Principal Investigator: Ismene Petrakis, M.D.

Co-Investigators: (including VA and WOC staff): While all research staff are trained to obtain informed consent, those identified with an asterisk (*) will obtain informed consent for this study. The PI and the listed research team will have access to PHI.
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Title of Project: Buprenorphine/Naloxone Treatment for Prescription Opioid Dependence

Purpose: Although buprenorphine/naloxone (BUP/NLX) treatment is effective for the treatment of prescription opioid dependence, previous studies have not determined the optimum dose of BUP/NLX for this patient population. The goal of this study is to determine if there are differences in clinical efficacy of BUP/NLX tablet in low dose range (less than or equal to 8/2mg) vs. high dose range (greater than or equal to 16, range 16-24mg). The main outcomes of interest will be treatment retention, use of opioids, and the use of other drugs of abuse.

Introduction:
Prescription opioid abuse, including oxycodone, hydrocodone, hydromorphone, morphine, codeine, propoxyphene, and methadone, has emerged as a major public health problem particularly in the United States, which represents about 5 percent of the world's population but consumes 80 percent of the global opioid supply and 99 percent of the global hydrocodone supply (Sehgal et al., 2012). Prescriptions for opioid medications have increased dramatically with 174 million prescriptions dispensed from retail pharmacies nationally in 2000, increasing to 257 million prescriptions by 2009 (Food and Drug Administration (FDA), 2010). According to data from the Centers for Disease Control and Prevention ((CDC), deaths due to prescription opioids went from 1.3 per 100,000 in 1999 to 5.0 per 100,000 in 2008, resulting in 14,800 prescription painkiller deaths in 2008 (Centers for Disease Control and Prevention, 2012). Furthermore, deaths from prescription opioids have dramatically increased over the past 10 years and are now the second leading cause of accidental death in the US (Okie, 2010).
Unlike other drugs of abuse, prescription opioid medications are primarily obtained from physicians, friends or family members and/or the Internet, rather than through drug dealers. Recently, there has been an increase in non-medical abuse of prescription opioids, defined as use without a prescription and/or in a manner other than intended or prescribed, with more than 12 million people reporting using prescription opioids non-medically in 2010 (SAMHSA, 2012). The use of opioid prescription drug use has also recently been shown to be a "gateway" to use of heroin (Jones, 2013). These figures underscore the importance of development of treatments for prescription opioid dependence.

Buprenorphine as a treatment for opioid dependence

Buprenorphine, a derivative of the opiate alkaloid thebaine, is a partial μ-opioid agonist and a weak k-opioid antagonist (Walsh and Eissenberg, 2003). In clinically used doses, buprenorphine effects are similar to the full μ-opioid agonist like morphine or methadone. At higher doses, however, the effects of buprenorphine plateau, and it acts like an opioid antagonist. This "ceiling" effect of buprenorphine decreases the risk of overdose even at high intravenous doses and limits its abuse liability (Walsh and Eissenberg, 2003). In addition, its slow dissociation from the opioid receptors allows flexible dosing ranging from several times a day to three times per week. Buprenorphine, formulated as a sublingual tablet or film, is available alone or in a combination tablet containing Buprenorphine and Naloxone in a ratio of 4:1 (Johnson et al., 2003). Since naloxone is poorly absorbed when taken orally or sublingually, naloxone effects are negligible when the medication is taken as directed. However, injection of this combination in dependent individuals would precipitate opioid withdrawal symptoms due to naloxone effects, and deter diversion of this product to injection drug use. A large number of studies have demonstrated the efficacy of buprenorphine as an agonist treatment in opioid dependent individuals. However, it is important to note that the majority of studies supporting the efficacy of BUP/NLX for opioid dependence were conducted in heroin-addicted patients.

Buprenorphine as a treatment for prescription-opioid dependence

Only a few studies systematically examined the characteristics of prescription-opioid dependent individuals as compared to those who are heroin dependent. Prescription-opioid dependent patients, compared to those who are dependent on heroin, are younger, have fewer years of opioid use, and are less likely to have a drug treatment history (Moore et al., 2007). Further, prescription opioid dependent patients, compared to heroin only, or heroin and prescription opioid users, are more likely to stay in buprenorphine treatment and have better treatment outcomes (Moore et al., 2007).

A recent study by Weiss et al. assessed the efficacy of a combination of the opioid substitute buprenorphine/naloxone (BUP/NLX) in 653 prescription opioid dependent patients (Weiss et al., 2011). In that study, subjects received standard weekly medical management with or without intensive opioid dependence counseling. The study had two phases: Phase 1: 2-week stabilization, 2-week taper, and 8 week post-medication follow-up. The main finding of the study was, out of 653 patients, 43 (6.6%) had a successful urine-test-confirmed outcome of no opioid use after phase 1 of treatment. Further, of the 360 patients who underwent phase 2, 177 (49.2%) had a successful outcome at week 12 of treatment, but this fell to just 31 (8.6%) at the 8-week follow-up visit. There was no difference observed between those who received adjunct counseling and those who did not. These findings are promising for the utility of BUP/NLX for prescription opioid dependence, but they also suggest that more effective treatment approaches are needed.

It should be noted that despite the prevalence of opioid dependence among military personnel and Veterans, there are no studies evaluating buprenorphine for opioid dependence in the Veteran population. Further, assessment of psychiatric symptoms among those with commonly occurring disorders, such as depression and post traumatic stress disorder (PTSD) have also not be systematically evaluated.

Proposed study: As summarized above, BUP/NLX treatment seems to be moderately effective for the treatment of prescription opioid dependent patients. The Weiss et al. study did not address if BUP/NLX is more effective in a lower or higher dose range (Weiss et al., 2011). The 16/4 mg of BUP/NLX was the most commonly prescribed dose. In a recent meta-analysis of BUP/NLX studies for opioid dependence (Fareed et al., 2012), higher doses of BUP (16mg or higher/day) were associated with better treatment retention and reduced opioid use than the lower dose range (less than 16mg/day). However, to our knowledge, no previous study has examined the optimum dose of BUP/NLX in prescription-opioid dependent patients.

Subjects: We plan to enroll approximately 200 participants. Veterans who meet the following criteria will be eligible for participation: 1) Males and females between the ages of 18 to 65, current dependence on prescription opioids as evidenced by fulfilling DSM-V criteria for Opioid Use Disorder, signs of opiate withdrawal as evidenced by a COWS score of 7 or greater, self-reported history of opioid dependence, and a positive urine toxicology for opiates; 2) willingness to be detoxified from opioids for buprenorphine maintenance ; 3) for women of childbearing age, a negative pregnancy test at screening with agreement to use adequate contraception to prevent pregnancy, with monthly pregnancy tests obtained during study participation. Exclusion criteria: 1) use of heroin for more than 4 days in the past month; 2) lifetime history of opioid dependence due to heroin alone; 3) ever used heroin intravenously; 4) requirement for current ongoing opioid treatment for adequate pain management; 5) current alcohol, benzodiazepine, barbiturate use with physiologic dependence as determined during screening history and physical, 6) serious unstable medical illness including bradycardia or other arrhythmias, major cardiovascular, renal, endocrine, or hepatic disorders for which buprenorphine treatment is contraindicated or which at the determination of the MD is medically dangerous; 8) serious psychiatric illness including psychosis, bipolar disorder with psychosis; 9) significant current suicidal or homicidal thoughts necessitating a higher level or care; 10) known allergy or intolerance to buprenorphine. Please note that individuals with commonly occurring psychiatric disorders, such as depressive disorders and post traumatic stress disorder, will be included in this "real world" study.

Privacy: All information that is obtained from subjects will be used for the specifically stated purposes that are described in this Project Description and have been approved by the HSS. The personal identifiers that are necessary for this research and that will be obtained are the following: Name, Medical Record Number, Social Security Number, Age, Gender, Medical and Psychiatric History, and Laboratory Examination. The procedures for data collection and recruitment of subjects, described elsewhere in the Project Description, are the least intrusive consistent with obtaining the information necessary to complete this project. All members of the research team will review, use, and record the minimum amount of information necessary to accomplish the goals outlined in the protocol. All members of the research team have been trained on VHA privacy regulations and policies and training are current. The settings in which informed consent discussions, other subject interviews or research procedures occur will provide the same privacy protections that would exist if these discussions, interviews, or procedures were carried out for required clinical care (private rooms, drawn curtains, etc.). The information will be used for this project, or disclosed to others, only as permitted by the Privacy Act, the HIPAA Privacy Rule, and VA policy.

Selection: Veterans will be recruited through VA clinics and from the New Haven area by newspaper advertisements and flyers. After the initial phone screening, potential subjects will undergo a comprehensive evaluation that will include medical, psychiatric, and drug use histories as well as physical, psychiatric, and laboratory examinations. Laboratory examination will include CBC, liver and thyroid function tests, serum electrolytes, BUN, creatinine, PT, PTT, RPR, random glucose, urine analysis (including urine pregnancy for women), and urine toxicology screening.

Research Plan:
This will be a randomized, open-label clinical trial. Veteran opioid dependent men and women will be randomized to one of two treatment groups: low dose range of BUP/NLX (Less then or equal to 8mg) vs. high dose range of BUP/NLX (Greater than or equal to 16mg). During induction into buprenorphine, all participants will be started at a dose of 2mg, and this dose will be increased as needed for stabilization of opioid withdrawal symptoms, up to 8mg for the low dose group, and up to at least 16mg for the high dose group, within about 7 day period. If a participant is randomized to the low dose group but is experiencing withdrawal symptoms that cannot be stabilized the participant will be discharged from the study. Participants will be clinically managed and will get monthly assessments. Participants will be seen on a daily basis (excluding weekends) for the initial 7 day induction. Once subjects are on maintenance dose of BUP/NLX (goal is within 5 days), they will be seen weekly by study RN for medical management, symptom evaluation, and medication refill. Participants will also complete study questionnaires at this time. At the end of the 12-week study, participants will either be referred to a buprenorphine clinic if they wish to continue this medication, or if they wish to be drug free, will undergo detoxification from BUP/NLX for up to a 4-week period. Follow-up visits, scheduled at 1, 3, and 6 months after study completion, will evaluate the durability of treatment effects on drug use and psychosocial outcomes.

Entry into Treatment: Triage will be done by a staff member and will take about 30 minutes. It will cover basic inclusion and exclusion criteria, as well as a brief description of the study, to determine if the subject is interested in participating. Treatment alternatives as described below will also be offered to the prospective subject. If s/he is appropriate and agrees to participate, full screening will be completed. Screening will be done by a research assistant and a clinician and take about 3 hours. During this time informed consent will be obtained, an explanation of the study will be provided, and evaluation of inclusion and exclusion criteria will be done. Laboratory examination will include ECG and complete blood count, serum electrolytes, BUN/Creatinine, liver and thyroid function tests, PT, PTT, RPR, random glucose, urinalysis and urine toxicology. A psychiatric evaluation and physical exam will be performed by a study physician, which will take an additional hour. In addition, a SCID utilizing DSM-V criteria will be completed. Should a subject present already in withdrawal and need to be started on BUP/NLX before lab results return or SCID can be completed, the SCID sections that address eligibility will be completed, and the rest will be completed within a week. The subject will also be given an intake package of questionnaires to complete.

Buprenorphine: Buprenorphine is available alone or in combination tablet containing buprenorphine and naloxone in a ratio of 4:1 (Johnson et al., 2003). In prescription-opioid dependent patients who are treated with BUP/NLX, the most common daily doses are 12 and 16

mg/day. In this study, a combination tablet will be used, since it is less likely to be diverted than the buprenorphine only formulation. Consistent with the clinical guidelines, before BUP/NLX is administered, participants will be instructed not to use any prescription opioids for 24 hours and be prepared to stay in the clinic for at least 2 hours following the first dose of BUP/NLX. On the induction day, participants in the low dose group will start with 2/.5 mg but may receive a maximum of 4/1 mg of BUP/NLX, and will be assessed by a physician in the clinic for up to 2 hours for signs and symptoms of opioid withdrawal. Participants in the high dose group will also start with a 2/.5 mg but may receive additional doses of BUP/NLX on the induction day if initial BUP/NLX doses do not suppress opioid withdrawal adequately. Between days 2 and 5, the dose may be gradually increased to the target dose based on the response of the patient: (1) low dose subjects will be held as low as tolerated with a maximum of 8 mg and (2) high dose subjects will be increased to at least 16 mg. At the end of the trial, subjects will receive *up to* a four-week buprenorphine taper depending on individual needs. Buprenorphine/Naloxone is a Schedule III drug that, in community settings, is often prescribed for up to a one month's supply at a time. Patients are generally seen on a weekly or monthly basis like those treated with other psychiatric medications. Buprenorphine/Naloxone will be delivered by the research pharmacy on the day of the participant's weekly appointment, and will be returned to the research pharmacy should the subject fail to present for the appointment. Buprenorphine/Naloxone treatment is generally well tolerated. Its side effects, such as abdominal pain, constipation, nausea, vomiting, headache, sweating, sedation, and allergic reaction are similar to other opioids. Increases in liver enzymes and hepatitis are rarely reported. Participants will be educated to keep their medication in a safe place to prevent unintentional exposure to others, especially children.

Medical Management: Medical Management (MM) will be provided for all patients in the study. It is a behavioral intervention designed for patients with alcohol dependence (Pettinati et al. 2000), and similar therapies have been used in other drug abuse trials (Weiss et al. 2011). The objective of MM is to approximate a primary care environment for delivering care for substance dependent patients. In this study MM will be provided by a trained registered nurse and will consist of 12 sessions. The initial visit will be 40-60 minutes and the focus will be on discussing negative consequences of substance use, and educating the patient on medication regiment and compliance. Consecutive sessions will be 15-20 minutes and will be focused on relapse prevention, monitoring of compliance with the medication and psychoeducation. Common elements of the sessions will be identification of high-risk situations and warning signs of relapse. Patients will be encouraged to attend support groups in the community (e.g. Narcotics Anonymous). This intervention was chosen because MM's focus on medical issues is highly compatible with a pharmacologic intervention.

Medication Compliance: In addition to MM we employ a number of strategies to insure maximum compliance with the medication regiment. All medications will be dispensed in clearly labeled prescription vials. During the induction phase all medication will be handled by the nurses on the detox unit. After that all visits and medication dispensing will be done by out nurse (Ms. Weiner). Before each visit each patient will receive a reminder phone call about his appointment and is also reminded to return the bottle with the study medication regardless of whether any medication is left over. At the beginning of each study visit the left over medication will be counted and the patient will be prompted to report any doubling of dose or missing days of study medication. The session will also provide an opportunity for subjects to review critical

issues and problem areas, the subjects' involvement in any ancillary treatments, and other clinically significant events. Other formal treatment concurrent with their study treatment (including self-help meetings) will be monitored and will be included as a covariate in the analysis.
Use of other drugs of abuse and program termination: At every clinic visit, the subjects will be asked to take a breathalyzer test as a measure of the blood alcohol levels. Subjects will be asked not to use alcohol throughout the study since alcohol may interact with BUP/NLX causing CNS toxicity and respiratory depression. If a breathalyzer reading is 0.04 or greater, the buprenorphine dose will be held until the breathalyzer reading falls below 0.04. If the breathalyzer levels do not fall below 0.04 until the dispensing hours end, subjects will not receive BUP/NLX for that day. If the reading is between 0.01 – 0.04, the subject will receive one-half of their BUP/NLX dose. If the level falls below 0.01 prior to close of dispensing that day, the subject can receive a full dose. If the breathalyzer reading is over the legal limit, 0.08 or more, the study physician will be notified. If the study physician determines that it is unsafe for the participant to leave the clinic, the participant may be taken to the Psychiatric Emergency Room for further evaluation and treatment.

During the final phase of the study, we estimate that approximately 20% of participants will opt for detoxification. In those cases, we will provide a detoxification or a two to four-week taper from buprenorphine depending on each individual's needs. Subjects will then be referred to appropriate outpatient substance abuse treatment (abstinence based). The rest of the subjects will likely request to continue on buprenorphine maintenance. We will refer those patients to the VA clinic.

At any point in the study, subjects will be withdrawn if they regularly miss medications (2 weeks in a row). Subjects may also be withdrawn from the program if urine toxicology screens show frequent use of benzodiazepines or barbiturates. Subjects withdrawn from the study will be offered detoxification from buprenorphine, possibly for naltrexone treatment or referral to methadone maintenance. Subjects will also be withdrawn from the study if the investigator has evidence that subjects' health or well-being may be threatened by continuation in the study. Should a pregnancy test become positive, the subject will be withdrawn from the study and referred to an appropriate treatment program.

Assessments: Trained research assistants and clinical staff will meet with the subject at various time-points to assess the subject on selected substance use and psychological functioning measures using structured interviews, self-report assessments, and to obtain urine samples for toxicology screens.
The following assessments will be completed at baseline:
1. Brief Pain Inventory-Short Form
2. Center for Epidemiologic Studies Depression (CES-D) scale
3. Clinical Opiate Withdrawal Scale
4. Columbia-Suicide Severity Rating Scale (C-SSRS)
5. Drug Use Inventory
6. Fagerstrom Tolerance questionnaire for determination of nicotine dependence
7. Medical and Psychiatric Evaluation (including laboratory blood work and EKG)
8. Post Traumatic Stress Disorder Checklist (PCL-C)

9. SAFTEE
10. SCID for DSM-V for diagnostic clarification of psychiatric and substance use dependence will be completed in an appropriate time period depending on patient's presenting symptoms.
11. Time Line Followback (TLFB)
12. Urine toxicology screening for drugs of abuse (i.e., cannabinoids, opiates, amphetamine, cocaine)
13. Vital signs (blood pressure, heart rate, weight)

The following measures will be completed weekly during study participation. The duration of the weekly assessments will be approximately 45 minutes.

1. Brief Pain Inventory-Short Form
2. Center for Epidemiologic Studies Depression (CES-D) scale Clinical Opiate Withdrawal Scale
3. Columbia-Suicide Severity Rating Scale (C-SSRS)
4. Drug Use Inventory
5. Post Traumatic Stress Disorder Checklist (PCL-C)
6. SAFTEE
7. Time Line Followback (TLFB)
8. Breathalyzer [additional assessment will be done if suspect alcohol use].
9. Urine Toxicology Screening for drugs of abuse (i.e., cannabinoids, opiates, amphetamine, cocaine)
10. Vital signs (blood pressure, heart rate)
11. Weight

The following measures will be completed at 1, 3 and 6 month follow-up:

1. Brief Pain Inventory-Short Form
2. Center for Epidemiologic Studies Depression (CES-D) scale
3. Clinical Opiate Withdrawal Scale
4. Drug Use Inventory
5. Time Line Followback (TLFB)
6. Urine Toxicology Screening for drugs of abuse

For women of childbearing age, a urine pregnancy test will be done at screening, and monthly during study participation.

A. <u>Laboratory Tests and Vital Signs:</u>

- Blood chemistries (chem 19 + GGT, CBC with differential, Thyroid functions, Urinalysis and urine toxicology) and EKG as well as a general physical examination will be performed at intake. Additionally blood chemistries will be taken at week 12.
- Urinalyses: Urines will be analyzed for the presence of drugs of abuse (including opioids, amphetamines, cocaine metabolite and marijuana) on a weekly basis. Breath analysis for alcohol will be performed on a regular basis, although current alcohol physical dependence is among the exclusion criteria.

- Vital signs including blood pressure, heart rate, and weight will be collected each week.

B. Psychosocial Assessments: A set of instruments will provide general patient information, including demographic data, substance use history, previous substance use and psychiatric treatment history, medical history and family substance abuse history. Assessments include:

- Brief Pain Inventory – Short Form: BPI-SF is a self-report questionnaire that assesses severity of pain, impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or the past week (Cleeland and Ryan, 1994).
- Center for Epidemiologic Studies Depression (CES-D) scale: CES-D is a 20-item self-report measure of depressive symptoms. The range of scores is from 0 to 60, higher scores reflecting increased depressive symptoms. The CES-D does not heavily depend on pathological items compared with other scales such as Beck Depression Inventory and does not define clinical depression. The CES-D has been shown to be a reliable and valid scale, and it has been used in several epidemiological studies including cocaine users (Bobo et al., 1998; Orme et al., 1986; Weissman et al., 1977). This measure will be obtained at baseline and weekly thereafter.
- Clinical Opiate Withdrawal Scale (COWS): Withdrawal signs and symptoms will be assessed using a 22-item withdrawal instrument that has been reliably used to assess opiate withdrawal. This scale rates the following items from 0 to 4: lacrimation, nasal congestion, yawning, sneezing, coughing, throat clearing, restlessness, nausea/vomiting, gooseflesh, sweating, stomach cramps, muscle cramps, and feeling hot/cold. This scale will be used on a weekly basis.
- Columbia-Suicide Severity Rating Scale (C-SSRS): designed to assess suicidal ideation and suicidal intent.
- Fagerstrom Nicotine Tolerance Questionnaire (FNTQ): This self-report measure assesses the degree of nicotine dependence and has been used widely in smoking studies (Fagerstrom, 1978). This instrument has demonstrated reliability and validity (Pomerleau et al., 1994; Tate and Schmitz, 1993).
- Post Traumatic Stress Disorder Checklist (PCL-C): to measure PTSD symptoms. The PCL-C is a self-report scale that shares similar reliability with the CAPS. (Weathers et al. 1996)
- Structured Clinical Interview for DSM-V (SCID) will be used to obtain DSM-V Opiate use dependence, and other Substance Use Disorder diagnoses. The number of dependence syndrome elements endorsed from the DSM-V criteria will assess severity of opiate and other substance use. This instrument will be administered at baseline or in as timely a manner as patient's condition warrants.
- Time Line Followback: At intake and weekly thereafter, assessments will be made of opioid and other drug use.
- Weekly cigarette smoking: At intake and weekly thereafter, self-reports will also be made on cigarette smoking.

C. SAFTEE: The SAFTEE is a technique for the systematic assessment of side effects in clinical trials. The SAFTEE will be reviewed by the study nurse and specific symptoms, as well as severity, will be recorded. The SAFTEE will be administered weekly.

Data Analysis Methods:

A. Sample Size and Power Analysis:

For this pilot study, we will recruit a total of 200 subjects, 100 subjects in each treatment arm. No previous studies have examined the influence of BUP/NLX dose on treatment outcomes in prescription-opioid dependent individuals. Our sample of 200 will require an effect size of .25 to detect differences between the two treatment groups for the number of opioid positive urines during the treatment period.

B. Statistical analysis:

The principal analyses will be done on the modified intention to treat sample, that is, subjects receiving at least one dose of BUP/NLX. First, we will determine the success of the randomization by comparing the two treatment groups on socio-demographic and baseline clinical characteristics using chi-square for categorical variables and ANOVA for continuous variables. Second, survival analysis will be used to determine differences between experimental groups in treatment retention. Third, random regression analyses (HLM), (Hedeker and Gibbons 1996) will be conducted to examine if the change in opioid use behavior over time varies as a function of the treatment factors.

Risks and Benefits:

Potential risks

1. Buprenorphine: Buprenorphine, formulated as a sublingual tablet, is available alone or in combination tablet containing buprenorphine and naloxone in a ratio of 4:1. The doses of buprenorphine/naloxone used here are within the recommended guidelines of the manufacturer (4-24 mg/day). In this study, combination tablet will be used, since it is less likely to be diverted than the buprenorphine alone formulation. Common side effects of buprenorphine/naloxone include abdominal pain, constipation, nausea, vomiting, headache sweating, sedation, and allergic reaction. Uncommon but more serious adverse effects of buprenorphine/naloxone include hepatic abnormalities, orthostatic hypotension and respiratory depression.
2. Buprenorphine/Naloxone detoxification: Detoxification from buprenorphine/naloxone can produce signs and symptoms of opiate withdrawal, including nasal congestion, abdominal symptoms, anxiety, myalgia, insomnia, sweating, and diarrhea.
3. Blood Drawing: Subjects will have approximately 80 cc of blood drawn as a result of their participation in the study. Blood drawing can cause some pain and may result in bruising and rarely, infection.
4. 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.

Risk/Benefit Ratio: This study may help to develop more effective treatment approaches for prescription opioid dependence.

Protection of subjects

a. Our inclusion and exclusion criteria will be applied by experienced professionals who will be carefully trained and monitored in order to accept only appropriate subjects into the study. Thus, effective screening will exclude subjects who would be placed at an unacceptable risk. This is determined by the medical and psychiatric history, drug use history, the physical

examination, and the laboratory studies done prior to beginning this research protocol (although as stated previously, should a potential participant present already in withdrawal, it will be the decision of the study MD whether or not to randomize the patient prior to laboratory results being available.)

b. Confidentiality will be protected by having records identified by code number only with the master list including names kept in locked file cabinets in Bldg. 36 . Confidentiality in this study is of the utmost importance to us. All information obtained will be stored in coded form. The paper files will be kept in locked file cabinets in Bldg. 36 and the electronic records will be kept within the VA intranet (M-drive).

c. Data and Safety Monitoring Plan: The study will be monitored by a Data and Safety Monitoring Board (DSMB). Risks associated with participating in this protocol are moderate. There is adequate surveillance and protection to discover adverse events promptly and keep their effects minimal. The Board will be composed of persons who are experienced in the conduct of clinical trials for the treatment of addictive disorders and who have appropriate expertise in substance abuse and psychopharmacology. There will be at least one physician on the board who is not directly involved in this trial, but who has the requisite expertise. In order for the DSMB to fulfill its mission of assuring the safety of human subjects and the scientific integrity of the study being conducted, the Board will review adverse event data no less than three times per year. During these meetings, the DSMB will review a table of adverse events at these four-month intervals. Following each DSMB meeting, written minutes will be prepared and distributed summarizing any recommendations, including any for interim analyses, as described above. These written reports will insure accurate preparation of any protocol amendments that might be necessary. After each DSMB meeting, this written report will describe all recommendations including additional safety steps. All serious adverse events such as deaths, hospitalizations, and unexpected toxicity will be reported to the IRB as well as our local hospital risk management committee under expedited reporting, i.e., immediately by telephone as the information is available to us, followed by written report within 48 hours. The procedures for written reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. Communication of recommendations and decisions are made back to the investigator in a timely manner. These reports will also circulate to the DSMB.

<u>Reporting of Adverse Events</u>

An adverse event is any physical or clinical change or disease experienced by the subject at any time during the course of the study, whether or not considered related to the use of the study drug. This includes the onset of new illness and the exacerbation of pre-existing conditions. Subjects will be questioned and / or examined by the investigator or his / her designee for evidence of adverse events. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, “How have you been feeling since your last visit?” The presence or absence of specific adverse events will not be solicited from subjects.
All adverse events will be recorded in the subject’s medical and / or research records. The onset and end dates, severity, and relationship to the study drug will be recorded for each adverse

event. Any action or outcome (e.g., hospitalization, discontinuation of therapy, etc.) will also be recorded for each adverse event.

All serious adverse events, whether or not deemed drug-related or expected, will be reported by the principal investigator or designee to the IRB within 24 hours (one working day) by telephone. A serious adverse event is any event that: is fatal, is life-threatening (life-threatening is defined as the patient was at immediate risk of death from the AE as it occurred), is significantly or permanently disabling, requires inpatient hospitalization or prolongs hospitalization, is a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Serious adverse events will get reviewed immediately by the PI. Otherwise, this moderate risk study will be monitored quarterly by the PI and the members of the DSMB, and reported to the IRB if trends in AEs emerge.

Informed Consent:
Recruitment will be through VA clinics, word-of-mouth, referrals from area programs and by advertisement. A research staff member will interview individuals that are interested in participating in the study over the phone or in person should a patient present directly to the research staff. If subjects pass the initial screening for the study, they will then come into the clinic for a full screening evaluation. Upon arrival, a research assistant will read the detailed consent form and will ask questions to make sure that the subjects understand the procedure and their rights, and informed consent will be obtained.

Confidentiality: Confidentiality in this study is of the utmost importance to us. All information obtained will be stored in coded form. The names of the subjects will be used in hospital records.

Location of Study: This study will be conducted at the VA Connecticut Healthcare System West Haven campus.

Payment: Subjects will be paid $30.00 for attending the screening/baseline sessions which includes the 5-day induction period, $20.00/week for the 12-week treatment period for attending outpatient visits, and $30.00 for each follow-up visits at 1, 3 and 6 months. Subjects may therefore receive a total of $360.00 compensation.

Source of Funds: This protocol is being funded by MIRECC.

Duration: The entire study will take approximately four years to complete.

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