YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2013-1)

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Prazosin to Reduce Stress-Induced Alcohol Craving and Relapse		
Principal Investigator: Rajita Sinha PhD	**Yale Academic Appointment: Professor**	
Department: Psychiatry		
Campus Address: 2 Church Street South Suite 209 New Haven		
Campus Phone: 203-737-5805	**Fax:** 203-737-1272	**E-mail:** rajita.sinha@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Julie Pinto, 2 Church Street South Suite 209, New Haven		
Campus Phone: 203-737-5489	**Fax:** 203-737-1272	**E-mail:** julie.pinto@yale.edu

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

❑ Yes x No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

❑ Yes x No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- ☐ Magnetic Resonance Research Center (MR-TAC)
- ☐ Yale Cancer Center/Clinical Trials Office (CTO)
- ☐ Yale Cancer Center/Smilow
- ☐ Yale-New Haven Hospital
- ☐ Cancer Data Repository/Tumor Registry
- ☐ Specify Other Yale Location:
- ☐ Yale University PET Center
- ☒ YCCI/Church Street Research Unit (CSRU)
- ☐ YCCI/Hospital Research Unit (HRU)
- ☐ YCCI/Keck Laboratories
- ☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

- ☐ APT Foundation, Inc.
- ☒ Connecticut Mental Health Center
- ☐ Clinical Neuroscience Research Unit (CNRU)
- ☐ Haskins Laboratories
- ☐ John B. Pierce Laboratory, Inc.
- ☐ Veterans Affairs Hospital, West Haven

☒ Other Locations, Specify: Yale Stress Center, 2 Church Street South, Suite 209, New Haven
☐ International Research Site (Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. April 2007 – June 2017

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☒
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☐ Clinical Research: Patient-Oriented
☒ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☒ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☒ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒

Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
   Yes ☐ No☐

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☐ No☒

If you answered "yes", this study will need to be set up in OnCore Support
http://medicine.yale.edu/ymg/systems/ppm/index.aspx

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No X *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Sinha, Rajita	Prazosin to Decrease Alcohol Craving, Normalize Stress Dysregulation and Prevent Relapse	NIAAA – 1R01-AA20504	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant- 1 R01 AA 20504-03 ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	Rajita Sinha PhD	Yale	Rs57
Role: Co-PI	Helen Fox PhD	Yale	
Role: Co-Investigator	Robert Beech MD PhD	Yale	
Role: Co-Investigator/ MD	Peter Morgan MD	Yale	
Role: Co-Investigator/MD	Gretchen Hermes MD	Yale	
Role: MD	Julia Shi MD	Yale	
Role: Coordinator	Rachel Hart	Yale	
Role: Post Doc	Verica Milivojevic	Yale	
Role: Research Associate	Gina Lombardi	Yale	
Role: Research Assistant	Christian Panier	Yale	
Role: Research Nurse	Mary Kurjanowicz	Yale	
Role: Research Assistant	Sheridan Finnie	Yale	
Role: Staff Affiliate	Nathan Grandpre	Yale	
Role: Staff Affiliate	Jennifer Weinberg	Yale	
Role: Research Assistant	Arielle Rabinowitz	Yale	
Role: Correspondent	Julie Pinto	Yale	Jg358

SECTION IV:
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

PI Name (PRINT) and Signature _____ Date _____

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

Advisor Name (PRINT) and Signature _____ Date _____

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____
Chair Name (PRINT) and Signature Date

_____
Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____
YNHH HSPA Name (PRINT) and Signature Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
To test the preliminary efficacy of 16.0 mg of Prazosin daily versus placebo in treatment seeking alcohol dependent individuals. This proposal is a laboratory and treatment outcome study to examine the effects of Prazosin on brief exposure to stress, alcohol cues and neutral situations on alcohol craving, mood and neurobiological reactivity in a sample of alcohol dependent individuals. Prazosin will be beneficial for reduction in stress and alcohol cue induced craving

and related neuroadaptations. In a sample of 150 alcohol dependent men and women, we propose to examine (a) differences in measures of alcohol craving, emotion state, hypothalamic-pituitary-adrenal (HPA) activation, physiological changes and plasma catecholamine response to stress imagery and to drug cue imagery as compared to neutral imagery; (b) reduction in alcohol abstinence symptoms; and (c) improvement in alcohol treatment outcomes as measured by increasing abstinence, reduction in alcohol use and increased treatment attendance.

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

Evidence from clinical surveys indicates that stress frequently leads to continued drug use and relapse (Marlatt and Gordon 1985; Bradley, Phillips et al. 1989; Wallace, 1989; Hodgins, el Guebaly, & Armstrong, 1995; Miller & Tonigan, 1996). Animal studies have shown that acute behavioral stress facilitates drug self-administration and reinstatement to drug seeking behavior in drug-addicted animals that have been drug-free for extended time periods (Shaham et al., 1995). Previous work in our laboratory has shown that exposure to previous stressful experiences consistently increases alcohol craving and stress-related brain changes in alcohol dependent individuals (Fox et al., 2007; Sinha & O'Malley, 1999, Sinha et al, 2008). These data suggest that attenuation of stress-induced alcohol craving and related neuroadaptations may be a useful target in alcohol relapse prevention.

Prazosin HCl (Prazosin) has an established history as an antihypertensive agent since it was first introduced by Pfizer in 1976. Prazosin is a lipophilic alpha-1 adrenergic antagonist making it also useful in treating behaviors linked to noradrenergic hyperresponsiveness. For example it has been shown to be effective in reducing the overall PTSD illness severity (Taylor et al.2006; Peskind et al 2003; Raskind et al.2000, 2002, 2003; Taylor & Raskind, 2002). Pre-clinical evidence has suggested that noradrenergic circuits may be involved in alcohol craving and relapse (Simpson et al., 2007). Prazosin therefore has been of particular interest as a potential pharmacologic treatment for alcohol dependence (Simpson et al., 2007; Walker et al, 2008).

Alpha-2 adrenergic agonists, such as clonidine, lofexidine and guanfacine significantly reduce stress-induced drug seeking in drug addicted animals that are drug free for over 4 weeks (Erb et al., 2000; Shaham et al., 2002). Taylor et al. (2000) report that the postsynaptic blockade of alpha-1 receptors will have similar effects to those of alpha-2 receptors.

On the basis of these data and previous preclinical research, we hypothesize that Prazosin will also decrease stress-induced and alcohol cue induced alcohol craving in laboratory sessions. We have developed a laboratory-based imagery induction method that reliably increases cocaine and alcohol craving after imagery of stressful and drug/alcohol cue events in cocaine dependent and in alcohol dependent individuals (Sinha et al., 1999; 2000; Fox et al., 2007). However, whether a medication suppresses stress and alcohol induced craving in alcohol dependent individuals has not been conclusively shown. In a sample of 150 alcohol dependent men and women, we will examine the effects of Prazosin on alcohol craving, subjective mood states, and neurobiological responses in personalized stressful imagery and drug cues imagery. All subjects will be exposed to three imagery sessions (neutral, stressful and drug cues) and the order of imagery conditions will be counterbalanced across subjects.

We expect that Prazosin will be easily tolerated as the effects are indirect. Unlike other less selective alpha blockers, which also block presynaptic alpha receptors, alpha-1 blockers do not prevent inhibition of noradrenaline release. Uninhibited noradrenaline release causes increased reflex tachycardia through the sympathetic baroreflex response that increases cardiac output. Prazosin therefore has a minimal effect on cardiac function due to its alpha-1 receptor selectivity (Arnsten et al., 1988).

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

One hundred and fifty treatment seeking alcohol dependent individuals (men and women) will be recruited to participate in this medication study. Subjects may or may not participate in laboratory sessions. Subjects will be recruited through flyers and advertisements in local newspapers and from community substance abuse treatment facilities. Subjects will participate in an initial screening and intake session to obtain informed consent, followed by physical examination and blood work to determine eligibility. Subjects will be randomized to Prazosin (PRZ) or placebo (PLA) and medication will be dispensed in a three times daily dosing schedule (t.i.d. dosing) with 5 mg in the morning, 5 mg in the afternoon and 6 mg at night reached at the end of the 2-week period, and maintained at this or their highest tolerated dose until week 11, followed by a 5-day taper in week 12, as in previous research. The titration schedule was as follows: 1 mg dose at bedtime for 2 nights, followed by a 1mg dose morning and night (8 AM/8 PM) on day 3, then 2 mg dose t.i.d., on days 4-6, 3 mg dose (2 pills each) morning and afternoon, and 4 mg dose (2 pills) at night for days 7-9, increased to 4 mg dosing t.i.d. on days 10-13, and from day 14 through week 11, 5 mg (1 pill) each in the morning and afternoon, and 6 mg for the night (2 pills) dose. Subjects will be maintained on this dose during the laboratory sessions (if completing the laboratory sessions) and until week 12 of the study at which point they will be tapered off the study medication over the course of five days. Some subjects may be tapered prior to completion of the 12 weeks. This taper is similar to what has been used with lofexidine in opiate withdrawal protocols (Bearn et al., 1996; Strang et al., 1997) and in our outpatient relapse prevention study of lofexidine with opiate dependent patients. We expect most subjects will tolerate a daily dose of 16.0mg. However, subjects who cannot tolerate a dosing schedule of 16.0 mg will meet with the study psychiatrist to discuss a reduction in dose down to 10mg/day. Based on the Physician Desk Reference (2007), which reports that dosage may be as high as 40mg daily, we anticipate that 16.0mg per day will be well tolerated by subjects. Subjects who cannot tolerate a minimum dose of 6mg/day will be removed from the study protocol.

Subjects will complete a variety of diagnostic, cognitive and psychological assessments, a comprehensive physical examination and blood work. If completing the laboratory component as inpatients, subjects will also be involved in development of imagery scripts from personal stress, drug-related cue and neutral situations during the first 3 weeks of their stay. After subjects have been substance- free for 21+ days, they will participate in an imagery/relaxation training and

habituation session. Between weeks 3 – 4, subjects will participate in a 3-day experiment in which during a 2-hour laboratory session on three consecutive days, subjects will be exposed by guided imagery to a personal stressful situation, a drug cue related situation and a neutral relaxing situation, one exposure per day. Order of imagery type will be randomly assigned across subjects.

Research Plan:

Subjects will have the option of participating in either the inpatient–outpatient plan, or the outpatient plan. The inpatient–outpatient plan involves 3 - 4 weeks of inpatient treatment followed by 8 - 9 weeks of outpatient treatment. Subjects completing the inpatient-outpatient plan may or may not complete the laboratory sessions. The outpatient plan involves outpatient treatment with 12-Step Counseling for 12 weeks. Subjects enrolled in the outpatient plan also have the option to complete 4 days of inpatient laboratory sessions. The provision of an outpatient alternative is added to provide an opportunity for participation to those subjects who are not able to participate in longer inpatient treatment due to childcare, employment, or other related obligations. The three alternatives are described below:

Inpatient-Outpatient Plan with laboratory sessions:

Once a subject is deemed eligible, those who are interested in the inpatient option will be admitted to the Clinical Neuroscience Research Unit (CNRU) of the Connecticut Mental Health Center (CMHC) for the 3 - 4 week stay that will involve medication initiation and laboratory sessions where subjects will be exposed to stress, drug cues and neutral-relaxing cues on three separate consecutive days. Lab sessions will take place either on the Clinical Neuroscience Research Unit (CNRU) or at the Yale Stress Center.

After completing the inpatient phase of the study, subjects will either taper off the study medication or participate in a 9-week outpatient medication trial. Those choosing to continue treatment will be seen 2 times per week in outpatient treatment at the Substance Abuse Center at CMHC, or at the Yale Stress Center at 2 Church Street South. Subjects will be maintained on 16.0mg dose of PRZ/PLA until week 12. In week 12, subjects will undergo a 5-day taper similar to what has been used with Lofexidine in opiate withdrawal protocols (Bearn et al., 1996; Strange et al., 1997) and in our outpatient relapse prevention study of Lofexidine and Guanfacine with opiate and cocaine dependent patients respectively. Urine monitoring, assessment of craving, alcohol abstinence symptoms, self report of drug use and stress and craving scales, heart rate and blood pressure will be assessed weekly in the trial.

Inpatient-Outpatient Plan without laboratory sessions:

The plan for subjects completing the Inpatient-Outpatient Plan without laboratory sessions, will be identical to the plan for the Inpatient-Outpatient Plan with laboratory sessions, minus the laboratory sessions, and all procedures related to the laboratory sessions, such as participating in imagery script development sessions. Once a subject is deemed eligible, those who are interested in the inpatient option will be admitted to the Clinical Neuroscience Research Unit (CNRU) of

the Connecticut Mental Health Center (CMHC) for the 3 - 4 week stay that will involve medication initiation.

After completing the inpatient phase of the study, subjects will either taper off the study medication or participate in a 9-week outpatient medication trial. Those choosing to continue treatment will be seen 2 times per week in outpatient treatment at the Substance Abuse Center at CMHC, or at the Yale Stress Center at 2 Church Street South. Subjects will be maintained on 16.0mg dose of PRZ/PLA until week 12.

Outpatient Plan:

Subjects who are deemed eligible, but are unable to commit to 3 - 4 weeks of inpatient treatment will be seen 2 times per week in outpatient treatment at the Yale Stress Center at 2 Church Street South. Outpatient appointments will include motivational enhancement, urine drug screens, breathalyzers, blood pressure monitoring, and counseling. Daily interactive voice response (IVR) telephone monitoring, or the smartphone app MetricWire, will prompt subjects to take study medication, and assess their alcohol use, craving, craving resistance and mood states. Blood draws will be done at weeks 4-5 to measure Prazosin levels. These levels will allow staff to ensure subjects are taking medication as prescribed. Medication compliance will also be monitored through the use of riboflavin as a marker. Riboflavin produces a bright yellow discoloration of the urine when the medication is taken 2 to 8 hours prior. After the first week all subjects will be taking morning and bedtimes doses of the medication. After this time, staff will easily be able to visually inspect the subject's urine to determine whether the morning dose has been taken. 25mg of riboflavin will be added to all doses of Prazosin and placebo by the pharmacist when capsules are made. Thirty-two cc's of whole blood will be also collected from patients at intake for the purposes of understanding genetic factors that may affect craving.

In the event that someone is unable to achieve any period of abstinence within a 4-week period, they will be offered inpatient treatment or referred to a higher level of care at another facility. In the event that someone achieves abstinence but has occasional relapses, outpatient treatment will continue until they either sustain abstinence or a higher level of care is clinically indicated. These clinical judgments will be made by the principle investigator. Subjects will be provided with dollar amounts for kept appointments. Rewarding subjects for kept appointments, regardless of whether their urine is clean or not, will enable us to maintain treatment compliance while allowing for test of efficacy of medication in this trial.

After a subject is able to abstain from substances for a period of 21+ days, they will have the option to complete a 3-night stay on the CNRU, where they will participate in imagery training and 3 laboratory sessions. After completion of the laboratory sessions, subjects will be discharged from the inpatient unit at least one day after the laboratory sessions.

Subjects will undergo the same titration onto study medication as outlined above. If the subject decides to complete the laboratory component, they will be maintained on 16.0mg dose of PRZ/PLA medication during the week of the inpatient laboratory sessions, after which they will undergo the above mentioned taper or continue to take their medication for 9 weeks in outpatient

treatment. In the event that someone continues to use alcohol while in the study, they may be asked to come in for more frequent appointments to assess for adverse symptomatology and meet with the study psychiatrist. Similar methods have been used in our outpatient lofexidine study and no adverse interaction events are anticipated.

Table 1: PRZ/PLA Dosing

	Prazosin PRZ (N = 75) (Male / Female)			Placebo (PLA) (N = 75) (Male / Female)		
Week 1	AM	PM	Evening	AM	PM	Evening
Days 1 -2 (1mg / 1mg)	0mg / 0mg	0mg / 0mg	1mg / 1mg	0mg / 0mg	0mg / 0mg	1mg / 1mg
Days 3 (2mg /1mg)	1mg / 0mg	0mg / 0mg	1mg / 1mg	1mg / 0mg	0mg / 0mg	1mg / 1mg
Days 4-6 (6 mg/4mg)	2mg/1mg	2mg/1 mg	2 mg/2mg	2mg/1mg	2mg/1 mg	2mg/2mg
Week 2						
Days 7-9 (10mg /8mg)	3mg / 2mg	3mg / 2mg	4mg /4mg	3mg / 2mg	3mg / 2mg	4mg /4mg
Days 10 – 13 (12mg/12mg)	4mg /4mg	4mg/4mg	4mg /4mg	4mg /4mg	4mg /4mg	4mg /4mg
Day 14 (16mg/16mg)	5mg/5mg	5mg/5mg	6mg/6mg	5mg/5mg	5mg/5mg	6mg/6mg

Follow-up:

Upon completion of outpatient treatment, follow-up interviews will be scheduled with all subjects. If a subject decides to complete only the inpatient phase, follow-up appointments will be scheduled after the inpatient phase is complete. Follow up interviews will be scheduled at 30 days. Urine monitoring, assessment of craving, cocaine abstinence symptoms, self report of drug use and stress and craving scales, will be assessed during the follow-up appointment.

Contact and collateral information will have been obtained from subjects at intake. We currently use procedures that make it possible to locate and re-interview more than 90% of the patients recruited into our treatment and laboratory research studies. Of note, in our recently completed stress study with cocaine dependent individuals we obtained a 92% completion rate. Our procedures include informing the patient of the importance of follow-up evaluations at the time of initial assessment, emphasizing the patient's role as a research subject, guaranteeing complete confidentiality of all information, obtaining permission, addresses and telephone numbers of three collaterals to be contacted in order to help us locate the subject, arranging for home visits and telephone interviews when subjects fail to keep appointments, mailing of appointment reminders that are followed by telephone calls, and provision of incentive payments for successful completion of follow-up evaluations. All of these procedures will be incorporated into this study.

Study Feasibility:

The Chronic Alcohol and Brain Stress Circuit Relapse (#22015) for alcohol addiction currently screens approximately 15 subjects per month. On average, approximately 6-8 patients meet criteria for the proposed study (not on other medications and otherwise healthy) and will be offered participation in this study. Thus we anticipate that 3-4 patients can be enrolled into the pilot study monthly, leading to a 15-20 month recruitment phase for this study. The subjects will be recruited from treatment seeking individuals who are being evaluated for alcohol treatment at clinical programs and from those responding to advertisements and flyers for inpatient treatment and research.

General Procedures:

All subjects will be screened and recruited into the study by the research assistant coordinator. Potential subjects will meet with the research assistant coordinator who will, after an initial screening over the telephone/in person, determine eligibility based on inclusion/exclusion criteria. The initial screening will collect basic demographic information and ask questions specific to the inclusion/exclusion criteria. The initial screening will take approximately 5-10 minutes. She will explain all study procedures and risk/benefits and obtain informed consent. Subjects will undergo breath alcohol testing/urine toxicology screens at each in-person appointment to confirm self-report of drug and alcohol use information.

Admission:

Subjects will then be scheduled for admission at the CNRU for inpatient treatment, or the SAC for outpatient treatment and participation in research procedures. Subject will participate in a comprehensive physical examination conducted at the Clinical Neuroscience Research Unit (CNRU) of the CMHC to rule out any subjects who may be medically or psychiatrically unfit to participate in the study. Routine laboratory studies will include CBC, ESR, glucose, BUN/creatinine, electrolytes, liver and thyroid function tests, and EKG. Abnormal findings will be further evaluated by the physician on staff at the CNRU and appropriate medical advice will be provided. Subjects who report any specific current medical conditions and require, or are

currently on medications for treatment of their medical condition will be excluded from the study. Subjects will participate in standard substance abuse treatment.

Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scores will be taken at admission to monitor alcohol withdrawal symptoms. Librium 50mg, Ativan 2mg or other treatment will be given as appropriate for clinical evidence of alcohol withdrawal symptoms. CIWA scores will be assessed every four hours for at least the first 48 hours and longer if clinically appropriate. In addition to assessing CIWA scores for PRN medication, subjects who have a history of major alcohol withdrawal symptoms (e.g. withdrawal seizures or delirium tremens) will be placed on a standing dose of Librium 50mg tid for the first 24 hours with continued treatment as clinically appropriate.

Baseline assessments will be completed over the course of the first week. If participating in the laboratory sessions, subjects will participate in an imagery script development session to provide descriptions of recent stressful, drug cue related and neutral relaxing situations to the research assistant, in the second week. At the start of week 3 or day 15, if participating in the laboratory sessions, subjects will participate in a relaxation and imagery training and habituation session (STUDY DAY 1), followed by three laboratory sessions on each consecutive day (STUDY DAY 2, 3, 4). Subjects will be offered Nicotine Replacement Therapy (NRT) if needed.

Subjects will participate in lab sessions after maintaining at least 14 days of sobriety. After completion of laboratory sessions, subjects will be discharged from the inpatient unit at least one day after the laboratory sessions. All subjects will be maintained on a dose up to 16.0mg of Prazosin/PLA until week 12. In week 12, subjects will undergo a 5-day taper similar to what has been used with lofexidine in opiate withdrawal protocols (Bearn et al., 1996; Strange et al., 1997) and in our outpatient relapse prevention study of lofexidine with opiate dependent patients. Some subjects may be tapered prior to week 12.

Subjects will be seen two times per week by research staff for urine monitoring, assessment of craving, alcohol abstinence symptoms, self report of alcohol use and stress and craving scales, heart rate and blood pressure in the trial. Subjects will be administered the first dose of study medication at the clinic and will remain at the clinic for 1-2 hours to assess side effects. Remaining medication at the same dose will be provided as take home to self-administer daily.

All subjects will also be seen two times per week in outpatient treatment at the Yale Stress Center. All subjects will participate in 1x per week standard individual drug counseling as outlined in the Individual Drug Counseling Manual (IDC, Mercer & Woody, 1998) during the outpatient trial. Each subject will be assigned a counselor with expertise in IDC .The general purpose of the counseling sessions as described in the manual are to: (1) acquire information about important concepts and aspects of recovery from addiction; (2) increase self-awareness of specific problems and issues in relation to addiction and recovery, and (3) learn new coping skills to deal with problems contributing to or resulting from the addiction and to improve functioning. The focus of this psycho-educational approach is on providing patients with frequent supportive contact, introduce them to key concepts about the recovery approach, and develop a sense of personal responsibility for recovery.

Relapse in the pilot study will be defined as the first day of any alcohol use as documented by self-report and/or positive urine and positive breathalyzer for alcohol. Treatment drop-out is defined as four consecutive missed research appointments for medication self-administration. Relapse to alcohol will be recorded in the data and subjects will continue in the protocol. Furthermore, it will be addressed by their counselor and doctor in therapy appointments. If subjects have missed four consecutive appointments, all attempts will be made to bring the subject back and after a full assessment of the subject's need, a formal referral will be made to appropriate residential, inpatient or intensive outpatient care. Subjects will be maintained in regular treatment until they have entered treatment at the next appropriate level of care. Other clinical deterioration such as exacerbation of psychiatric or withdrawal symptoms will be assessed on a case-by-case basis by the study investigators. When clinically indicated and necessary, psychotropic medication or discontinuation of study medication will be initiated and/or a referral will be made to intensive outpatient, residential or inpatient care.

Physiological Assessments

During the physical, 8ml of whole blood will also be drawn to analyze molecular adaptations. Microarray profiling will be used to detect these molecular changes by comparing the molecular profile of the blood drawn during the physical to another 8ml of blood drawn during one of the laboratory sessions. A total of 16ml of whole blood will be drawn to examine molecular changes in the blood.

During the physical, all female subjects will have 8ml of whole blood drawn to determine estradiol levels. Estradiol levels drawn during the physical will be compared to another 8ml of blood drawn during one of the laboratory sessions. A total of 16ml of whole blood will be drawn to measure estradiol levels.

Laboratory Sessions:

Rationale for Use of Personalized Imagery Procedures. Emotional imagery paradigms have been widely used in behavioral research studies examining the pathophysiology of anxiety disorders, including panic disorder, obsessive compulsive disorder and PTSD (Cook, Melamed, Cuthbert, McNeil, & Lang, 1988; Foa & Kozak, 1986; McNeil, Vrana, Melamed, Cuthbert, & Lang, 1993; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987; Shalev, Orr, & Pitman, 1993; Orr et al., 1998; Orr, Pitman, Lasko, & Herz, 1993). These procedures are known to activate the same physiological, subjective and behavioral components as the emotion trigger situations, thus being a useful clinical research procedure for inducing stress/emotional states. Similar imagery induction procedures have been successfully adapted by our group in previous studies to induce specific emotion states in normal volunteers and stress and alcohol cues in alcohol dependent individuals (Sinha, Lovallo, & Parsons, 1992; Sinha & Parsons, 1996; Sinha, Catapano, & O'Malley, 1999a; see Preliminary Studies section C1, C2, C6).

Imagery procedures have also been used in the alcohol abuse literature to induce alcohol cue-induced alcohol craving and stress/negative mood induced alcohol craving in the laboratory (Cooney, Litt, Morse, & Bauer, 1997; Payne, Rychtarik, Rappaport, & Smith, 1992; Rubonis et al., 1994; Sinha et al., 1999a). Tiffany and colleagues compared imagery induction vs. in-vivo exposure to cues, and found that while both methods were equally effective in eliciting high levels of self-reported craving, physiological reactivity was greater with the imagery manipulation. Furthermore, our previous work in cocaine dependent individuals showing activation of the HPA axis and increases in plasma catecholamines with stress and with drug cue imagery indicates that the method is effective in inducing drug craving and in activating brain stress circuits (Sinha et al., 1999a). Thus, the imagery procedure includes the following distinctive components based on prior experience:

(i) Personal stressful, drug cue and neutral situations rather than standard situations will be selected because personal events show greater physiological reactivity and generate more intense emotional reactions than imagery of standardized non-personal emotions (Cook et al., 1988; McNeil et al., 1993; Miller et al., 1987).

(ii) Based on Lang's network theory on emotion processing and Tiffany's cognitive model of drug use and urges (Tiffany, 1990; Tiffany & Drobes, 1990) and our previous work, the addition of physiological, subjective and behavioral response descriptors are included in the imagery script so as to produce stronger activation of the experience.

(iii) To minimize subject variability in the imagery induction procedure, we include an imagery training session, in which each subject receives training on how to generate and maintain a mental image for 2-3 minutes. The imagery training procedures have been extensively used in previous studies by Lang and his colleagues and by the PI in her previous work on emotions and stress work with cocaine abusing samples.

Imagery Script Development Session: In a session prior to the laboratory sessions, scripts for the guided imagery induction will be developed. The stress imagery script will be based on subjects' description of a recent personal stressful event that they had been experienced as "most stressful". "Most stressful" is determined by having the subjects rate the perceived stress experienced by them on a 10-point Likert scale where "1=not at all stressful" and "10=the most stress they felt recently in their life". Only situations rated as 8 or above on this scale are accepted as appropriate for script development. Stressful situations that involved drug-related stimuli, such as being arrested for possession of drugs or being caught in a police chase, are not allowed. Examples of acceptable stressful situations include breakup with significant other, a verbal argument with a significant other or family member or unemployment-related stress, such as being fired or laid off from work. As stressful situations often occur in the context of alcohol use, these situations are thought to be associated with alcohol use and therefore elicit alcohol craving.

The alcohol-related script will be developed by having subjects identify a recent situation that included alcohol-related stimuli and served as a trigger for subsequent alcohol use (e.g. buying alcohol, being at a bar and watching others drink alcohol; getting together with alcohol drinking buddies). Alcohol-related situations that occurred in the context of negative affect or psychological distress will not be allowed, i.e., going to a bar after a marital conflict, or feeling depressed and calling an alcohol drinking buddy. A neutral-relaxing script will be developed from the subjects' commonly experienced neutral-relaxing situations. Neutral-relaxing events

that involve drug cues will not be allowed. A 'script' or description of each situation will be developed using Scene Development Questionnaires which obtain specific stimulus and response details, including specific physical and interpersonal context details, verbal/cognitive attributions regarding the people involved, and physiological and bodily sensations experienced for the situation being described. The three scripts for each subject will then be recorded on an audio-tape for guided imagery in the laboratory sessions. The order of stress, neutral and drug cue scripts will be assigned randomly, and counterbalanced across subjects. Detailed procedures are outlined in the Imagery Development Procedures Manual (Sinha, 2001b).

Interview sessions may be videotaped. Subjects will be asked for their signed permission to videotape their interview sessions and will be paid an additional $20 for each interview session we videotape. Subjects are informed of the possibility of videotaping in the consent form, in additional to a separate videotaping consent form. Subjects will know when they are being videotaped. Videotapes will be used to evaluate the interviewer, train new staff, and rate the subject using a behavioral observation scale. Videotaping will not affect the subject's study participation or treatment in any way.

Manipulation Check for Script Development: All three scripts will be rated on a Likert scale from 1 to 10 on a standard rating form (Independent Rating Scale) by two objective independent raters for stressful and emotional content. If a script scores below a rating of 8 for stressful content on a five-point rating scale the subject will be asked to develop a new script at the next appointment prior to the laboratory sessions. These procedures ensure that the stress and drug cue scripts of all subjects are equated in intensity and content. It further ensures that differences in stress reactivity are not due to differences in intensity and emotional content of the stressor. The procedures for development of imagery scripts, rating of scripts for content and physiological activation are similar to those used by Miller et al. (Miller et al., 1987) and have been successfully used in our previous work on emotions (Sinha et al., 1992; Sinha & Parsons, 1996) and on stress reactivity with cocaine dependent individuals (Sinha et al., 1999a).

Imagery and Relaxation Training and IV Habituation Day- STUDY DAY 1. On the afternoon of DAY 1, an indwelling catheter will be inserted in the subject's arm for one hour, so that subjects can habituate to the stress of an IV insertion. We have found that this period of adaptation is critical for stable baseline measurements on testing days. No blood will be drawn on the training day. After insertion of IV catheter, the subject will be provided with relaxation training followed by general imagery and physiological response training, as described in the imagery training procedures manual (Lang, Levin, Miller, & Kozak, 1983). The imagery training involves subjects' visualizing some commonplace scenes as they are presented to them. The scenes are neutral and non-emotional in content, such as reading a popular magazine. Following the imagery, the subject is asked questions about the visualization and given pointers regarding the process of imagining the scene. The subject also imagines scenes that are non-emotional but physically arousing in nature, such as doing sit-ups in gym class. With these scenes subjects are asked whether they notice any changes in their physiological response, such as change in heart rate or change in breathing. Once again, pointers with regard to imagining the situation "as if" they were really present in the situation are presented. This session takes approximately one hour and was developed to insure that all subjects are trained on the method of generating an image and maintaining it for 2-3 minutes.

Laboratory Sessions. On DAY 2, 3, and 4 of the study, subjects will be brought into the research testing rooms of the CNRU at 8:00 AM after a smoke break at 7:30 AM. Breakfast will be withheld from the subject until after the laboratory session. The subject will then be prepared for physiological assessments. An indwelling intravenous (IV) catheter will be inserted by the research nurse specialist in the antecubital region of the subject's non-preferred arm for blood sampling. Blood samples will be obtained periodically for assessment of ACTH, cortisol, prolactin, NE and EPI levels. A blood pressure cuff will be placed on the subject's preferred arm to monitor blood pressure (BP) periodically. On-line assessment of physiological measures will be obtained at specified time periods during the laboratory sessions. Self-reports of emotional state, anxiety and alcohol craving will also be assessed periodically.

After preparation of assessments and a 40 minute adaptation period, a –20 minutes and –5 minutes blood draw will be conducted. After the –5 blood draw, a 5-minute baseline period will follow to assess continuous pulse rate and BP assessments. Following the baseline period, instructions for conducting imagery will be provided. The order and content of the imagery condition will not be revealed to the subject or to the research staff conducting the sessions. In the imagery task the subjects will be asked to imagine the situation being described vividly, 'as if' he/she is in the specific situation and actively participating in it, until asked to stop. The imagery script will be played to the subject over headphones and the subject will be required to imagine the situation for 5 minutes. A tape recording for each subject's script will be developed prior to the testing situation and read by the same person for each subject. Timeline for assessments are summarized in Table 3.

TABLE 3: Schedule for Laboratory Sessions

DAY 1:	Imagery and Relaxation and Habituation Session (1 hour)
DAY 2, 3 and 4:	IMAGERY SESSIONS
8:00 AM	Set-up for plasma (IV insert) measures; physiological setup - HR, BP
8:10 AM	Stabilization and Adaptation period, BP reading
8:40 AM (-20)	Initial Blood Draw, craving/DES ratings, physiological assessments
8:50 (-10)	BASELINE Period; on-line physiological recordings
8:55 (-5)	Baseline blood draws; craving/DES ratings, BP assessments
9:00	IMAGE Period (Stress/Drug Cues/Neutral); physiological assessments
9:05 (0)	Post-Image blood draw; craving/DES ratings; Imagery Vividness ratings
9:10 (+5)	RECOVERY Period; 5-min physiological assessments; craving/DES ratings;
9:20 (+15)	Recovery1: Blood draws, craving/DES ratings; 5 minute physiological assessments
9:35 (+30)	Recovery2: Blood draws, craving/DES ratings; physiological assessments
9:50 (+45)	Recovery3: Blood draws, craving/DES ratings; physiological assessments
10:05 (+60)	Recovery4: Blood draws, craving/DES ratings;
10:20 (+75)	Recovery5: Blood draws, craving/DES ratings; physiological assessments
10:30 AM	Relaxation tape; assess physiological levels and subjective state for return to baseline

Relaxation instructions will be provided to ameliorate any residual effects of imagining personal stressful and drug cue situations. Subjects will then be free to leave the testing room and eat breakfast on the unit. Relaxation instructions have been found to be effective in reducing alcohol cue-induced craving (Margolin, Avants, & Kosten, 1994; Sinha et al., 1999a) in the laboratory and we will use these instructions to reduce any residual alcohol craving. All subjects will also remain on the inpatient unit for at least one more day after the laboratory sessions. Previous research and our clinical research experience indicates that laboratory induced drug craving returns to baseline after the laboratory sessions with little impact after laboratory exposure.

Laboratory Assessments.

a. Self-Reports (a) Differential Emotion Scale (DES; 246). Subjects will be asked to rate their current emotional state for the following: anger, fear, sadness, anxiety, joy, neutral-relaxed feelings. These ratings will be conducted for each assessment period during the imagery session (as indicated in Table 3). An abbreviated version of the DES (Izard, 1972) includes five adjectives (a total of 30 items) are used to describe each affect state and subjects are required to rate on a 5-point scale the extent to which each word describes the way she feels at the present time. The DES has been used in human laboratory studies to assess subjective states after induction of moods either via imagery or other standard tasks such as mental arithmetic, Stroop test or in a confederate situation (Schwartz & Weinberger, 1980; Schwartz, Weinberger, & Singer, 1981). It has provided useful emotion state data for alcohol dependent individuals during stress exposure and in alcohol craving (Sinha et al., 1999a; Sinha, Fuse, Aubin, & O'Malley, 2000; Sinha et al., 2002a; a copy of the abbreviated DES is provided in Appendix A2.3). (a) Alcohol Craving: All subjects will be asked to rate alcohol craving during the laboratory sessions at time-points specified in Table 3. Alcohol craving will be measured using the Alcohol Urge Questionnaire (Bohn, Krahn et al., 1995), which is a brief 8-item self-report craving scale, and is designed so that it can be used in laboratory studies that require repeated assessments of alcohol craving such as in cue-reactivity studies (AUQ). The AUQ has high test-retest reliability (0.84) and was found to be a valid measure of alcohol urges that was significantly associated with drinking measures and dependence severity. We have previously used the AUQ in our laboratory study assessing the effects of naltrexone on craving and ad-lib drinking in alcoholics (O'Malley, Krishnan-Sarin et al, 2002).

b. Physiological Measures.

A pulse sensor will be attached to the subject's forefinger to obtain a measure of pulse rate. Blood pressure will be measured using the IBS dynamap.

c. HPA and Catecholamine Measures.
To assess plasma levels of ACTH, prolactin, cortisol, norepinephrine (NE) and epinephrine (EPI), 5ml of plasma (15 ml of whole blood) will be collected at each time point (total of 360 ml over 3 days). The samples will be split into five heparinized tubes (.15 ul of heparin) and the tubes will be placed on ice immediately after blood drawing. Within 30 minutes of collection, the blood will be centrifuged at 4C and the serum removed into separate test tubes, 1 ml of plasma each for ACTH, cortisol, prolactin, NE and EPI. Similar blood drawing procedures have been established successfully on the CNRU for previous studies with psychiatric and substance

abusing populations and in our previous studies with alcohol dependent individuals. All tubes will be stored at -70C until they are ready for shipping to the Kreek laboratories. ACTH, prolactin and cortisol will be measured using standard radioimmunoassay procedures.

In addition, saliva samples will be collected at the same time points as the plasma samples. Saliva samples will be processed by the YCCI core laboratories. This will be done to compare salivary cortisol measurements with the plasma cortisol assessments.

Catecholamine samples will be analyzed by Dr. Anderson's laboratory at the Yale University Medical School. These samples will be labeled with a serial number and will not have any identifying information. These samples will be used to determine adreno-medullary and sympathetic response to the challenges employed. Although both plasma norepinephrine (NE) and epinephrine (EPI) levels increase rapidly with a range of stressors, differential response is often seen (Goldstein, 1998). The plasma concentrations of NE and EPI will be determined in serial blood samples using high performance liquid chromatography (HPLC). Catecholamines will be alumina-extracted from 1.0 ml plasma samples, separated by reverse phase ion pair chromatography and detected using coulometry (Coulochem II, ESA, Inc.). Concentration detection limits of 1-2 pg/ml are observed; typical baseline plasma NE and EPI levels are 150 pg/ml and 20 pg/ml, respectively. Within-day and day-to-day coefficients of variation are less than 10%.

For both HPA and catecholamine assays, data will be analyzed for the time-points outlined in Table 3. In addition, as each measure may show different response profiles over time, we will also assess maximal or peak response and area under the curve (AUC) for each measure. Peak and AUC assessments of these measures are commonly used methods to reduce variability in responses and have been used in several studies (Kirschbaum, Wust, Faig, & Hellhammer, 1992; O'Malley, Krishnan-Sarin et al. 2002).

Standard Individual Drug Counseling: All subjects will participate in weekly standard individual drug counseling as outlined in the Individual Drug Counseling Manual (IDC, Mercer & Woody, 1994) during the outpatient trial. Each subject will be assigned a counselor with expertise in IDC who will see the patient for the 9 or 12 week outpatient trial. The general purpose of the counseling sessions as described in the manual are to: (1) acquire information about important concepts and aspects of recovery from alcohol addiction; (2) increase self-awareness of specific problems and issues in relation to addiction and recovery, and (3) learn new coping skills to deal with problems contributing to or resulting from the addiction and to improve functioning. The focus of this psycho-educational approach is on providing patients with frequent supportive contact, introduce them to key concepts about the recovery approach, and develop a sense of personal responsibility for recovery.

Assessments: A trained research assistant will meet with the client at various time-points to assess the client on selected substance use and psychological functioning measures using structured interviews, self-report assessments and to obtain urine samples for toxicology screens. A description of the assessment battery follows, and Table 1 lists the schedule of administration of assessments.

Screening Assessments:

Sociodemographic/general patient information. Demographic data, medical history, and family psychiatric history will be assessed with interviews and self-report forms that provide data on age, race, socioeconomic status, marital status, psychiatric family history, educational and occupational levels, and significant medical history.

The Structured Clinical Interview for DSM-IVTR (SCID, First et al., 1995) will be used to obtain DSM-IVTR Alcohol Dependence and other substance use disorder diagnoses. The SCID's reliability and validity among substance-using populations has been established in large-scale surveys (Kranzler et al., 1996). The number of dependence syndrome elements endorsed from the DSM-IVTR substance abuse/dependence criteria will assess severity of alcohol and other drug dependence. The SCID will also be used to obtain previous psychiatric diagnoses.

Medical History and Physical Examination: All patients will be required to participate in a physical examination including a medical history, electrocardiogram (EKG), blood and urine laboratory assessments prior to initiation of Prazosin to ensure eligibility for Prazosin study protocol. These will be conducted at the CNRU.

Short Form 36 Health Survey (SF-36) is a 36-Item questionnaire used in to assess the subjective quality of life of respondents.

Drug and Alcohol Use Measures:

Addiction Severity Index (ASI: McLellan et al., 1992) is a structured interview that assesses the severity of substance use and substance-related problems in the areas of medical, employment, legal, family/social and psychiatric functioning. The ASI is the most widely used instrument for assessment of substance use and related problems and its psychometric properties are well-established (Cacciola et al., 1997). The ASI will be used at pre-treatment and week 9. Follow-up ASI interviews will be conducted at 30 days post-treatment.

The Substance Use Calendar was developed by Miller and DelBoca (1994) and is based on the Time-Line Follow-Back Method (TLFB) (Sobell, Maisto et al. 1980). The SUC uses a calendar prompt and a number of other memory aids (e.g., holiday, payday, and other personally relevant dates) to facilitate accurate recall of daily drug use during the targeted period. It has demonstrated adequate levels of reliability and validity when administered as an in-person interview, over the telephone, and when administered via computer (e.g. Carey, 1997; Sobell, Brown, Leo, & Sobell, 1996; Sobell, Sobell, Leo & Cancilla, 1988). It's reliability and validity in drug abusing samples has also been established (Fals-Stewart, et al., 2000). In the current study we will use to obtain self-report of day to day use of alcohol and drugs, for the 60 days prior to treatment, weekly during treatment, and at the 30 day follow-up interviews.

Alcohol Dependence Scale (ADS) is a 25 item to measure severity of alcohol dependence; the Alcohol Use Questionnaire (AUQ) consists of 8 items to determine the respondent's alcohol craving; Smoking History Questionnaire

Abstinence Measures:

Clinical Institute Withdrawal Assessment-Alcohol Revised (CIWA-Ar) is a 13 item scale that measures alcohol withdrawal signs and symptoms. The assessment will be administered at intake and weekly.

Urine Toxicology and Breathalyzer Screening: A urine toxicology screen will be conducted at intake to confirm alcohol use. During treatment, urines will be collected 3 times weekly to confirm sobriety during inpatient stay using the CNRU laboratory. In addition, urine samples will be taken 2 times weekly during outpatient treatment and at follow-up appointments using on-site TESTCUP5 Drug Screen (Roche Diagnostics Inc., Totowa, NJ) to monitor opiate and other drug use. The TestCup5 kit provides results for opioids, cocaine, THC, PCP and barbiturates. In addition, breath alcohol levels will also be assessed with the Alcosensor III Intoximeter at each face-to-face contact, 2 times weekly.

Assessment of Psychological Symptoms:
A number of self report measures of psychological functioning will be obtained weekly to examine Prazosin's effects on psychological functioning. The following well-established and reliable instruments will be used:
The Hamilton Anxiety Scale is a widely used anxiety rating scale comprised of 14 symptom-oriented questions; The Center for Epidemiologic Studies Depression Scale (CES-D) a screening test for depression and depressive disorder; Childhood trauma Questionnaire (CTQ) is a 28-item self-report inventory that provides a brief screening for histories of abuse and neglect; The Emotion Regulation Scale (ERS) is a 36-item questionnaire to provide a comprehensive measure of the difficulties in emotion regulation; Global Perceived Early Life Stress Scale (GPELS) measures the occurrence of stressors in early life ; Interpersonal Support Evaluation Lists (ISEL) is a 40 item assessment to measure the perceived availability of four relatively independent social support resources; Positive and Negative Affective States (PANAS) is a 20 item assessment comprised of two mood scales, one measuring positive affect and the other measuring negative affect. Obsessive Compulsive Disorder Scale (OCDS) is a 14 item test to measure obsessionality and compulsion; Pittsburgh Sleep Quality Index (PSQI) measures the quality and patterns of seven areas of sleep; Stanford Sleepiness Scale uses a 7 point scale to measure the degree of sleepiness

Stress-Related Assessments:
Perceived Stress Scale (PSS; Cohen et al., 1983) assesses the degree to which situations are appraised as threatening or otherwise demanding and that there are insufficient resources to cope with the situation. This global measure of perceived stress has been widely used in the behavioral medicine literature to examine the effects of stress on disease and treatment outcome. The PSS is a 14 item self-report measure with adequate reliability and both predictive and construct validity. It has been shown to predict smoking reduction in a smoking cessation treatment program (Cohen et al., 1983; Cohen & Lichtenstein, 1990). It will be used to assess stress levels weekly in study patients during treatment and at follow-up appointments.(copy included in Appendix B).
Chronic Stress Checklist

Cognitive assessments
All tasks are administered at baseline (day 4 of inpatient admission) and following three weeks of prazosin treatment. All CANTAB tasks incorporate testing modes suitable for use across multiple time-points and are presented on a touch-screen computer.

1) Motor Screening: familiarizes subjects with the equipment and provides an index of motor performance. Ten flashing crosses are presented (one at a time) on the screen and subjects are required to place their index finger on the center point of each cross to stop it flashing (2 min)

2) Pattern and Spatial Recognition: Pattern recognition: participants are shown 12 colored abstract patterns, one at a time, for three seconds. A recognition phase follows where the 12 "target" patterns are shown in reverse order and paired with a novel pattern. Participants must touch the pattern they recognized from the presentation phase. Spatial recognition: five white boxes are presented, one at a time for three seconds, in different locations on the screen. In the recognition phase, five "target" boxes are shown again in reverse order and paired with a second box, located in a novel location. Participants must touch the box that is in the same location as the one shown in the presentation phase. Response latency and errors are recorded in both tasks (5 min each).

3) Paired Associates Learning: Six white boxes are presented in a circle around the screen. Each of the boxes open up in a random sequence revealing an abstract pattern "inside". The patterns are then displayed individually in the center of the screen and participants are requested to touch the box in which they had seen each of the patterns. Participants perform 2-trials of one pattern-location association, 2-trials of two pattern-locations and 2-trials of three pattern-locations. One-trial of six pattern-locations and 1-trial of eight pattern-locations is then presented. If an error is made, a "reminder" phase is shown. Participants are allowed nine "reminder" phases for each trial, making a total of 10 attempts prior to the task being terminated. Number of presentations required on each trial; total number of patterns successfully located on initial presentation and total number of errors made on each trial are recorded (10 mins)

4) Spatial working memory: Participants must search through a display of boxes to find "hidden" blue tokens. Only one token is hidden at any one time, and once a token is found in a particular box, that box is not used again to conceal other counters. There are two types of search error: a) returning to a box in which a blue token has already been found ("Between Search Error") and b) returning to a box (in the same search sequence) that is empty ("Within Search Error"). Each participant is required to attempt four 3-box trials, four 4-box trials, four 6-box trials and four 8-box trials. In addition, participants receive a "search strategy" score reflecting ability to employ an optimal strategy to minimize errors. (8 mins)

5) Three-Dimensional IDED: The ability to form, maintain and shift attentional set is assessed through learning a series of two alternative forced choice discriminations and their reversals. Stimuli vary along three possible dimensions (color, shape, number). In the "intra-dimensional shift" stage, the relevant dimension (color) remains unchanged despite the introduction of two completely novel stimuli. In the final "extra-dimensional shift" stage participants are required to "shift" response set to a previously irrelevant dimension (shape). Participants must achieve 6 correct successive discriminations. If these discriminations are not achieved following 50 attempts, the task is terminated. Errors and response latencies are recorded. (10 min)

6) Affective Go/No Go: A series of words appearing rapidly on the center of the screen. All words are taken from two of three different affective categories: Positive (joyful), Negative (hopeless), and Neutral (element). The subject is given a target category, and is asked to press

the pad only when they see a word matching this category. Commission and omission errors latency are recorded. (10 min)

7) Stop/Signal Task: In the first part of this test, participants are required to press the left hand button when they see a left-pointing arrow and the right hand button when they see a right-pointing arrow. Sixteen practice trials are presented. In the second part, participants are told to continue pressing the buttons when they see the arrows, as before, but, if they hear an auditory signal (a beep), they should withhold their response. Direction errors, proportion of successful stops, and relevant reaction times are recorded. (20 min)

8) Stroop Color Word Test (Golden, 1976). On the initial trial participants are given 45 seconds to read as quickly as possible a list of 100 color words (red, green, blue) randomly arranged and printed in black ink. On the second trial participants have 45 seconds to identify as quickly as possible the color of 100 "XXXX" printed in either red, green or blue ink. The final trial consists of the 100 words presented in the initial trial in the colors presented in the second trial. In all cases, the word (i.e. red) is different from the color it is printed in (i.e. blue. (e.g. "red"). Subjects are given 45 seconds to name the color of the ink as quickly as possible. The number of raw items read for each trial is recorded and converted to standardized T scores. (5 min)

9) RAVLT (Rey, 1964). This involves the repeated administration of a word list (List A) across five learning trials. Free recall immediately follows each presentation. After the last learning trial a second "interference" list (List B) is presented prior to the free-recall of List B. Immediately following recall of List B, participants are again required to recall List A, without additional presentation. After a 40 minute delay, they are again asked to recall List A without presentation. No time limit is applied to the recall trials and participants are prompted to recall words in any order. Both stimulus word lists (A and B) are presented to the participants on tape, at a rate of one word per second. Following the delayed recall trial, a recognition word list is presented comprising 45 words, (15 target words from List A; 15 from List B; 15 phonologically or semantically similar to those in List A). Recall, recognition and error scores are recorded as well as interference, learning rate and forgetting (10 min)

Other Relevant Measures:

(q) **Safety and Side Effects Measures**: The following safety measures will be assessed at each contact with the patient: (i) Sitting vital signs: including heart rate, systolic and diastolic blood pressure will be assessed daily for inpatient subjects, and 2 times a week for outpatient subjects. (ii) **Laboratory chemistry** will be assessed upon treatment entry and during the week of labs. (iii) Adverse Events/Side Effects: A Systematic Assessment of Treatment Emergent Events (SAFTEE) will be assessed at each visit to assess any adverse events of side effects that may have occurred in patients during the treatment study. The scale will assess physical or health problems since the last visit, including changes in physical appearance and changes in functioning due to physical condition (see Appendix B, SAFTEE assessment page 1). If the subject describes any changes a detailed assessed of the symptom or complaint will be conducted using the SAFTEE form pages 2-4. An adverse events form developed by our group will be completed for the event according to the criteria outlined in the Data Safety Monitoring Plan in the Human Subjects section. Thus, study staff and investigators will evaluate all adverse events, and an adverse event report will be completed and the Yale HIC, the CMHC pharmacy, and the

YCCI Research Subject Advocate, will be notified (see Data Safety Monitoring Plan for procedures for safety monitoring and reporting of adverse events). Adverse events/side effects will be assessed weekly throughout the study.
(r) The Commitment to Abstinence Scale adapted by Hall, Havassay and Weissman (1990) from Marlatt, Curry & Gordon (1980) will be included at baseline and monthly. Commitment to abstinence is assessed by asking subjects to endorse one of six abstinence goals: (a) total abstinence, never use again; (b) total abstinence but realized that a slip is possible; (c) occasional use when urge strongly felt; (d) temporary abstinence; (e) controlled use; (f) no goal. Ratings are also made of desire to abstain, expected success in abstaining and the expected difficulty of abstaining using 10-point scales.
(s) The Change Assessment Scale, a 32-item self-report, was developed to assess readiness for change according to Prochaska and DiClemente's model (Prochaska & DiClemente, 1982). It will be used at baseline and monthly to assess motivation to change alcohol use behaviors.

TABLE 1: Schedule of Assessments

Purpose/Measure	Rater	Timing of Assessments: Baseline	2-3x/wk	Weekly	Monthly	Post-Tx	Follow-up
Screening, Inclusion/Exclusion Criteria							
Socio-demographic Info	RA	X					
Physical Examination	Phy						X
Medical History	Phy/PSY		X				
SF-36	P	X					
Laboratory chemistry	Phy/PSY	X					
Psychiatric							
Psychiatric Evaluation	PSY	X					
SCID -I & II	PC						X
Assessment of Outcome							
Vital signs	N/PSY	X	X		X	X	
Withdrawal Ass (CIWA)	P/N	X	X		X	X	
Adverse Events/Safety	N/PSY	X	X		X	X	
Substance Use:							
ASI	RA	X				X	
ADS	P	X			X	X	
AUQ	P	X	X		X	X	

Urinalysis	RA		X	X				X		X		
Substance Use Cal.	RA		X		X		X	X		X		
Treatment Services Rev.		RA		X				X		X		
Smoking History Q		RA		X				X		X		
Psychological Symptoms												
Hamilton Anxiety Scale		P		X	X			X		X		
CESD		P		X	X			X		X		
CPI-SO		P		X								
CTQ		P		X								
ERS		P		X								
ISEL		P		X								
NPAS		P		X								
OCDS		P		X								
Stanford Sleepiness Sc		P				X						
Stress Measures												
Perceived Stress Sc.	P				X			X		X		
Chronic Stress Checklist		P		X								
GPELS		P		X								
Cognitive Measures												
Motor Screening		RA		X					X			
Pattern & Spatial Recog		RA		X					X			
Paired Associates Learning		RA		X					X			
Spatial Working Memory		RA		X					X			
IDED			RA	X					X			
RAVLT		RA		X					X			
Stroop			RA	X					X			
Stop/Signal Test		RA		X					X			
Go /NoGo												
Other Measures												
SAFTEE	P				X							

¬_¬____

Note: N/PC: Study Nurse/Project Coordinator; Phy: CMU Physician; PSY: Study Psychiatrist; RA=Research Assistant; P=Patient;

4. Genetic Testing N/A ☐

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned

ii. the plan for the collection of material or the conditions under which material will be received

iii. the types of information about the donor/individual contributors that will be entered into a database
iv. the methods to uphold confidentiality

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

Thirty-two cc's of whole blood will be collected from patients during day 1 of the laboratory sessions for the purposes of understanding genetic factors that may influence the way in which the subject behaves/feels in response to alcohol. For subjects completing the outpatient plan, this blood draw will be done at their intake appointment. Samples will be marked only by study ID numbers and no other personal identifying information will be sent to the laboratory. Once genetic analysis are conducted the data will be sent back to our laboratory and the genetic data will be stored in computerized research records that will then be analyzed by group analysis. There is no plan to return specimens back. If the subject chooses to withdraw their sample, the subject will be informed that the genetic blood sample will be stripped of all identifiers (anonymized) including study id number.

No immortalization of cell lines, animal studies or whole exome or genome sequencing is/are currently planned. Samples are stored in a de-identified sense, and candidate genes will be explored to assess treatment response to prazosin. We have no current funding to conduct genetic analysis. All treatment outcome data are de-identified and there is no way to link subject PHI to genetic or clinical outcome data. Samples may also be contributed to the NIH data bank for analysis of treatment response. Individual level donor's personal health information will not be included; race, gender, age and education level are the only variables included but these do not provide individual level information, but rather are aggregated as group level data.

The sharing of materials and/or distributing for future research projects is limited to contributing to the NIH data bank, as NIH is the funding source. Individual level donor's personal health information will not be included; race, gender, age and education level are the only variables included but these do not provide individual level information. Widespread sharing of materials is not planned.

The MetricWire smartphone app, has been designed to be compliant with HIPAA regulations. The app encrypts data on participants' phones and while data is wirelessly transferred. The app randomly generates a 24-digit identification code that contains numbers and letters, and remains consistent for each subject throughout the smartphone assessment phase. This identification code

will be linked by the research team with the numerical Subject ID that is assigned to subjects upon their initial laboratory visit.

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

One hundred and fifty treatment seeking alcohol dependent individuals (men and women) will be recruited to participate in this laboratory and medication study. Subjects will be recruited from the community without regard to sex, racial, or ethnic background. We expect a representative sample will drawn from the community.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

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

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

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

One hundred and fifty subjects who meet current DSM-IV criteria for alcohol dependence and are seeking treatment will be recruited to participate in this study. The following inclusion and exclusion criteria will be followed:

Inclusion Criteria:
i. Male or female individuals, ages 18 and above, meeting current DSM-IV criteria for alcohol dependence.
ii. Meet current DSM-IV criteria for alcohol dependence
iii. Subject has voluntarily given informed consent and signed the informed consent document.
iv. Able to read English and complete study evaluations.

Exclusion Criteria:
i. Meet current criteria for abuse or dependence on another psychoactive substance, excluding cannabis, nicotine and caffeine;

ii. Current use of any psychoactive drugs, including anxiolytics, antidepressants (except SSRIs), naltrexone or antabuse;
iii. Any psychotic disorder or current Axis I psychiatric symptoms requiring specific attention, including need for psychiatric medications for current major depression and anxiety disorders
iv. Significant underlying medical conditions such as cerebral, renal, thyroid, hepatic, or cardiac pathology which in the opinion of study physician would preclude patient from fully cooperating or be of potential harm during the course of the study;
v. Hypotensive individuals with sitting blood pressure below 90/60 mmHG.

8. How will **eligibility** be determined, and by whom?

All subjects will be screened and recruited into the study by the research assistant coordinator. Potential subjects will meet with the research assistant coordinator who will, after an initial screening over the telephone/in person, determine eligibility based on inclusion/exclusion criteria. The initial screening will collect basic demographic information and ask questions specific to the inclusion/exclusion criteria. The initial screening will take approximately 5-10 minutes. She will explain all study procedures and risk/benefits and obtain informed consent. After obtaining written informed consent for participation in the study, one of the study physicians will interview the subject and review all medical and psychiatric data prior to enrolling the subject and beginning medication.

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

i) Alcohol Detoxification:

The risks associated with stopping drinking may include: anxiety, shakiness, confusion, rapid heart rate, fever and in rare cases, life-threatening seizures. To achieve abstinence from alcohol dependence, participants are reinforced for abstinence using the fishbowl and monitored three times weekly. The Clinical Institute Withdrawal Assessment – Alcohol Revised (CIWA-Ar) will be used during this period to assess withdrawal symptoms. In the case of moderate symptoms of alcohol withdrawal (CIWA score between 8-12), study physician, Dr Gretchen Hermes will provide initial treatment and monitoring and we will facilitate referral for detoxification at Southern Connecticut Rehabilitation Center (SCRC), with whom the study PI and the Stress Center research staff have a good working relationship for such transfers. Please note that the SCRC facility is only 2 blocks away from the Yale Stress Center. In cases of severe alcohol withdrawal (CIWA-Ar scores at 13 or above), the subject will be immediately transported to the Yale New Haven Hospital Emergency Room (Yale ER) for full medical assessment and treatment of alcohol withdrawal. After the subject completes detoxification he/she will be allowed to return to the study for enrollment and participation. We will continue to monitor for alcohol withdrawal throughout the study period and facilitate referral to higher level of care such as inpatient treatment, as needed. If the subject is unable to stay abstinent from alcohol, he will be withdrawn from the study and also referred to inpatient and intensive outpatient treatment for alcohol use disorders.

Alcohol Detoxification in the Inpatient Unit: To achieve abstinence from alcohol dependence, participants that are recruited into the inpatient portion of the study are simultaneously admitted to a clinical inpatient unit (the CNRU) for clinical treatment. This is separate from the research protocol which begins after detoxification (please see consent form) and does not guarantee participation into the research study. However, following clinical admission to the CNRU a few participants may be required to go through medicated detoxification which, in rare case, may result in life-threatening seizures. The risks of stopping drinking and the medical care provided for these possible risks will be thoroughly reviewed upon entry into the CNRU by the qualified medical staff. Detoxification medications will be administered by medical staff on the CNRU based on need in order to ensure a safe withdrawal. Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scores will be taken at admission by CNRU staff to monitor alcohol withdrawal symptoms. Librium 50mg, Ativan 2mg or other treatment will be provided as appropriate for clinical evidence of alcohol withdrawal symptoms. If CIWA scores are greater than 13, monitoring will occur every two hours around the clock. If CIWA scores are less than 8, monitoring will occur every 6 hours while awake. In addition to assessing CIWA scores for PRN medication, subjects who have a history of major alcohol withdrawal symptoms (e.g. withdrawal seizures or delirium tremens) will be placed on a standing dose of Librium 50mg tid for the first 24 hours with continued treatment as clinically appropriate.

ii) Prazosin Treatment:

Prazosin (marketed by Pfizer) is an alpha-1-adrenergic agonist, that is known to preferentially bind to post-synaptic alpha1-adrenergic receptors that are highly concentrated in the prefrontal cortical regions (Taylor & Raskind, 2002). It has been shown to have beneficial effects on PTSD symptoms (Taylor et al., 2006; Taylor & Raskind, 2000) and recent data has supported it's use in alcohol/cocaine dependence (Simpson et al., in press; Zhang & Kosten, 2005). The major advantage that Prazosin has over clonidine is that it is less sedating and with less hypotensive effects than clonidine. More specifically, Clonidine is a non-selective agonist of alpha 2a, 2 b and 2c receptors, which accounts for its sedative and hypotensive effects. Conversely, Prazosin and guanfacine are preferential for the alpha-1 and alpha-2a receptors respectively; thus, limiting sedative and hypotensive effects (Arnsten et al., 1988). Additionally, the plasma half life of Prazosin is 2-3 hours, compared to 4-10 hours for clonidine (Physician Desk Reference, 2007), allowing rapid titration and limiting accumulation of the drug.
Studies using Prazosin in patients with PTSD and alcohol dependence have used doses ranging from 2 to 16 mg/day. Commonly reported side effects with Prazosin have been fatigue, sedation and light-headedness, which are generally rated as mild in intensity. Possible side effects commonly associated with Prazosin include: low blood pressure, some drowsiness, dryness of mouth and/or throat and dizziness. No serious side effects have been noted in adult populations. There is no evidence that Prazosin will pose a greater risk to the pilot study population. Subjects will not be started on the study medication until no alcohol is present in their system. Throughout the study, subjects will be monitored for alcohol consumption. If a subject were to resume using alcohol, study medication will be discontinued.

iii) Laboratory Sessions:

(a) Intravenous (IV) Catheter: When an IV is started, there is some risk that subjects may develop a bruise or bleeding where the vein is punctured. If this occurs, appropriate treatment will be instituted immediately. On extremely rare occasions, fainting, blood clot or infection may occur.

(b) Drawing of Blood: During each laboratory session, about 120ml of blood will be drawn to measure stress hormone levels that may change during the session. The amount of blood drawn for each of the five tests over three laboratory sessions is equal to a little over one-half the blood obtained during a regular blood donation. The total amount of blood drawn over the entire study period is 424 ml of blood (360ml total for laboratory sessions, 32 ml for genetic measures, 16 ml to measure molecular changes, and 16ml to measure estradiol levels). The total amount of blood drawn is within HHS guidelines of 450 ml within 8 research weeks. People who are in good health are not usually affected by this kind of blood loss. However, to be safe, subjects will be warned against donating blood for at least eight weeks after completing this study.

(c) The Imagery Procedures: The imagery method involves reliving a personal stressful event and can be somewhat anxiety provoking at the time of the task. Our previous experience has shown that once the task is over, there is very little anxiety that carries over, thus posing minimal risk. The alcohol cue imagery involves reliving a personal experience involving alcohol-related stimuli associated with alcohol use. While subjects may feel aroused by the alcohol cue imagery, relaxation procedures have been shown to be successful in reducing the physiological changes associated with cue exposure and stressful imagery. It is likely that moderate craving for alcohol, may occur due to subjects' imagining and reliving stressful events and alcohol cue related events. It is also possible that craving for alcohol may linger even after the task.

iv) Breath and urine collections
Breath screening and urine collections are performed primarily as safeguards to contamination of data and should add no risks other than those normally associated with these procedures.

v) Rating Scales and Questionnaires
These are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. Our past experience with these measures indicates that they are acceptable to subjects. Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only patients' code numbers will be recorded on the forms themselves to protect confidentiality.

vi) Nonspecific Risks. Other risks from the counseling, rating scales and urine collections are not beyond usual clinical procedures in a substance abuse treatment program. Confidentiality of these results are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the Principal Investigator or Data Manager.

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

i) Alcohol Detoxification

As this protocol includes patients with alcohol use disorders and requires abstinence from alcohol, some patients may require medical detoxification from alcohol and thus this protocol has been deemed a greater than minimal risk protocol. Detoxification from alcohol typically lasts between 1 to 4 days and in some rare cases up to a week. While detoxification from alcohol presents greater than minimal risks, including the possibility of life-threatening seizures, clinical staff and assessments are in place at the Yale Stress Center to ensure that the risks are minimized to the greatest extent possible. The risks of all treatment procedures including acute medical detoxification are thoroughly explained to all patients by the trained clinical research staff at the YSC. Research staff are fully trained in administering the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) and protocols are in include the PI, and medical staff, Dr Gretchen Hermes and research nurse Mary Kurjanowicz for consultation and referral to the YNHH –ER and/or to SCRC for medical detoxification if required.

ii) Prazosin treatment:
Inclusion criteria and the use of trained research assistants in the initial screening will help to avoid the acceptance of subjects that are inappropriate for the study. There are no known serious adverse effects of Prazosin. The following precautions will be taken: 1. Vital signs (heart rate, blood pressure, body temperature) will be assessed daily during the inpatient phase of the study, and 2 times weekly during the outpatient phase of the study. Additional vital sign readings will be taken if subjects report symptoms and when medication dosage is changed. 2. Any clinically significant cardiac signs or other adverse symptoms will be monitored closely at each visit to the clinic.

iii) Laboratory Procedures:
The laboratory sessions will be conducted while subjects are hospitalized in the treatment and research inpatient unit (CNRU). Since subjects will be treatment-seeking individuals, they will participate in inpatient treatment during their stay on the CNRU. For subjects who have difficulty reducing their craving levels, relaxation procedures will be conducted to return craving levels to baseline after the imagery sessions. We have found that relaxation procedures are particularly effective in reducing craving levels after alcohol cue exposure (Margolin et al., 1994; Sinha et al., 1999a).

To enhance their response to relaxation procedures, subjects will also be trained on relaxation procedures in a session prior to the laboratory sessions.

Any subject that reports residual alcohol craving or emotional discomfort after completion of laboratory sessions will receive an individual counseling session by a licensed psychologist (the PI or her designee) who are experienced in relapse prevention therapy. The focus of this session will be coping with high-risk situations and cravings.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? This protocol has been deemed a greater than minimal/ moderate risk protocol.
b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
c. Copy, paste, and then tailor an appropriate Data and Safety Monitoring Plan from http://www.yale.edu/hrpp/forms-templates/biomedical.html for
    i. Minimal risk
    ii. Greater than minimal/moderate risk
    iii. High risk

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

Greater Than Minimal Risk DSMP

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

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

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

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

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

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:
1. Mild adverse event
2. Moderate adverse event
3. Severe

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

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

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

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

The principal investigator will report the following types of events to the IRB:
Any incident, experience or outcome that meets ALL 3 of the following criteria:
1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.
Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects. Please note that adverse events are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

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

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

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:
x All Co-Investigators listed on the protocol.
□ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
x National Institutes of Health
□ Food and Drug Administration (Physician-Sponsored IND #_____)
□ Medical Research Foundation (Grant_____)
□ Study Sponsor
x DSM

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

As participants are not enrolled into the research study until they are in good medical health this study does not require a data safety monitoring board. However, as this protocol includes patients with alcohol use disorders and requires abstinence from alcohol, some patients may require medical detoxification from alcohol and thus this protocol has been deemed a greater than minimal risk protocol. Detoxification from alcohol typically lasts between 1 to 4 days and in some rare cases up to a week. While detoxification from alcohol presents greater than minimal risks, including the possibility of life-threatening seizures, clinical staff and assessments are in place at the Yale Stress Center to ensure that the risks are minimized to the greatest extent possible.

a) The risks of all treatment procedures including acute medical detoxification are thoroughly explained to all patients by the trained clinical research staff at the YSC.

b) Research staff are fully trained in administering the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) and protocols are in include the PI, and medical staff, Dr

Gretchen Hermes and research nurse Mary Kurjanowicz for consultation and referral to the YNHH –ER and/or to SCRC for medical detoxification if required.

As this is a phase II clinical efficacy study, we have established a data safety monitoring board. The DSMB for this trial is composed of the following three clinical investigators as listed below who are not affiliated with this study, and do not have an interest in the outcomes of this study.

1). Dr. Gerard Sanacora is Professor at the Department of Psychiatry at Yale University. He is an experienced clinical researcher who is familiar with the population under study. He is PI on several pharmacological and behavioral treatment and laboratory studies and is extremely familiar with the NIH requirements for data safety monitoring. He is also a member of the Yale Human Investigation Committee and is therefore very familiar with safety monitoring procedures.

2). Dr. Graeme Mason is an Associate Professor jointly appointed at the Department of Diagnostic Radiology in the Division of Bioimaging Sciences and the Department of Psychiatry at Yale University. He is the Director of Psychiatric MRS and the Director of Metabolic Modeling. He is PI on several imaging studies, including studies related to addiction.

3). Dr. Suchitra Krishnan-Sarin is an Associate Professor at the Department of Psychiatry at Yale University. She is PI and Co-PI on several NIH funded studies examining at risk adolescents, addiction treatment and the neuroscience of addiction.

The DSMB members will evaluate all Adverse and Serious Adverse Events, and will assist the PI in preparing and sending the pertinent expedited reports to the appropriate persons as outlined below. They will monitor the study quarterly and review all adverse event sheets completed during that period. They will assist the PI in making critical decisions regarding a particular subject continuing in a study for safety reasons. They will review the summary of all Adverse Events for this study, which will be reported annually to the Yale Human Investigation Committee (HIC) and study sponsors.

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

Power Analysis: Sample size estimates for the laboratory study is based on our preliminary study of Prazosin (Fox et al., 2011) and previous pilot trials of Prazosin (Simpson et al., 2009). Moderate to large effect sizes were obtained for significant interaction effects in alcohol craving (2-way: **f** =.44; 3-way: .81), anxiety (2-way: **f**=1.16; 3-way: .87) and Cortisol/ACTH ratio (2-way: **f**=.83 and **f**=.71; 3-way: **f**=.65). A conservative effect size of **f** =.44 for detection of significant interactions, and with power=.80, with $p<.05$, sample size estimates (Cohen, 1988, p.384) indicated that we would require 18 subjects per cell to detect the specified interaction hypotheses of the laboratory study. Including a 5-10% attrition rate, we estimated that 20 subjects per cell would provide adequate power to test the laboratory aims.

Sample size estimates for the clinical trial outcomes were determined from effect sizes derived from Simpson et al (2009). In this study, 6/7 PZ subjects remained abstinent and drank an average of 3.2 drinking days/wk after achieving full dose compared to the PL group where 4/10 were abstinent and drank on 5.5 drinking days/wk. These data yielded large effect sizes (d=1.26 for mean drinking days; and w=1.23 for proportion abstinent). As we proposed a 2X 2 design

with medication and alcohol withdrawal/anxiety, we used a conservative effect size of d= .60 for detection of significant main effects and possible interactions in the clinical trial. At this effect size and power=.80, with p<.05, sample size estimates from Cohen (1988, p.258) indicated that we would require 25 subjects per cell to adequately assess the proposed hypotheses for the clinical trial (total N =100). Including a 15-20% drop-out after enrollment, we estimated recruitment of 120 AD patients into the trial to ensure adequate power for the trial.

Data Analysis for Laboratory Study: Repeated measures ANOVA and mixed model procedures to assess treatment group differences in alcohol craving and stress related changes (heart rate, blood pressure, HPA and catecholamine responses) during laboratory exposure to stress and drug cues as compared to neutral imagery conditions. Non-parametric tests will be used to assess occurrence of side effects, treatment retention rates, alcohol use measures, CIWA scores and perceived stress scores during the outpatient treatment phase. The number and type of AE's for the two treatment groups will be conducted using t-tests, chi-square tests and ANOVAs as appropriate. Findings will be used to estimate effect sizes for the medication and guide the larger randomized clinical trial.

Data Analysis for the 12-week clinical trial Study: For this phase, the following moderator and primary and secondary outcomes are specified:

Primary Moderator Measure: Alcohol withdrawal symptoms, as measured by the CIWA alcohol withdrawal scale,

Primary Outcome Measures in the outpatient treatment phase: These are: (1) Heavy drinking days (5 or more for men, 4 or more for women) during the 12 week period, and (2) Any drinking days. Both will be assessed daily using smartphone or interactive voice recording surveys completed by the patients and also with weekly urine drug screens/breathalyzer reports and self report of drug use on the Substance Use Calendar.

Secondary Outcome Measures in the outpatient treatment phase: Secondary outcome measures will include alcohol craving scales, anxiety (Hamilton Anxiety Scale) and depression (CES-D) and sleep quality using the Pittsburgh Sleep Quality Index – PSQI).

Data Analytic Procedures: Since patients will be randomly assigned to the Prazosin and PLA treatment groups and Intent-to-Treat (ITT) analyses will be conducted for the clinical outcomes. We do not expect the groups to be different on demographic, prior drug use history or other predictor variables. Nevertheless, prior to undertaking the specific analysis for each aim, we will compare the treatment groups on demographic variables, substance use characteristics and previous psychiatric history/predictor variables using t-tests/chi-square analyses as appropriate. If any group differences are found, the specific variable will be entered as a covariate in all of the specific analyses. As there are no established thresholds for AW effects on drinking outcomes in outpatient treatment, baseline AW will be assessed as continuous measure in all overall analyses. Thus, intent-to-treat (ITT) analyses with baseline AW severity (mean-centered continuous CIWA-Ar scores) as a moderator of Time (Pre-Full Dose(FD): weeks 1-2; Post FD: weeks 3-12) were conducted with linear or generalized linear mixed effect (LME/GLME) piecewise growth models for continuous and binary outcomes. Due to a positive skew, number of drinks per day

(AvgD) will be log-transformed. Control variables in all analyses will be gender (0=male), inpatient (0=outpatient), and dropout (0=completer, 1=dropout/withdrawn prior to 4 weeks, 2=dropout/withdrawn after 4 weeks). For secondary outcomes linear mixed models with random intercepts will be used to assess the effect of AW, Treatment and Week (factor 1-12, or Weeks 4, 8 and 12) on the secondary outcome variables. All control variables from the main outcome analyses are included in the secondary outcome analyses. If significant interactions with AW are observed for primary or secondary outcome analyses, a median split of AW scores will be conducted to obtain Low and High AW groups and assess contrasts by treatment.

Aims and Hypotheses for Laboratory and Treatment Outcome Components: All analyses of the laboratory and the treatment components will be based on the following specific aims and hypotheses:

Specific Aim 1: To evaluate the effects of Prazosin on stress-induced alcohol craving and associated neuroadaptations in alcohol dependent individuals. Hypothesis 1: Prazosin will decrease stress-induced alcohol craving and negative emotions in the laboratory as compared to placebo.

This aim will be tested using mixed model analysis of variance procedures for each of the following dependent measures: VAS alcohol craving scale; VAS anxiety scale; brief CCQ; DES emotions of anger, sadness and fear; heart rate, blood pressure and HPA measures o ACTH and cortisol and NE and EPI.

Specific Aim 2: To evaluate the efficacy of Prazosin versus Placebo in high alcohol withdrawal individuals on primary outcomes of: (a) heavy drinking days (HDD) over 12 week period; (b) Any drinking days (DD%).

Hypothesis 2: In high alcohol withdrawal individuals, Prazosin group will show significant reductions in HDD% and DD% during the 12 week treatment period as compared to Placebo group. No differences between medication treatment groups in the Low alcohol withdrawal individuals will be observed.

Secondary outcome measures such as alcohol craving, Anxiety, depression and sleep quality will be assessed. Findings PSS, COPE and LES scores will be examined.

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

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

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Prazosin (marketed by Pfizer Inc) is an alpha-1-adrenergic agonist that is known to preferentially bind to post-synaptic alpha1-adrenergic receptors. Walker et al (2008) found that Prozaosin was effective in suppressing excessive alcohol consumption in rats, suggesting the involvement of the noradrenergic system in alcohol dependence. Sinpson et al. (2007) found similar findings in a pilot trial using prozosin for treatment of alcohol dependent men and women. Prazosin therefore is an excellent candidate for treating alcohol seeking behaviors. It may also be more easily tolerated than those medications which directly modulate these transmissions.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:
a. What is the Investigational New Drug (IND) **number** assigned by the FDA? N/A
b. Who holds the IND?
c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☒ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☒ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☒ Yes ☐ No

iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☒ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☒ Yes ☐ No

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

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or
more of the following (check all that apply):
☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

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

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

Exempt Category 3

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

Exempt Category 4

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

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

Prazosin has been an approved medication by the FDA as a treatment for hypertension. This pilot study is designed to examine the potential effect of Prazosin on alcohol cravings. Prazosin has been used extensively off-label. Prazosin does not pose any greater risk with the proposed study subjects than in subjects previously administered this medication. As it is advised that alcohol should not be consumed while taking Prazosin, subjects will be closely monitored to ensure they are not drinking alcohol while taking the study medication.

Studies using Prazosin in adults with PTSD or alcohol dependence have used doses ranging from 2.0 to 20 mg/day (Raskind et al., 2002; Peskind et al., 2003; Raskind, 2003, 2002; Simpson et al, 2007, July; Raskind et al., 2007). Prazosin was well tolerated with no reported serious adverse

effects both in research and in clinical use (PDR, 2007). Commonly reported side effects have been dizziness and light-headedness, drowsiness, headaches, lack of energy, and dryness of mouth. All side effects reported have been mild in nature and simple remedial action such as withholding a dose or adjusting the dose to a lower tolerated dose has been shown to reduce such side effects (Taylor et al, 2002).

Simpson et al (2007) report that when administering 16mg per day of the drug, blood pressure changes were more evident in the prazosin group; however, the drop was still within the normal range. Raskind et al. 2002, prescribed up to 20mg a day of the study medication. Three of the 36 subjects reported orthostatic dizziness, headache, and lethargy, however no subject experienced syncope or a fall. The researchers report that previous administration of Prazosin for hypertension and benign prostate hypertrophy has shown that adverse effects tend to occur at initial lower does rather than at higher doses. Raskind et al, 2007 used a maximum dosage of 15mg which was maintained for 8 weeks. No significant differences in supine or standing blood pressure were found between the placebo and Prazosin groups. Transient dizziness was reported by some subjects, however, most of these subjects were also receiving concurrent antihypertensive or psychotropic medication, and was also reported by subjects in the placebo group. Therefore, it appears that a maximum maintenance dosage of 16mg of prazosin will be generally tolerable and safe for use in the proposed adult sample of subjects.

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

Commercially available Prazosin capsules will be used. Prazosin HCl (generic) is marketed by Mylan Pharmaceuticals Inc in capsules containing 1mg, 2mg, or 5mg of prazosin as the hydrochloride. The placebo medication will be prepared by the CMHC pharmacist. Both the Prazosin and the placebo will be dispensed by the CMHC pharmacist / YNHH IDS.

Prazosin pills will be purchased through the CMHC pharmacy / YNHH IDS, and the research pharmacist will make up identical active and placebo capsules for medication administration. Subjects will be randomly assigned to three times daily dosing of Prazosin/placebo (with the exception of day 1 which is once daily, and days 2-3 twice daily).

During weeks 1-4, inpatient subjects will self-administer study medication three times daily under supervision by nursing staff on the CNRU who will also monitor vital signs three times daily and side effects. Urines, alcohol craving, abstinence symptoms, mood and perceived stress scale and side effects will be assessed three times weekly.

Outpatient subjects will come in for 2x weekly appointments and complete motivational enhancement, urine drug screens, breathalyzers, blood pressure monitoring, and counseling. Medication compliance will be monitored by blood draws done at week 4-5, to measure Prazosin levels, and through the monitoring of riboflavin as a urine marker. Riboflavin produces a bright yellow discoloration of the urine when the medication is taken 2 to 8 hours prior. After the first week all subjects will be taking morning and bedtimes doses of the medication. After this time, staff will easily be able to visually inspect the subject's urine to determine whether the morning

dose has been taken. 25mg of riboflavin will be added to all doses of Prazosin and placebo by the pharmacist when capsules are made.

Outpatient subjects will self-administer study medication, and will be reminded via daily interactive voice response (IVR) telephone monitoring or through the smartphone app MetricWire. Daily IVR telephone monitoring or MetricWire will be used to prompt patients to take study medication, and also to assess alcohol use, craving, craving resistance and mood states. Concordance between daily IVR or MetricWrire reports and alcohol positive urines will be evaluated for daily versus retrospective reporting.

The MetricWire app (developed and owned by MetricWire Inc), has previously been utilized in clinical and academic research, and is HIPPA compliant. Subjects will complete a training session where we will assist them in installing the app on their smartphone device. At the end of the study, we will assist subjects in removing the app from their smartphone. If a subject does not own a smartphone, one will be supplied for their use, for the duration of the study, once a separate smartphone agreement is understood and signed.

We expect most subjects will tolerate a dose of 16mg. However, subjects who cannot tolerate a dosing schedule of 16mg will meet with the study psychiatrist to discuss a lower dose. Subjects who cannot tolerate a minimum dose of 16mg will be maintained on maximum tolerated dose of Prazosin (up to 16.0 mg/day) and during week 12 the medication will be tapered down to 0 over the course of seven days. Some patients may be tapered prior to week 12.

All study staff will remain blind to medication condition. Randomization will be conducted by the CMHC Pharmacy / YNHH IDS, which have extensive experience in random assignment of patients in medication trials.

b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
If yes, by whom?

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

Check applicable Investigational Drug Service utilized:

☒ **YNHH IDS**
☒ **CMHC Pharmacy**
☐ **PET Center**
☐ **Other:**
☐ **Yale Cancer Center**
☐ **West Haven VA**
☐ **None**

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

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

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

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

No other available therapies

b. State the maximum total length of time a participant may receive placebo while on the study.
Subjects may receive placebo for 12 weeks.

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

d. Describe the procedures that are in place to safeguard participants receiving placebo.
N/A

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☒ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☒ No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at YNHH, e.g., YNHH Operating Room or YNHH Heart and Vascular Center? Yes ☐ No ☒

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol
150 alcohol dependent men and women

b. If this is a multi-site study, give the total number of subjects targeted across all sites

N/A

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

☒ Flyers	☒ Internet/Web Postings	☐ Radio
☐ Posters	☒ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☒ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☒ YCCI Recruitment database	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	
☐ Other (describe):		

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.
b. Describe how potential subjects are contacted.
c. Who is recruiting potential subjects?

Subjects will be recruited through flyers and advertisements in local newspapers, internet/web postings, through YCCI's recruitment systems: Epic's Enterprise electronic medical record (EMR), OnCore, Yale's clinical research management system (CRMS), and from community substance abuse treatment facilities. Subjects will participate in an initial phone screening and intake session to obtain informed consent with the research coordinator or research assistant, followed by physical examination and blood work to determine eligibility.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No
b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☒ Names
☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
☒ Telephone numbers
☐ Fax numbers
☒ E-mail addresses
☐ Social Security numbers
☐ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers

☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ Device identifiers and serial numbers
☐ Web Universal Resource Locators (URLs)
☐ Internet Protocol (IP) address numbers
☐ Biometric identifiers, including finger and voice prints
☐ Full face photographic images and any comparable images
☐ Any other unique identifying numbers, characteristics, or codes

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

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

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

If yes, describe the nature of this relationship.

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

Choose one: For entire study: _____ For recruitment purposes only: X

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data; N/A
ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data; Signed authorization is impracticable as subjects are screened over the phone

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

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

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   - ☐ Compound Consent and Authorization form
   - ☒ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

   Rachel Hart, Gina Lombardi, Nathan Grandpre, Jennifer Weinberg, Verica Milivojevic, Christian Panier, Arielle Rabinowitz

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

   Alcohol-dependent, treatment-seeking subjects will be interviewed by a research assistant to determine interest in participating in this inpatient/outpatient trial. After obtaining written informed consent for participation in the study, one of the study physicians will interview the subject and review all medical and psychiatric data prior to admitting the subject and beginning medication.

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

    The Investigator will not enroll subjects in the study who are determined to have limited decision-making capacity. Prior to consent procedures, breathalyzers will be conducted. Subjects whose breathalyzer registers above the legal limit will not be consented for the study. Subjects will be assessed throughout the consent process to ensure their understanding of consent procedures.

11. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

    4 Consents:
    Inpatient consent
    Inpatient with outpatient option consent
    Outpatient consent
    Inpatient no labs
    1 smartphone agreement

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

Non-English speaking subjects are not enrolled into this study

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

☐ **Not Requesting a consent waiver**
☒ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☒ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☒ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

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

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

substance use. It will be collected at intake, during 2x weekly appointments, and at follow-up interviews.

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

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

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

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

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

Do all portable devices contain encryption software? ☐ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

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

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

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

All de-identified data will be available to the research investigator PI, Co-Investigator, statistician, DSMB, research staff responsible for entering data, NIAAA, Yale HRRP, and Yale's HIC. Protected Health Information will be available to the research physician, and research staff only when deemed necessary. De-identified data may also be shared with Governmental agencies to whom certain diseases (reportable diseases) must be reported.

g. If appropriate, has a Certificate of Confidentiality been obtained? Yes, a Certificate of Confidentiality has been obtained from the National Institutes of Health.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

Mandatory reporting of incidents of abuse or neglect of a child or elderly person as required by Connecticut State law will be complied with. Additionally, certain reportable infectious diseases such as HIV and Hepatitis B and C will be reported to the appropriate state agency. We may also need to intervene and report information regarding threat of injury to self or others to the proper authorities. All of these requirements will be complied with.

SECTION IX: POTENTIAL BENEFITS

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

There are no known potential benefits. There may be benefits to society which would result from increased knowledge about treatments for alcohol addiction.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Subjects need not participate in this study to receive treatment for substance dependence.

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

   Subjects completing the Inpatient-Outpatient Study with laboratory sessions, will be paid $25 for the interview session, $25 for the imagery and relaxation training session, and $100 for each of the 3 laboratory sessions. Subjects will be paid a $50 bonus for completing the inpatient phase. Research interview sessions and study medication will be free of charge. If subjects are only completing the inpatient phase, follow-up appointments will be scheduled after the inpatient phase is complete. Subjects will receive $50 for the 30-day follow-up interview. If a subject decides to complete only the inpatient phase, they will receive a total of $450.

   Subjects completing the Inpatient-Outpatient Study without the laboratory sessions, will be paid $20 for each intake appointment (2- 3), and $25 for each week that they are inpatient. Subjects will be paid a $50 bonus for completing the inpatient phase. Research interview sessions and study medication will be free of charge. If subjects are only completing the inpatient phase,

follow-up appointments will be scheduled after the inpatient phase is complete. Subjects will receive $50 for the 30-day follow-up interview. If a subject decides to complete only the inpatient phase, they will receive a total of $235.

If a subject continues on to complete the outpatient phase, they will earn chances to win dollar prizes for kept appointments to encourage appointment attendance. The prizes are in increments of $1, $5, $20, and $100. For every two biweekly appointments they attend, the chance will increase by one. Subjects will participate in this at every biweekly appointment they attend. If they miss any appointment, or fail to take study medication, the chances will be reset back to one. For example, if no appointment are missed the subject will have a total of 12 chances at the last appointment. Each prize increment that is won from the 12 attempts is then added together into a lump sum. There is no limit on the amounts that can be won. Subjects participating in IVR or MetricWire will be reimbursed at $2 a day, or $20 a week, for the duration of the outpatient phase. In addition, subjects will receive $25 for week 4, $25 for week 8, $25 for week 12, and a $25 bonus for completing the outpatient phase. Subjects completing both the inpatient and outpatient phases, will have follow-up appointments scheduled after the outpatient phase is complete. The total that subjects may be reimbursed if they complete all aspects of the Inpatient–Outpatient study with the laboratory sessions, and the follow-up interviews will be $730 plus the various amounts won for keeping appointments during the outpatient phase. The total that subjects may be reimbursed if they complete all aspects of the Inpatient–Outpatient study without the laboratory sessions, and the follow-up interviews will be $515 plus the various amounts won for keeping appointments during the outpatient phase.

Subjects completing the Outpatient Study will earn chances to win dollar prizes for kept appointments. The prizes are in increments of $1, $5, $20, and $100. For every two biweekly appointments they attend, the chance will increase by one. Subjects will participate in this at every biweekly appointment they attend. If they miss any appointment, or fail to take medication, the chances will be reset back to one. For example, if no appointments are missed the subject will have a total of 12 chances at the last appointment. Each prize increment that is won from the 12 attempts is then added together into a lump sum. There is no limit on the amounts that can be won. In addition, subjects will receive $20 for each intake appointment, $25 for week 4, $25 for week 8, $25 for week 12, and a $25 bonus for completing the study. Subjects will also receive $50 for the 30-day follow-up interview. Subjects participating in IVR or MetricWire will be reimbursed at $2 a day, or $20 a week. The maximum amount that subjects will receive for completing all aspects of the outpatient study, without completing the laboratory sessions, is $415, plus various amounts won for keeping appointments. If a subject decides to complete the laboratory sessions, they will receive an additional $25 for the imagery and relaxation training session, and $100 for each of the 3 laboratory sessions. They will also receive a $50 bonus for completing all aspects of the inpatient laboratory study. The total that will be paid if all aspects of the outpatient study are completed, including the laboratory sessions, is $825 plus the various amounts won for keeping appointments.

Subjects will incur no costs for participation in this research outside of potential costs for parking or transportation that may be reimbursed.

If subjects are asked to have any of their interview sessions videotaped, they will be paid $20 per videotaped session.

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

   There will be no costs charged to subjects who participate in this study. All evaluations including interviews, physical exams, diagnostic tests will be provided at no cost to the subjects.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs?
   b. Where and from whom may treatment be obtained?
   c. Are there any limits to the treatment being provided?
   d. Who will pay for this treatment?
   e. How will the medical treatment be accessed by subjects?

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

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