyses will employ false discovery rate (FDR) to control for Type I error.

Specific Analyses

Specific Aim 1: To examine the effects of pioglitazone on stress-induced relapse risk in a laboratory model. ***Hypothesis 1a:*** *Participants receiving pioglitazone will show decreased stress reactivity (heart rate, blood pressure, salivary cortisol) compared to those receiving placebo.* ***Hypothesis 1b:*** *Participants receiving pioglitazone will show decreased alcohol craving (subjective, alcohol demand) compared to those receiving placebo.*

For hypothesis 1a, GLMM will model each stress reactivity outcomes (primary: heart rate, blood pressure, and salivary cortisol) as a function of the main effects and higher-order interactions between time (baseline to Week 8), treatment (pioglitazone vs. placebo), and CPT measurement point (pre-CPT vs. post-CPT). Follow-up analyses will examine lower-order interactions longitudinally as well as cross-sectional changes from pre- to post-CPT at each time point. Variable relationships and analyses for hypothesis 1b will follow the patterns stated above for Hypothesis 1a, with craving in place of stress reactivity.

Specific Aim 2: To examine the effects of pioglitazone on drinking, stress/anxiety, and alcohol craving in the natural environment. ***Hypothesis 2a:*** *Participants receiving pioglitazone will show greater reductions in weekly psychometric measures of stress/anxiety. Primary measures: PSS and*

HAM-A) compared to those receiving placebo. ***Hypothesis 2b:*** *Participants receiving pioglitazone will show greater reductions in weekly psychometric measures of alcohol craving (primary measures: PACS) compared to those receiving placebo.* ***Hypothesis 2c:*** *Participants receiving pioglitazone will show greater reductions in past week alcohol use (primary measures: heavy drinking days as defined by* >3 drinks/occasion for women and >4 drinks/occasion for men*, average drinks/day) compared to those receiving placebo.*

For all hypotheses, GLMM will model primary outcome measures as a function of the main effects and interaction between treatment and time.

Sample Size and Power Considerations

Frequentist Analyses. Power for **Specific Aim 1** is based on the rate at which we may detect the three-way interaction between time, treatment, and CPT measurement point for a given measure of stress reactivity (transformed for normality) across k = 1000 Monte Carlo simulations (executed via SAS 9.4). Calculations assume the following conditions: $\alpha = 0.05$, an autocorrelation of $r = 0.50$ between consecutive observations (with a decay of $r = -0.10$ for subsequent observations), and a small correlation of $r = 0.05$ for observations occurring at the same time point across groups. Based on these assumptions, the different sample sizes (pragmatic and pessimistic) stipulated in **Table 3** each provide power to detect small-to-moderate effect sizes (treatment group differences expressed as Cohen's D, with effects unfolding in linear fashion over time). Power for **Specific Aim 2** is based on evaluating reductions in drinks per week. Estimates are derived using G*Power 3.1.9.2. Assuming $\alpha = 0.05$ (two-tailed) and an average baseline of drinks/week across participants (calculated as an average from 14 and 7 drinks/week for a 3:1 ratio of males to females, respectively), the different sample sizes (pragmatic and pessimistic) stipulated in **Table 3** each provide power to detect varying decreases in alcohol consumption.

Bayesian Analyses. The Bayesian analyses in the current proposal will provide probabilistic estimates of effects for all hypotheses irrespective of statistical power. Moreover, the MCMC approaches utilized in Bayesian analyses do not rely on large sample size assumptions. Bayesian analyses will focus on posterior probabilities ≥ 0.75 (equivalent to a Bayes factor = 0.33 or 3.0) that parameter estimates are greater or less than zero to emphasize the value in discerning model effects.

Table 3. Power estimates for Aims 1 and 2 given different sample and effect sizes.

N (N/group)	SA1: Group Difference (Cohen's D)			SA2: % Decreased Consumption		
	D = 0.50	D = 0.40	D = 0.30	-12.0%	-11.0%	-10.0%
50 (25/25)	100.0%	97.8%	84.6%	97.8%	95.2%	90.8%
40 (20/20)	99.8%	95.0%	71.8%	88.6%	82.5%	74.6%

Cohen's D for observed within-subject effects sizes from our Preliminary Data are as follows: HR (0.8), BP (systolic - 0.5, diastolic - 1.6), cortisol (0.13), PSS (2.1), HAM-A (1.3), BDI (1.2), PACS (1.5), Drinks/week (1.3), Heavy drinking (0.8). Note that Table 3 effect sizes represent between group differences unfolding over time.

STUDY TIMELINE

The time frame illustrated in **Table 4** below is based on conservative estimates. We will continuously monitor our procedures and implement measure to enhance progress as indicated. Our goal is to enroll 60 subjects to achieve 25 completers/group. However, we will continue to enroll subjects based on available resources and subject attrition. Pre-award preparations following pre-award requests (just-in-time (JIT)) will include submitting an initial IRB protocol. Startup will include hiring and training of study staff. Over the course of the study, preliminary and final results will be presented at appropriate scientific conferences (e.g., Research Society on Alcoholism, College on Problems of Drug Dependence, Research Society on Alcoholism, etc.).

Table 4. Study Timeline.

	Year 1													Year 2										
	Month													Month										
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Pre-award prep																								
	Startup																	IRB	NUI	BE	: H	C-N	S-1	-092
				Phone screens: 250														IRB APPROVAL				DAT	: 1(	11/2

				Intake evaluations: 100											
					Enrollment and randomization: 60 (~3-4 subjects/month)										
							Completion of protocol (~3-4 subjects/month)								
															Data cleaning & analysis, write-up paper/grant renewal preparation

PROTECTION OF HUMAN SUBJECTS

E.1. Risk to the Subjects

E.1.1. Human Subjects Involvement and Characteristics

The 2-year project will enroll male and female individuals (18 and older) regular alcohol users with past month excessive use of alcohol. Research data will be collected at screening, baseline, and weekly study visits.

This study is funded by the National Institute on Alcohol and Alcoholism (NIAAA). All studies funded by NIAAA, including this study, now submit data to the National Institute of Mental Health Data Archive (NDA) at the National Institutes of Health (NIH). All subject data will be de-identified by using a computer-generated global unique identifier (GUID) within the NDA database.

The single study site is the Center for Neurobehavioral Research on Addiction (CNRA) at the University of Texas McGovern Medical School, Houston. The CNRA is centrally located in a large U.S. metropolitan area known to have an adequate and representative alcohol-using population [see Facilities and Other Resources]. Moreover, the site has demonstrated its ability to recruit and retain the appropriate population using various recruitment strategies.

We plan on recruiting 4 participants/month over the course of 20 months for a total of 80 enrolled participants. We estimate that 60 participants (75%) will complete the study, based on previous studies from our group. Recruitment strategies will include local advertising in print media, public service announcements on radio, and referrals to CNRA in the Houston metropolitan area. Additionally, we will utilize the SONA system, which provides University of Houston students credit for participating in various research studies. Potential participants will complete a brief phone screen to assess initial eligibility and subsequently invited to undergo a comprehensive baseline screening following informed consent. The baseline screening will include a full medical evaluation by the CNRA Medical Director (Dr. Weaver. Co-I). All participants will meet the following selection criteria.

Inclusion criteria. Be treatment-seeking individuals diagnosed with AUD (DSM-5); be at least 18 years old and fluent in English; past month excessive alcohol use (>7 drinks/week for woman, >14 drinks/week for men, >3 drinks/occasion for women>4 drinks/occasion for men)[35]; exhibit baseline measures of either 1) 8-23 on HAM-A indicative of mild to moderate anxiety, 2) 14-26 on PSS Score indicative of moderate stress, or 3) ≥2 on DMQ-R questions related to drinking indicating that individuals drink at least "some of the time" to cope; and exhibit increased stress reactivity (increased physiological response and/or self-report) at the baseline stress reactivity assessment.

Exclusion criteria. Exhibit severe scores on the HAM-A, PSS, or PTSD checklist (PCL-5) – may be enrolled at the discretion of the admitting physician (Dr. Weaver); physical dependence on alcohol (CIWAA > 10); greater than mild substance use disorder on drugs other than alcohol, nicotine, and marijuana; contraindications for taking pioglitazone; medical conditions (e.g., congestive heart failure, clinically significant edema, clinically significant liver disease, hypoglycemia, diabetes, history of bladder cancer) contraindicating pioglitazone pharmacotherapy or taking contraindicated medications (e.g., CYP2C8 inhibitors or inducers, antihyperglycemic medications); be pregnant, nursing, or planning on becoming pregnant during the course of the study; females will need to agree to use of barrier methods of contraception due to pioglitazone's effects on plasma concentrations of oral contraceptives; have any other illness, condition, or use of medications, which in the opinion of the PI and/or admitting physician would preclude safe and/or successful completion of the study.

E.1.2. Sources of Materials

We will obtain information about subjects from structured interview evaluations, physical examinations, self-report measures, biological samples, and behavioral laboratory tasks. T[illegible] and will be collected at

specified time points during the study. The biological specimens obtained from all subjects will include urine, blood, salivary cortisol, and breath samples for alcohol detection. All materials will be obtained for the specific purposes of this research.

E.1.3. Potential Risks

Medication. Pioglitazone (trade name Actos) is approved by the FDA for the treatment of type II diabetes. According to the prescribing information for Actos "Over 8500 patients with type 2 diabetes have been treated with ACTOS in randomized, double-blind, controlled clinical trials, including 2605 patients with type 2 diabetes and macrovascular disease treated with ACTOS in the PROactive clinical trial. In these trials, over 6000 patients have been treated with ACTOS for 6 months or longer, over 4500 patients have been treated with ACTOS for one year or longer, and over 3000 patients have been treated with ACTOS for at least 2 years."

In addition, several studies have taken place in non-diabetic patients. Sixty non-diabetic patients with hypertension were treated with pioglitazone or placebo in one trial, finding a significant reduction in diastolic blood pressure in the pioglitazone treated group[113].

Another larger study in non-diabetic hypertensive patients found a significant reduction in biomarkers of insulin resistance and chronic systemic inflammation in pioglitazone treated patients[114]. An additional pilot study administered pioglitazone to 29 non-diabetic patients with Alzheimer's disease at a dose up to 45mg daily for 18 months. No adverse events leading to treatment discontinuation were seen in this trial. Peripheral edema was the principal side effect noted in pioglitazone treated subjects, but this side effect was not severe enough to lead to medication discontinuation[115].

Common adverse events from clinical trials that occurred more frequently than placebo include upper respiratory tract infections, edema, headache, sinusitis, myalgia, and pharyngitis.

Hypoglycemia: Patients treated with insulin or other antidiabetic medication in addition to pioglitazone may be at increased risk of hypoglycemia. Due to this risk subjects with diabetes will be excluded.

The most significant potential side effect of pioglitazone is exacerbation of congestive heart failure. Due to this potential side effect, all subjects will be carefully screened for congestive heart failure (CHF) using Framingham criteria and no subjects with CHF will be enrolled, and weight will be monitored closely for increased fluid retention. Also, EKGs will be repeated every two weeks to monitor for changes.

Hepatic effects: Although there was no evidence of drug induced hepatotoxicity from clinical trials, post-marketing reports of fatal and non-fatal hepatic failure have been made in patients taking pioglitazone for diabetes. Due to this risk, liver function tests will be performed every two weeks during the trial.
Urinary Bladder Tumors: Tumors were observed in the urinary bladder of male rats in a two-year carcinogenicity study (https://general.takedapharm.com/actoplusmetpi/). In clinical studies, two 3-year trials in which pioglitazone was compared to placebo or glyburide, according the prescribing information "there were 16/3656 (0.44%) reports of bladder cancer in patients taking ACTOS compared to 5/3679 (0.14%) in patients not taking ACTOS. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on ACTOS and two (0.05%) cases on placebo. There are too few events of bladder cancer to establish causality."

Fractures: In female patients with diabetes treated for a year with pioglitazone there was a higher rate of bone fractures (5.1%) compared to placebo (2.5%). There was no increase in fractures in male patients.

Laboratory Values: Clinical trials showed a slight reduction in hemoglobin and hematocrit (2-4%) over 12 weeks of treatment, likely related to increased plasma volume and not associated with any clinically significant hematologic effects.

Ovulation: Pioglitazone can increase ovulation in non-postmenopausal women. In addition, other medications in this same class have reduced the plasma concentrations of oral contraceptives. Because of these facts, female subjects must agree to an effective barrier method of contraception.

Pregnancy: Pioglitazone is pregnancy Category C. There are no known adverse events of pioglitazone during pregnancy but there are inadequate studies in humans. Animal studies using doses 10 to 40 times the maximum recommended human dose showed increased rates of post-implantation loss, delayed development, reduced fetal weights, and delayed parturition. Due to these issues all female subjects must agree to an effective barrier method of contraception.

Safety data from our pilot trial suggest a highly favorable risk/benefit profile for pioglitazone. Thirty men and women with CUD received randomly assigned treatment of pioglitazone (n=15) or placebo (n=15) in double-blind fashion for 12 weeks. Safety and tolerability were assessed via a weekly side effects questionnaire composed of 38 common symptoms, along with nurse evaluation of any adverse or serious adverse events. **The most frequent side effects reported by at least 10% of participants included not sleeping well, diarrhea, stomach pain, cough, and increased urination.** All were rated mild with none occurring significantly more frequently in the pioglitazone group. One participant in the placebo group experienced a serious adverse event (coronary artery vasospasm) that was diagnosed as cocaine-induced and required an emergency department visit.

Blood draw: The principal risk is hematoma at the venipuncture site, which is not serious and disappears after several days. CNRA phlebotomists drawing blood will are trained in venipuncture techniques to minimize extravasation.

Stress Reactivity: Cold pressor task. Individuals with cardiovascular disorders and neurological disorders should not participate in the cold-pressor task due to cardiovascular change induced by the testing. This information will be obtained during medical screening. Due to individual variation in pain and cold sensitivity, for some subjects the cold water may become too painful to sustain immersion for 120 seconds. There are no lasting effects from placing the hand and wrist in ice water (~0° Celsius) for 120 seconds.

Psychological. Items on certain questionnaires and interviews might be perceived as psychologically discomforting to some subjects. While subjects may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low.

Alternative Treatments. Participants seeking treatment will be referred to appropriate treatment options.

E.2. Adequacy of Protection against Risks

E.2.1. Recruitment and Informed Consent

Participants will be self-referred in response to various study advertisements via newspaper and radio. Individuals who call for information will be given a brief description of the study. Those interested will then be asked to answer questions about their current substance use. A trained research assistant will conduct this telephone-screening interview. Eligible subjects will be scheduled for an in-person intake visit at which time a research staff member will present the informed consent form. The consent form will detail the requirements of study participation (e.g., # of visits, type of data collected, time commitment, etc.).

Subjects will be told that the purpose of the study is to evaluate a medication's effect on their alcohol use in their natural environment and following exposure to an acute stressor. Information about each study procedure will be explained. Subjects will be informed that they will attend weekly clinic sessions and to take their medication. Other information on the consent form will include a full description of study requirements, reimbursement, risks, benefits, alternatives, and the role of the local IRB. All questions will be answered before written consent is requested.

E.2.2. Protection Against Risk

Thorough screening of all subjects including history and physical examination, serum chemistry and hematology, EKG, urinalysis and Urine Drug Screen as well as structured psychiatric interviews will be completed on all subjects. Exclusion criteria include subjects at greatest risk of side effects of pioglitazone, including those with congestive heart failure, significant liver disease, edema, and diabetes, as well as risks of alcohol use (pregnant women). Monitoring of weight to capture potential fluid retention will occur at each visit. Weekly assessment for edema and urine pregnancy will occur. Twice monthly serum chemistry and hematology will take place to monitor liver functions and hemoglobin/hematocrit. In addition twice monthly EKGs will be done. Female subjects must agree to use an effective barrier method of birth control to minimize risk of pregnancy.

Confidentiality will be protected in several ways. All information collected solely for research purpose will be kept in locked, restricted access files. Subject records will be coded and filed by a number code. Subject identities will not be revealed in any publication of the data. Individual subject information will be transferred to outside sources only with the express written request of the subject. Subjects will receive a copy of their signed consent form.

E.3. Potential Benefits of the Proposed Research to the Subject and Others
There are no potential benefits for participants. However, knowledge gained from the current proposal may benefit future individuals with AUD.

E.4. Importance of the Knowledge to be Gained
Results from the current proposal may help develop novel pharmacotherapies for AUD based on mechanisms targeting PPAR. AUD is a public health issue with substantially negative effects on health and society. Results from the current proposal will help inform future medication development efforts.

The above stated risks are relatively mild in degree and procedures have been designed to minimize their probability. We believe this protocol has an extremely favorable risk/benefit ratio. The clinical research at the CNRA has an excellent track record in conducting controlled trials with the utmost attention to safety.

DATA SAFETY MONITORING PLAN

This plan describes the general data and safety monitoring procedures for the proposed study. A detailed DSM plan will be submitted for approval prior to starting the study.

1. The Principal Investigators (Yoon, Lane) will be responsible for knowing the policies of the local IRB. In this capacity, they will maintain accurate documentation of IRB correspondence and reports and oversee the handling of all possible study-related adverse events. The CNRA has longstanding data collection and safety monitoring system in place that will be available for the proposed study. This includes staff training, manual driven processes, weekly audit of data collection/entry, medical screening with results reviewed by on-site nurse and physician, use of standardized assessments, continued medical monitoring during treatment, use of a certified (CLIA) analytical laboratory to perform urine toxicology testing, procedures to monitor medication compliance (e.g., riboflavin), collaboration with the statistician who oversees data analysis and system management. The PI will assure that the above systems are in place and functioning properly for the duration of the study.

2. A DSM Board will be formed to provide additional, independent oversight of data related to patient safety. Membership will include Drs. Jan Blalock (UT-MDA Cancer Center), Edward Fann (Baylor College of Medicine-Psychiatry), Daryl Ishaq Shorter (Baylor College of Medicine), and Claudia Pedrozo (UTHealth). Selected individuals have relevant expertise and experience in monitoring clinical trials. This committee will perform the following activities: (a) review the research protocol and plans for data and safety monitoring; (b) evaluate study progress, including data quality, participant recruitment rates, retention rates, outcome and adverse experience data, and risk versus benefit profile; (c) make recommendations to terminate the trial because of safety concerns; and (d) protect the confidentiality of the tria the results of monitoring.

3. Adverse events (AE) will be reported to the local IRB on an annual basis. Serious adverse events will be reported immediately (verbally within 24 hours) to the IRB, the DSMB, and to the NIDA. A written report will follow as soon as possible but in no more than three days. The written report will be in the format required by the IRB and will contain information regarding the date of the AE, description of the AE, severity rating (Grade 1 to 4), assessment of cause, whether the AE indicates an increased risk for current or future subjects, and whether changes to the informed consent form are necessary.

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