A Phase II, Randomized, Double-Blind Trial of Varenicline for the Treatment of Cocaine Dependence

Principal Investigator Kyle Kampman, M.D.
Department of Psychiatry
Treatment Research Center
3535 Market Street, Suite 500
Philadelphia, PA 19104
215-746-2764

Regulatory Sponsor: Kyle Kampman, M.D.Department of Psychiatry
Treatment Research Center
3535 Market Street, Suite 500Philadelphia, PA 19104
215-746-2764

Funding Sponsor: *NIDA*

Study Product: *Varenicline (Chantix™)*

Protocol Version Number: *ChC2 v.13*

IND Number: *77,735*

Date: **Version 1, 10/17/2011**
Amended: **Version 2, 05/11/2012**
Amended: **Version 3, 06/28/2012**
Amended: **Version 4, 07/31/2012**
Amended: **Version 5, 08/21/2012**
Amended: **Version 6, 01/22/2013**
Amended: **Version 7, 07/11/2013**
Amended: **Version 8, 08/25/2014**
Amended: **Version 9, 02/17/2015**
Amended: **Version 10, 04/21/2015**
Amended: **Version 11, 03/24/2016**
Amended: **Version 12, 07/25/2016**
Administrative Change: **Version 13, 02/01/2017**

- **Version 13 Correction 02/15/2017**
- **IRB approved 28 Jan 2019**

CONFIDENTIAL

This document is confidential and the property of the University of Pennsylvania. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the study sponsor.

Signature Page

I agree to conduct this clinical trial according to the principles and methods set forth in this protocol and in accordance with GCP, and applicable regulatory requirements.

_____ _____

Kyle Kampman, M.D. Date
Principal Investigator

Table of Contents

Study Summary

Title	A Phase II Randomized, Double-blind, Placebo-Controlled, Trial of Varenicline (Chantix™) for the Treatment of Cocaine Dependence
Short Title	Chantix for Cocaine Dependence
Protocol Number	ChC2 Version 13, 01/27/2017
Phase	Phase II
Methodology	Randomized, double-blind, placebo-controlled trial
Study Duration	5 years
Study Center(s)	Single-center – University of Pennsylvania Treatment Research Center
Objectives	To determine the efficacy of varenicline (Chantix™) for the treatment of cocaine dependence
Number of Subjects	200
Diagnosis and Main Inclusion Criteria	Cocaine dependence. Men and women ages 18-65. Subjects must have current DSM IV diagnosis of cocaine dependence and a recent history of cocaine use. Subjects must be in good health and psychiatrically stable. They must have no other current substance dependence except nicotine or alcohol.
Study Product, Dose, Route, Regimen	Varenicline (Chantix™), oral 1.0 mg BID.
Duration of administration	12 weeks
Reference therapy	Placebo
Statistical Methodology	**Hypothesis 1:** Cocaine use will be measured with three-times-weekly urine benzoylecgonine (BE) levels and self-reports of use from the Time Line Follow Back, combined to yield daily use/no-use indicators for each study day. We plan to use a mixed effects model. Mixed-effects models have two parts: a fixed effects component (comprising the explanatory variables included in the model) that describes the mean values of the outcomes across the time points, and a random-effects component defining the variances and covariances of the outcomes. In our models, the primary fixed effects are group, and time, together with possible interaction terms. The effect of time will be broken into linear, quadratic and, possibly, cubic, trends across the 13 weeks. A generalized estimating equations (GEE) model will be used to model the effects of medication group and time on the log-odds of use across the treatment period. The explanatory variables in these models will be a binary factor for medication, and terms for time effects, and group by time interaction

Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Therapies with both partial agonist and antagonist properties (e.g., buprenorphine) are highly effective in treating opiate abuse and dependence. By both providing a low level of reinforcement and down-grading any "high" associated with concurrent administration of the abused drug, such therapies promote both initial and sustained abstinence. Unlike treatment for opioid dependence, currently there are no efficacious pharmacotherapies for cocaine dependence. Based on the efficacy of partial agonists and antagonists in opioid treatment, by extension psychostimulants such as methylphenidate may be considered to be good candidates for treating cocaine dependence. However, that such psychostimulants are in and of themselves abusable drugs makes them relatively impractical treatment alternatives.

Increased acetylcholine release in the midbrain due to psychostimulant use (e.g., nicotine or cocaine) appears to increase dopamine and glutamate activity. It is believed that acetylcholine release in the midbrain triggers both pre-synaptic α7 receptors found on glutamatergic terminals (GLU) and post-synaptic α2β4 receptors found on dopamine cell bodies (DA). It is hypothesized that this interaction of the cholinergic, dopaminergic and glutamatergic systems in midbrain structures (e.g., nucleus accumbens, ventral tegmental area, amygdala and prefrontal cortex) is responsible for the development of psychostimulant abuse and dependence (c.f., Kelley 2002). As such, reduction in cholinergic activity at α7 and α2β4 receptors would likely reduce dopaminergic and glutamatergic activity in the midbrain, potentially halting or reversing the neural processes associated with development of psychostimulant abuse and dependence.

Based on varenicline's specific affinity for the nicotinic acetylcholine receptors that are implicated in cocaine reward circuitry (c.f., Schoffelmeer et al., 2002), it appears to be a good candidate for treatment of cocaine dependence. In addition to its partial agonist activity at heteromeric α2β4 nicotinic acetylcholine receptors, varenicline has also been shown to be a full agonist at homomeric α7 nicotinic acetylcholine receptors (Mihalak et al., 2006). That full agonism at α7 may be key in reducing cocaine withdrawal and craving during early cocaine abstinence, and thus reducing relapse, as α7 receptors are implicated in the neural reward circuitry activated by cocaine use. In addition, varenicline's ability to occupy the α7 and α2β4 nicotinic receptors, effectively blocking cocaine, would reduce the high derived from cocaine ingested during varenicline treatment. Evidence in support of this comes from the specific α7 antagonist methyllycaconitine, which attenuates the reinforcing effects of cocaine (Panagis et al., 2000).

Varenicline (Chantix™) is a partial agonist for the α2β4 nicotinic acetylcholine receptor subtypes. It has demonstrated efficacy as a treatment for smoking cessation (Oncken et al., 2006; Nides et al., 2006) and relapse prevention (Tonstad et al., 2006). Varenicline partially mimics nicotine's dopamine agonist properties, providing some reinforcement that mirrors that of nicotine, and thus reduces nicotine withdrawal and craving. In rat studies, extracellular dopamine in the nucleus accumbens after varenicline dosing was about half what is typically seen with acute

nicotine dose administration. In addition to its partial agonist effects, varenicline acts as an antagonist in the presence of nicotine, effectively downgrading nicotine-derived reinforcement (Johnson 2006). Based on its specific affinity for receptors implicated in both nicotine and cocaine reward, varenicline may work both for initiating and maintaining cocaine abstinence.

In contrast to the abuse liability associated with psychostimulants, less than 1 in 1000 subjects in the varenicline Phase III clinical trials reported euphoria with varenicline treatment, and any reports of increased positive subjective effects due to increased dosing are accompanied by reports of increased negative subjective effects, indicating a relatively low abuse liability for varenicline. In addition, there are no indications that tolerance to varenicline develops with repeated dosing.

In our recently completed pilot trial of varenicline for cocaine dependence we found that varenicline reduced cocaine use as compared to placebo (Plebani et al., 2011). In addition, varenicline reduced cocaine reinforcement.

1.2 Investigational Agent

(Taken from Chantix™ Package insert

CHANTIX™ tablets contain the active ingredient, varenicline (as the tartrate salt), which is a partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes.
Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3 \bullet C_4H_6O_6$.

Varenicline binds with high affinity and selectivity at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at a sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to $\alpha_4\beta_2$ receptors.
Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate $\alpha_4\beta_2$ receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to $\alpha_4\beta_2$ receptors than to other common nicotinic receptors (>500-fold $\alpha_3\beta_4$, >3500-fold α_7, >20,000-fold $\alpha_1\beta\gamma\delta$), or to nonnicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein

binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism/Elimination
The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Pharmacokinetics In Special Patient Populations
There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

1.3 Dose Rationale and Risk/Benefits

For the proposed trial, we chose a dose of 2.0 mg per day (1.0 mg BID) for several reasons. First, that dose has shown the best outcomes in smoking cessation trails with varenicline. In addition, few side effects are reported at that dose, making it both safe and efficacious.

Potential Risks: The potential risks of this study include adverse reactions to varenicline, cocaine and the small risk incurred by venipuncture.

Most adverse effects from varenicline have been mild and transient and have rarely required the withdrawal of therapy.

Common side effects are categorized below:
GASTROINTESTINAL
Nausea, Abdominal Pain, Flatulence, Dyspepsia, Vomiting, Constipation, Gastroesophageal reflux disease, Dry mouth
PSYCHIATRIC DISORDERS
Insomnia, Abnormal dreams, Sleep disorder, Nightmare
NERVOUS SYSTEM
Headache, Dysgeusia, Somnolence, Lethargy
GENERAL DISORDERS
Fatigue/Malaise/Asthenia
RESPIR/THORACIC/MEDIAST
Rhinorrhea, Dyspnoea, Upper Respiratory Tract Disorder
SKIN/SUBCUTANEOUS TISSUE
Rash, Pruritis
METABOLISM & NUTRITION
Increased appetite, Decreased appetite/Anorexia

Treatment-emergent adverse events reported by participants **during Chantix clinical trials:**
BLOOD AND LYMPHATIC SYSTEM DISORDERS. ***Infrequent:*** Anemia, Lymphadenopathy. ***Rare:*** Leukocytosis, Thrombocytopenia, Splenomegaly.
CARDIAC DISORDERS. ***Infrequent:*** Angina pectoris, Arrhythmia, Bradycardia, Ventricular

extrasystoles, Myocardial infarction, Palpitations, Tachycardia. ***Rare:*** Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome.
EAR AND LABYRINTH DISORDERS. ***Infrequent:*** Tinnitus, Vertigo. ***Rare:*** Deafness, Meniere's disease.
ENDOCRINE DISORDERS. ***Infrequent:*** Thyroid gland disorders.
EYE DISORDERS. ***Infrequent:*** Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. ***Rare:*** Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters.
GASTROINTESTINAL DISORDERS ***Frequent:*** Diarrhea, Gingivitis. ***Infrequent:*** Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. ***Rare:*** Gastric ulcer, Intestinal obstruction, Pancreatitis acute.
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS. ***Frequent:*** Chest pain, Influenza like illness, Edema, Thirst. ***Infrequent:*** Chest discomfort, Chills, Pyrexia.
HEPATOBILIARY DISORDERS. ***Infrequent:*** Gall bladder disorder.
IMMUNE SYSTEM DISORDERS. ***Infrequent:*** Hypersensitivity. ***Rare:*** Drug hypersensitivity.
INVESTIGATIONS. ***Frequent:*** Liver function test abnormal, Weight increased. ***Infrequent:*** Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal.
METABOLISM AND NUTRITION DISORDERS. ***Infrequent:*** Diabetes mellitus, Hyperlipidemia, Hypokalemia. ***Rare:*** Hyperkalemia, Hypoglycemia.
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS. ***Frequent***: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. ***Infrequent:*** Arthritis, Osteoporosis. ***Rare:*** Myositis.
NERVOUS SYSTEM DISORDERS. ***Frequent:*** Disturbance in attention, Dizziness, Sensory disturbance. ***Infrequent:*** Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. ***Rare:*** Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect.
PSYCHIATRIC DISORDERS. ***Frequent:*** Anxiety, Depression, Emotional disorder, Irritability, Restlessness. ***Infrequent:*** Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. ***Rare:*** Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation.

> ***Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking Chantix.***

RENAL AND URINARY DISORDERS. ***Frequent:*** Polyuria. ***Infrequent:*** Nephrolithiasis, Nocturia, Urine abnormality, Urethral syndrome. ***Rare:*** Renal failure acute, Urinary retention.
REPRODUCTIVE SYSTEM AND BREAST DISORDERS. ***Frequent:*** Menstrual disorder. ***Infrequent:*** Erectile dysfunction. ***Rare:*** Sexual dysfunction.
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS. ***Frequent:*** Epistaxis, Respiratory disorders. ***Infrequent:*** Asthma. ***Rare:*** Pleurisy, Pulmonary embolism.

SERIOUS SKIN REACTIONS
There have been postmarketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients using CHANTIX
SKIN AND SUBCUTANEOUS TISSUE DISORDERS. ***Frequent:*** Hyperhidrosis. ***Infrequent:*** Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria. ***Rare:*** Photosensitivity reaction.
VASCULAR DISORDERS. ***Frequent:*** Hot flush, Hypertension. ***Infrequent:*** Hypotension, Peripheral ischemia, Thrombosis.

The U.S. Food and Drug Administration (FDA) notified the public that varenicline may be associated with a small, increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. History of significant heart disease or dysfunction is exclusionary criteria for this study.

In a controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, certain cardiovascular events were reported more frequently in patients treated with CHANTIX than in patients treated with placebo. These included treatment-emergent events (on-treatment or 30 days after treatment) of angina pectoris (13 patients in the varenicline arm vs. 7 in the placebo arm), and the serious cardiovascular events of nonfatal MI (4 vs. 1) and nonfatal stroke (2 vs. 0). During non-treatment follow up to 52 weeks, serious cardiovascular events included nonfatal myocardial infarction (3 vs. 2), need for coronary revascularization (7 vs. 2), hospitalization for angina pectoris (6 vs. 4), transient ischemic attack (1 vs. 0), new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (5 vs. 2). Serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by an independent blinded committee. CHANTIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a health care provider of new or worsening symptoms of cardiovascular disease.

Black Box Warning

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS
Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.
All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre- existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established.
Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve. The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Drug Interactions
Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions.

Prior research examining the attenuating effects of the nicotinic acetylcholine receptor antagonist methyllcaconitine (MLA) on cocaine-derived reinforcement in rats showed no adverse interactions between cocaine and MLA (Panagis et al., 2000). Evidence for the lack of interactive effect between acetylcholine agonists and cocaine comes from prior research investigating the acetylcholinesterase inhibitor donepezil (Aricept®) as a treatment for cocaine dependence (Kampman et al., 2005). In that study, there were no adverse events stemming from the concurrent use of cocaine and donepezil. Taken together, these studies suggest that the partial agonist activity, as well as the antagonist activity of varenicline on nicotinic acetylcholine receptors should not interact in a clinically meaningful way with cocaine.

In our recently completed pilot trials of varenicline for cocaine dependence and varenicline for alcohol dependence, we have encountered no medication associated serious adverse events. A total of 77 participants have been randomized in our varenicline for cocaine dependence (n = 37) or varenicline alcohol dependence (n = 40) pilot trials. There have been no medication associated serious adverse events in either trial. Adverse events have been mainly mild. Adverse events possibly related to study medication reported by at least 5% of participants, including placebo treated participants, are: nausea (15%), aches and pains (13%), sedation (13%), diarrhea (10%) headache (8%), insomnia (8%) and vomiting (6%). Significant interactions between varenicline and cocaine, alcohol and the combination of cocaine and alcohol were not noted in the varenicline for cocaine dependence trial. There were no reported cocaine or alcohol associated serious adverse events, or significant changes in vital signs noted at study visits. Thus, based on the data from the pilot trial, varenicline appears to be safe to study in cocaine dependent participants.

Interactions between varenicline and cocaine
There is experimental evidence that neither actylcholine agonists or antagonists interact in a clinically meaningful way with cocaine.

Conclusions: Varenicline appears to be well-tolerated with a minimal side-effects profile as evidenced from adverse events reported in smoking cessation trials. The selection of a dose of 1.0 mg BID (2.0 mg per day) of varenicline is within the accepted dosing ranges recommended on the package insert.

Consent Procedures: All study procedures will be described in detail for the subjects by the research nurse, a physician, or other trained staff person in an individual consent session. The consent form and session will include the following information: Detailed information about the medication; that is, a description of the medication, rationale for why it is being studied, frequency of dosing and length of treatment, potential side effects, safeguards and emergency procedures. Information will also be provided about the psychosocial treatment, frequency of visits and length of treatment, safeguards and emergency procedures, etc. Collection of lab specimens (number of venipunctures and urine specimens required) will be reviewed. Eligibility will be reviewed. The number and frequency of the research interviews and self-assessments will be reviewed.
In addition, subjects will be assured that their participation is voluntary and that withdrawal from the study does not jeopardize current or future treatment. Subjects will also be told that if at any time during the study the research team feels that the subject needs more intensive, standard treatment, the subject will be referred to one of the available inpatient or outpatient treatment programs near their place of residence.
All subjects will be informed of potential risks and benefits involved in the study. Potential medication side effects will be described to all subjects. Subjects will be informed that their participation in the treatment trial may be discontinued at any time because of serious medication side effects, their noncompliance with treatment, missing appointments or if continued participation is considered an endangerment to their welfare.
At the end of the consent session, a quiz is given. Subjects scoring below 100% correct will receive additional instruction regarding the study and consent form. Incorrect questions from the quiz will be administered again until all questions are answered correctly.

Protection of Subjects: Potential subjects will be screened for medical illnesses that would preclude the use of varenicline. Subjects selected for the study will be monitored closely. Subjects will be evaluated three times a week while receiving study medication. Adverse events will be monitored by research staff at weekly visits, and the psychiatrist or nurse will be available at other visits to assess the subject if needed. At the conclusion of medications, an end of study physical will be completed and the baseline laboratory tests, including EKG, will be repeated. Subjects will be given a 24 hour emergency number they can call if necessary. Adverse events: If the subject is discontinued in treatment due to a serious adverse event, the subject will be followed clinically by medical staff until the adverse experience resolves itself and becomes stable.
Subjects taking concomitant medications will be monitored closely for signs of toxicity. Subjects with a history of current severe psychiatric symptoms, use of any investigational medication within the last 30 days, AIDS or other serious illness which may require hospitalization during the study, impaired renal function or known liver disease, will be excluded from the study. Pregnant women or women who refuse to use acceptable forms of birth control will be excluded from the study. Urine pregnancy tests will be performed monthly.
The dose of varenicline will be started at 0.5 mg BID and increased to 1.0 mg BID by the end of the first week of medication therapy.

Venipuncture will be carried out with good aseptic technique by a nurse or physician. Venipuncture sites will be monitored carefully for signs of infection.
If a subject experiences an adverse event, appropriate evaluation and management will be undertaken. This may include medical management, a reduction in study of medication, a temporary cessation of study drug, or early termination from the trial, if necessary
Strict confidentiality will be maintained. Clinical records will be stored in a restricted location and only the research team and clinical staff assigned to the care of the individual subjects will have access to the records. An exception to this rule will be made for representatives of the FDA and the National Institute on Drug Abuse (NIDA) and contract monitors and or auditors. The subject will be informed of these exceptions in the informed consent document.
Because data regarding cocaine use is being obtained, a certificate of confidentiality was obtained for this study. Subjects will be informed of this in the informed consent document.

Potential Benefits: Subjects will benefit from close medical and psychiatric attention over and above that which they will receive in an intensive outpatient treatment program.
The potential benefits to society include decreased cocaine use with a resultant decrease in cocaine morbidity and mortality, as well as a reduction in the overall social cost of cocaine dependence.

Risk Benefit Ratio: The potential benefits of this study far outweigh the potential risks. Cocaine dependence is a serious problem and treatment is difficult. Even in the best programs, relapse rates are high. Subjects accepted into the study will receive close medical and psychiatric monitoring, as well as treatment in an outpatient treatment program free of charge. Varenicline has been shown to be safe and well tolerated at doses to be used in this study. Subjects will be screened prior to admission into the study, and those at risk for adverse reactions will be excluded. Those selected for participation will be monitored closely for adverse effects.

2 Study Objectives

The proposed 5-year project will evaluate the efficacy of 2.0 mg/day of varenicline for the treatment of 200 treatment-seeking cocaine dependent outpatients in a double-blind, placebo-controlled 13-week trial. Study medications will be given by medical practitioners, trained to provide Medical Management (developed as part of NIAAA's COMBINE study). In addition, participants will receive weekly individual psychosocial treatment sessions utilizing Cognitive Behavioral Coping Skills Therapy (CBT), (CBT manual is part of NIAAA's Project MATCH and has been adapted for this population through prior consultation with Dr. Kathleen Carroll).

3 Study Design

3.1 General Design

This is a Phase II double-blind randomized controlled clinical trial. The hypotheses in the proposed study will be tested with a 2-group design to assess the efficacy of varenicline as compared to placebo. We will follow NIAAA's COMBINE Medical Management (MM) manual in weekly dispensing medications, safety checks and medication adherence. The psychosocial treatment will be Cognitive Behavioral Coping Skills Therapy (CBT). Subjects will be 200 men and women with current DSM-IV diagnoses of cocaine dependence that will be randomized to receive either varenicline or placebo (100 subjects per group). All subjects will

receive weekly sessions of CBT. The study length for each subject is comprised of 1-4 weeks of screening (referred to as "week 1") and a 12-week double-blind, placebo-controlled trial with CBT (medication phase). *At the end of the study subjects will be referred to continuing care programs in the community.*

3.2 Primary Study Endpoints

Primary Hypothesis:

- Subjects receiving varenicline will have higher rates of cocaine abstinence than will those receiving placebo, as determined by urine assay for benzoylecgonine (BE), the primary metabolite of cocaine.

3.3 Secondary Study Endpoints

Secondary Hypotheses:

- We further hypothesize that within the varenicline group, medication compliant participants ($\geq$80% of pills taken) will have higher rates of cocaine abstinence than those who are non-compliant (<80% of pills taken).

- We expect that the varenicline group will report less craving for cocaine than will the placebo group, as measured by lower scores on the Cocaine Craving Questionnaire (Tiffany et al., 1993) and the Minnesota Cocaine Craving Scale (Halikas et al., 1991) during the medication treatment phase.

- We expect that the varenicline group will show greater decreases in cigarette smoking than will the placebo group, as evidenced by CO and cotinine levels.

- **Primary Safety Endpoints**

A nurse or physician will assess for adverse events weekly. Adverse events will be monitored by research staff at all other visits, and the psychiatrist or nurse will be available at other visits to assess the subject if needed. At the conclusion of medications, an end of study physical will be completed and the baseline laboratory tests, including EKG, will be repeated. If the subject is discontinued in treatment due to a serious adverse event, the subject will be followed clinically by medical staff until the adverse experience resolves itself and becomes stable.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Males and females, 18 to 65 years old.

2. Meets DSM-IV criteria for Cocaine Dependence, as determined by the Structured Clinical Interview for DSM-IV (SCID).
3. Live within a commutable distance of the Treatment Research Center (TRC) at the Penn/VA Center for Studies of Addiction, University of Pennsylvania**. We define this to be a distance within the service area of Septa, within an hour drive, or a distance that both the participant and Principal Investigator (PI) find acceptable.**
4. Understands and signs the informed consent.

4.2 Exclusion Criteria:

1. Current DSM-IV diagnosis of any psychoactive substance dependence other than cocaine, alcohol or nicotine dependence, as determined by the SCID.
2. Subject is, in the investigator's opinion, at risk of requiring medical detoxification for alcohol dependence during the study.
3. Concomitant treatment with psychotropic medications.
4. Current gambling problems. **This will be assessed by the participant's self-report.**
5. Participants mandated to treatment based upon a legal decision or as a condition of employment who will use participation in this study to fulfill their court mandated treatment requirement.
   This will be assessed by the participant's self-report.
6. Current severe psychiatric symptoms, e.g., psychosis, dementia, suicidal or homicidal ideation, mania or depression requiring antidepressant therapy in the opinion of the **Principal Investigator (PI).**
7. Use of any investigational medication within the past 30 days.
8. Subject **has serious heart, lung, kidney, immune system, GI tract (ulcerative colitis, regional enteritis, or gastrointestinal bleeding) disease.**
9. Current use of naltrexone, disulfiram, modafinil, stimulants, haloperidol, benzodiazepines or anticonvulsants. **Anticonvulsants (e.g., gabapentin) prescribed for pain is not exclusionary.**
10. Known hypersensitivity to varenicline.
11. Participants with **known** AIDS or other serious illnesses that may require hospitalization during the study.
12. Female subjects who are pregnant or lactating, or female subjects of child-bearing potential who are not using acceptable methods of birth control. Acceptable methods of birth control include:
    a. barrier (diaphragm or condom) with spermicide
    b. intrauterine progesterone contraceptive system
    c. levonorgestrel implant
    d. medroxyprogesterone acetate contraceptive injection
    e. oral contraceptives
    f. tubal ligation.
13. Participants with impaired renal function as indicated by corrected creatinine clearance below 60 ml/min as determined by the modified Cockcroft equation.
14. Clinical laboratory tests (CBC, blood chemistries, urinalysis) outside normal limits that are clinically unacceptable to the Medical Director. EKG-1st degree heart block, sinus

tachycardia, left axis deviation, and nonspecific ST or T wave changes are allowed; liver function tests [LFTs] <5 x ULN are acceptable).

4.3 Subject Recruitment and Screening

The proposed project will be conducted at the University of Pennsylvania's Treatment Research Center (TRC). The TRC is a community-based (non-veteran) outpatient addiction treatment-research program that is part of the University of Pennsylvania Center for the Study of Addictions (Dr. Henry Kranzler, Director). The TRC offers outpatient addiction treatment for individuals from the greater Philadelphia area who are seeking treatment for their addiction and who qualify for one of our grant-sponsored treatment studies on alcohol, cocaine, dual cocaine-alcohol, marijuana, heroin or nicotine dependence. Subject recruitment is ongoing and accomplished through community, professional, and self-referrals from the greater metropolitan Philadelphia area. Most of the TRC callers seeking treatment who are approved for intake (via phone pre-screen) and give written consent (93%) are subsequently randomized (85%) into a treatment-research study. All subjects enrolled at the TRC receive medical monitoring and high-quality treatment—at no cost. Female-focused recruitment strategies, including direct appeals to female-medical specialties such as OB-GYN offices, has increased our ability to recruit female cocaine and alcohol dependent subjects.

Prior to participating in treatment-research studies at the TRC, all subjects undergo a medical and psychosocial intake to determine health and potential eligibility for treatment in one of the TRC's research programs. Routine measures obtained on the first day the subject arrives at the TRC are a psychosocial history, medical history, and the Beck Depression Inventory (BDI).

Before study-specific eligibility criteria are assessed, subjects are asked for their consent. At the consent session, all assessments, lab procedures and information on study medications are fully explained. Subjects are given information about confidentiality, study payments and under what circumstances they may be prematurely discontinued from treatment. Subjects are told that a blood alcohol concentration (BAC) reading will be required at each TRC visit, and that the reading must be below 0.02, otherwise the visit will be rescheduled. If their BAC reading is 0.08 or higher, they will be detained until arrangements are made for them to be escorted home or the reading decreases to an acceptable level (e.g., 0.02). At the end of the session, subjects take a consent "quiz" that can be re-taken until all of the questions are answered correctly. Subjects then give written consent and are given phone numbers of key project staff and a 24-hour emergency number. After signing informed consent, subjects continue with screening assessments to determine if they meet eligibility criteria.

Subsequent screening procedures include blood chemistry, CBC, urinalysis, psychiatric interview, assessment of baseline drug and alcohol use using the Timeline Follow Back, Addiction Severity Index.

4.3.1 *Genetics of Addiction*

The TRC has a Genetics Research Bank to collect and store samples from individuals participating in research studies at the University of Pennsylvania Treatment Research Center (TRC). Individuals providing blood samples will have screened and/or participated in various research studies focused on an addictive disorder. These samples will be used to study various candidate genes and/or whole genomes and their relationship to clinical and demographic data collected as part of the other research studies that the individual has participated. The Genetics of

Addiction study stopped recruitment on 01/07/2015. Persons participating in the intake process for research studies at the TRC are no longer eligible to sign a separate consent for the Genetics of Addiction study. Persons reporting for intake have usually undergone a telephone or in-person screening to see if they are eligible for ongoing studies at the TRC. Participants who signed consent for the Genetics of Addiction study during the recruitment phase had two vials of blood drawn to analyze their genotype, as outlined in the Genetics of Addiction protocol.

This study (Varenicline for Cocaine) does not have any genetic hypotheses. As such, the information obtained from the genetics blood bank will not be shared with the Principal Investigator of this study by Dr. Oslin, the Principal Investigator of the Genetics of Addiction study. As such, the below language (taken from study consent) addresses the non-linkage between the two studies:

> "In addition to your participation in this trial, you may have also consented to a separate study of the Genetics of Addiction. If you consented to the Genetics of Addiction study, those results are separate from this trial and will not be combined with the results from this trial. If you have any concerns about your participation in the Genetics of Addiction study, please discuss with the research staff."

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Clinical Trial Discontinuation Criteria: All randomized subjects are included in the intent-to-treat analysis. All subjects who prematurely discontinue treatment will be scheduled for a final evaluation, the end-of-trial visit. Subjects will also be given appropriate treatment referrals. Subjects are not dropped from all study activity unless they request they not be contacted, or the subject cannot be located for assessment. Subjects will be informed at the consent session that medications may be discontinued due to: 1) Intolerable side effects; or 2) Extreme lab values with a repeat test. In these two cases, the subjects may continue with the CBT part of the treatment, as well as receive medical attention. Subjects will be informed at the consent session that he or she may be discontinued from all treatment due to: 1) Development or exacerbation of significant psychiatric or medical symptoms that necessitate inpatient admission or a more aggressive therapeutic intervention than provided by the protocol; these subjects would not be invited back to take study medication but will be followed for data collection and may remain eligible for psychosocial treatment; 2) A return to significant cocaine use or emergence of another substance abuse problem which necessitates inpatient admission or a more aggressive treatment than provided by the protocol; subjects who are admitted for inpatient stabilization for cocaine use may return for data collection and psychosocial treatment after discharge to complete the 12 week trial, but study medication will not be restarted if they miss more than two weeks of study medication; 3) Incarceration > 1 week; subjects may return for data collection and psychosocial treatment after discharge to complete the 12 week trial but study medication will not be restarted if they miss more than two weeks of study medication 4) subject's behavior compromises subject's safety. The reason the subjects are discontinued from medication and/or the clinical trial and any referrals made are documented in a Note to File found in the subject's source document binder or medical chart. Study medications will not be restarted in subjects missing more than two weeks of study medications because this would necessitate restarting the dose titration schedule and may result in

a significant confound in the analysis of medication response. Varenicline can be abruptly stopped in patients without significant adverse effects.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Standard procedures developed here at TRC are used to help locate missing subjects. These include the identification and verification of home and work phone numbers, emergency contacts and collateral contacts. Subjects who have missed an appointment are re-contacted initially by phone, then by letter and finally by registered mail. Emergency and other collateral contacts are used when subjects themselves cannot be contacted. Contacts are attempted daily for a minimum of one week then less frequently by mail. Subjects are not considered lost to follow up until the entire study is completed and the database is ready to be closed.

5 Study Drug

5.1 Description

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism/Elimination

The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Study medication will be prepared by the Research Pharmacist at the Hospital of the University of Pennsylvania by over-encapsulating varenicline 0.5 and 1.0 mg capsules.

5.2 Treatment Regimen

Study medication will be initiated in Week 2. The research physician or nurse will explain the dosing regimen and subjects will be randomized to receive either varenicline or placebo. The statistician will randomize subjects to either varenicline or placebo using a computer-generated program of urn randomization, based on specified criteria that are described below.

The dose of varenicline will begin at 0.5 mg daily, and will be titrated up to the target daily dose of 2.0 mg/day at the start of the second week of medication (see Table 1). If adverse events occur, the physician or nurse may keep the dose the same or reduce to fewer pills. If the side effects subside, subjects can be re-challenged or kept at a lower number of pills. During the last week of the medication phase of the trial, varenicline will be reduced to 1.0 mg daily.

Pharmacotherapy will be completed by the end of the 13th week. If tolerated, subjects will be taking the maximum daily dosage (2.0 mg of varenicline or identical appearing capsules) for 10 weeks (Weeks 3-12).

Table 1. Dosing Schedule (taken from package insert)

Wk.	Daily Dose
2 (days 1-3)	0.5 mg
2 (days 4-7)	0.5 mg BID (1.0 mg daily)
3	1.0 mg BID (2.0 mg daily)
4	1.0 mg BID (2.0 mg daily)
5	1.0 mg BID (2.0 mg daily)
6	1.0 mg BID (2.0 mg daily)
7	1.0 mg BID (2.0 mg daily)
8	1.0 mg BID (2.0 mg daily)
9	1.0 mg BID (2.0 mg daily)
10	1.0 mg BID (2.0 mg daily)
11	1.0 mg BID (2.0 mg daily)
12	1.0 mg BID (2.0 mg daily)
13	0.5 mg BID (1.0 mg daily)

There have been no severe interactions noted between varenicline and any other drugs. Nonetheless, in the proposed study, weekly monitoring by a nurse or physician provides a safety net. We will be monitoring adverse events via self-reports, BAC readings, and liver enzymes collected routinely during the trials. Side effects can be treated by lowering the dose of study medications or discontinuing the study medications when necessary. The subject will be discontinued from medications if he or she has experienced a medication associated serious adverse event (SAE), cannot tolerate minimum dosages of study medication, or becomes pregnant. Any subject who is discontinued from the study medications can still complete the CBT portion of the treatment. If the subject reports an SAE, the subject will be followed until the event is resolved. Federal, sponsor, and institutional guidelines are followed for reporting SAEs.

Clinical Deterioration and/or Suicide Risk Management: All of the investigators have had experience managing and referring subjects under these conditions. We follow the TRC's standing emergency policy when managing clinical deterioration related to addiction or psychiatric symptomatology for all of our subjects. At the weekly visit, subjects are evaluated for the presence or persistence of any symptoms indicative of clinical deterioration due to a rapidly increasing problem with cocaine use, drinking, and/or psychiatric symptoms, including suicidality. Between visits, subjects are instructed to contact their treating physician or an authorized research staff member in the event that disturbing symptoms become evident. In all cases, these subjects are immediately evaluated, and if deemed appropriate, are referred to clinical treatment. If possible, they will be maintained in the trial as long as all it is deemed safe to do so. Also, any additional treatment is recorded for data analysis purposes. At any time, subjects who are severely suicidal or at high risk of medical or physical harm will be immediately discontinued from the trial. All subjects who are discontinued from the trial are still encouraged to attend the end of treatment visit.

5.3 Method for Assigning Subjects to Treatment Groups

Urn Randomization: We will use urn randomization to stratify subjects across the two experimental conditions. In the randomization scheme, we will stratify subjects on 2 baseline variables: 1. Gender; 2. Cigarette smoking status. We have no reason to suspect gender differences to mediate outcomes; however, it certainly is possible, given our sparse knowledge about female alcohol and drug abusers. Also, because we estimate that fewer than 30% of our final sample will be females, based on TRC census data over the past 5 years, it is imperative that we use gender as one of the urn variables in randomizing.

5.4 Preparation and Administration of Study Drug

Study medication will be prepared, stored and dispensed by the Research Pharmacist at the Hospital of the University of Pennsylvania. Ken Rockwell can be contacted at 215-349-8817.

5.5 Subject Compliance Monitoring

Medication Adherence: Medication adherence will be monitored via observed dosing at each study visit and by pill counts upon the weekly return of the blister card. These will also serve as the basis for actively enhancing medication adherence done as part of Combine's Medical Management procedures. Blister cards can be organized by row and column and clearly marked per daily dose. The design of the HUP blister cards makes it easy to titrate the dosage up at the initiation of the trial. Blister packs provide the subjects with easy access for viewing the number of pills missing vs. remaining for each day since each pill is individually packaged and daily dosages are clearly marked. Subjects will be given one blister card each week and are asked to bring it with them at each study visit and to return it the following week. Each blister card contains the dose per day for each of the seven days of the week. Doses for a given day are designated in a single row, with rows numbered consecutively to represent the days of the week.

We purposely chose not to use the Medication Event Monitoring system (MEMs) cap bottles to dispense medications in this study due to their prohibitive costs. We chose not to use a riboflavin marker to measure adherence because riboflavin has been shown to be an unreliable indicator of compliance due to difficulty in determining visual thresholds for the presence/absence of riboflavin. Therefore, we will use pill counts in the presence of a returned blister pack to secondarily assess medication adherence. We reimburse the participant $5 for each blister card returned, empty or not. We have been doing this for over 5 years, with our IRB's approval. This procedure has netted us 80-90% return of blister cards by our research participants.

Subjects who are significantly noncompliant with treatment medication (indicated by less than 50% of doses taken) will be counseled by the nurse assigned to MM therapy. If that does not result in improved medication compliance, these subjects will meet with the PI of the study for further counseling.

5.6 Prior and Concomitant Therapy

Concomitant medications will be recorded for 30 days prior to consent throughout the end of treatment phase. Medications that will not be allowed during screening week and the randomization phase include antidepressants, antianxiety medications, antipsychotic medications,

naltrexone, disulfiram, modafinil, stimulants, anticonvulsants, benzodiazepines, haloperidol. Anticonvulsants (e.g., gabapentin) prescribed for pain will not be exclusionary.

Additional psychosocial therapies, including self-help groups, will be allowed during the randomized medication phase, but will be measured using the Treatment Services Review (TSR). Subjects admitted to inpatient detoxification during the trial may be invited back to continue psychosocial treatment and medications as outlined in section 1.1.2 above.

5.7 Packaging

Study drug will be dispensed weekly. It will be dispensed in blister packs with each daily dose clearly marked. Blister packs will be labeled with the name and address of the research Pharmacy, the name and 24 hour phone number of the PI, subject initials, randomization number, name of the study drug, study week, and # of capsules and instructions. Each row on the blister pack represents a day's dose, with the two daily doses clearly identified.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Study drug is to be supplied by Pfizer or purchased and will be over-encapsulated by the Research Pharmacy at the Hospital of the University of Pennsylvania. The matching placebo will be produced and over-encapsulated by the Research Pharmacy at the Hospital of the University. All study medication will be stored and dispensed by the Research Pharmacy at the Hospital of the University of Pennsylvania.

5.8.2 Storage

Study medication will be stored at the Research Pharmacy at the Hospital of the University of Pennsylvania. A portion of the packaged medication will be stored on-site in a locked cabinet in order to be available for participants in the treatment phase of the study. Per FDA guidelines, all study medication both on-site and at the pharmacy will be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

5.8.3 Dispensing of Study Drug

. After randomization, study drug will be dispensed to each subject according to his or her randomization number. Medication will be dispensed by blister pack each week. A pill count log will be maintained in each subject's CRF indicating how many capsules were dispensed and how many collected at the end of the week. A dispensing log will also be maintained at the Research Pharmacy.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.8.4 Return or Destruction of Study Drug

All unused study drug will be returned to the Research Pharmacy. At the completion of the study, there will be a final reconciliation of drug obtained from the Research Pharmacy, drug consumed, and drug returned. This reconciliation will be logged on the drug reconciliation form, signed and

dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

DESCRIPTION OF INSTRUMENTS (in alphabetical order)

1. **Addiction Severity Index** (ASI) (McLellan et al., 1992). The ASI is a 45-minute interview which yields composite scores, ranging from 0 to 1, of problem severity over the past 30 days in 7 areas: medical, employment, drug use, alcohol use, legal, family/social, and psychiatric. Studies have shown moderate to excellent interrater and test-retest reliability. The ASI will be used to characterize baseline demographic and drug use variables for each subject. The composite scores will be used as secondary outcome measures. The ASI is administered research staff at Baseline, at Week 7 and at medication completion (Visit 40).
2. **Adverse Events** (AE) Adverse events will be collected at every visit and recorded in the CRF. Severity, expectedness, relatedness to study drug, action taken, and outcome will all be recorded (Visits 1-40).
3. **Brief Substance Craving Scale** (BSCS) (Somoza et al 1995). This instrument is to be used to assess craving once weekly. The instrument was designed by the Craving Subcommittee of the NIDA Medications Development Research Units (MDRU). It is an expansion of the Cincinnati Craving Scale. Reliability data for the intensity and frequency questions has been collected at the Cincinnati MDRU. The questions regarding Length, Number and Time were added by the Subcommittee. The BSCS will be administered weekly and at the end of the randomized medication phase (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40)
4. **Clinical Global Impression Scale** (CGI) (Guy, 1976). The CGI is a brief clinical rating of severity of illness (at time of interview) and global improvement (from admission) using a 7-point Likert scale. The CGI is done by an observer (CGIO) and the subject (CGIS) to assess clinical progress, global improvement and to assess the severity of the subject's illness at regular contacts over the course of the study. The CGI is done once during baseline by the observer and subject, weekly during the medication phase of the trial by the observer and subject and once at the end of randomized medication phase by the nurse or physician and subject, (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).
5. **Clinical Institutes Withdrawal Assessment for Alcohol, Revised** (CIWA-AR) (Sullivan and Sellers 1989). The CIWA-AR is a valid and reliable measure of alcohol withdrawal symptom severity. It will be used to verify the need for alcohol detoxification prior to randomization and to measure alcohol withdrawal symptom severity among subjects who relapse to alcohol use during the trial. The CIWA-AR will be administered at least once during the baseline.
6. **Cocaine Craving Questionnaire** (CCQ) (Tiffany et al. 1993) This instrument will be administered once weekly, and at the end of randomized medication phase, to specifically assess cocaine craving (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).
7. **Cocaine Selective Severity Assessment** (CSSA) (Kampman et al., 1998). The CSSA is a 10-minute, 18-item study personnel-administered cocaine withdrawal scale developed at the TRC. The scale measures items that commonly occur after abrupt cessation of cocaine use, including: cocaine craving, depressed mood, appetite changes, sleep disturbances, lethargy, and bradycardia. Individual items are scored on a 0-7 scale and a total score is derived from a sum

of the individual item scores. The CSSA has been found to be a reliable and valid measure of cocaine withdrawal symptoms. The CSSA will be administered by research staff at each visit during baseline, weekly during the medication phase of the trial and at the end of randomized medication phase (Visits 1, 2, 3, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).

8. **Concomitant Medications** (CONMEDS) Concomitant medications will be recorded starting from 30 days prior to consent to the end of the randomized medication phase. They will be recorded weekly by the study nurse or physician, once at the end of randomized medication phase, and once at end of treatment (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).
9. **Delay Discounting Questionnaire** (Kirby & Marakovic, 1996) This questionnaire asks participants to repeatedly choose between two hypothetical monetary rewards: immediately available (smaller sooner rewards) and temporally delayed for time period between 10 and 75 days (larger later). The questionnaire allows for calculation of an indifference point, which is the value at which a participant switches from preferring the smaller sooner to the larger later reward. This indifference point is a measure of impulsivity, and can be tracked through repeated administration of the Delay Discounting questionnaire to assess changes in impulsivity over time (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).
10. **Fagerstrom Nicotine Tolerance Questionnaire** (FNTQ 25) is a 5-minute, 8-item, self-report designed to measure physical dependence to nicotine. The validity and reliability of this scale have been supported in numerous studies. Scores range from 0 (no dependence) to 11 (high dependence). A score of 8 or more is considered to be indication of high dependence and 4-7 moderate dependence. This questionnaire will be administered once in the screening weeks (Visit 1).
11. **Medical history & Physical exam (PE)** A complete medical history and physical exam will be conducted by the nurse or physician at Visit 1. The physical exam will be repeated at visit 40.
12. **Minnesota Cocaine Craving Scale** (MCCS) (Halikas et al., 1991). The MCCS is a valid and reliable measure of cocaine craving. Craving is assessed over three dimensions, intensity, duration, and frequency and subjects are asked to evaluate their craving for the prior week. The MCCS will be administered at baseline, weekly throughout the medication phase of the trial, once at the end of randomized medication phase (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).
13. **Multiple Choice Procedure (MCP)** (Griffiths, Troisi II, Silverman & Mumford, 1993) This adaptation of the MCP asks participants to choose between a hypothetical static amount of cocaine and hypothetical variable amounts of money. Repeated administrations of the MCP allow for assessment of changes in the relative reinforcing effects of cocaine over time, evidenced by shifts in how much participants are willing to "pay" for a static amount of cocaine (visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).
14. **Pill Count** The number of capsules of study medication dispensed and the number returned each week will be recorded in the CRF (visit 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).
15. **Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), Mini-International Neuropsychiatric Interview (MINI)** (Sheehan et al., 2002), The substance abuse module (Module E) of the SCID-IV will be used to diagnose substance abuse problems. The major depressive episode modules (Modules A and B) of the MINI Plus will be used to diagnosis current and past episodes of major depression and current episodes of major depression with melancholic features. Other lifetime DSM-IV Axis I and II diagnoses will be obtained from the MINI. The SCID/MINI/MINI Plus will be done once during baseline to confirm diagnoses

of cocaine and alcohol dependence and determine if Axis I, Axis II or other substance disorder diagnoses are present. Time of administration will be 45 minutes. The SCID/MINI/MINI Plus will be administered by a clinically-trained Diagnostic Interviewer.

16. **Timeline Follow Back Interview** (TLFB) (Sobell and Sobell, 1995). The TLFB is a 15-30 minute, semi-structured interview adapted by our laboratory to collect information about daily cocaine, alcohol, and nicotine use. Critical life events are reviewed retrospectively to prompt recall of cocaine use measured in days used and dollars worth of cocaine used. Nicotine use is measured by number of cigarettes (or other forms of tobacco) per day. Cocaine, and nicotine use are recorded on a personalized calendar. Other drugs and any days spent in a controlled environment are also recorded on the calendar. The TLFB will be given by trained research staff at baseline to cover 3 months immediately preceding treatment entry and will be updated at each research visit to determine any time spent in a controlled environment and cocaine, nicotine, and other drug use during the period since the last visit. The composite of these assessments will be additive over the course of the study so that we will have continuous data on cocaine and nicotine use (Visit 1 through 40).
17. **Treatment Group Prediction Form** Integrity of the study blind will be evaluated by having the nurse or physician, therapist, research staff and subject predict which medication group assignment (active or placebo). (Week 7 and Visit 40).
18. **Treatment Services Review** (TSR) (McLellan et al., 1992). The TSR is a 5-minute interview given by the research staff to record the subject's use of services received in 7 areas covered in the ASI since the last visit. Test-retest reliabilities are high (McLellan et al., 1992a). The measure is given during baseline week, weekly throughout the medication phase, at the end of randomized medication phase and at the end of treatment visit so that there is a continuous record of non-study treatment services throughout the trial (Visits 1,4,7,10,13,16,19,22,25,28, 31, 34, 37, 40). These data will be used to compare utilization of ancillary treatments during the trial in the varenicline and placebo groups.
19. **The Symptom Checklist 90 Revised** (SCL-90-R) (Derogatis, 1977) is a ninety item self report measure that measures psychiatric symptom severity on a 4 point scale from 0 "not at all" to 4 "extremely." Nine factor scores are generated including depression, anxiety, phobic anxiety, somatization, interpersonal sensitivity, paranoia, psychoticism, obsessive-compulsive, and hostility. This scale is a standard measure used clinically at the Treatment Research Center. It has been shown to correlate well with clinician rated improvement and provides a measure of self-perceived symptom reduction. It will be administered at baseline and the end of the randomized medication phase (Visits 1 and 40).
20. **Risk Assessment Battery** (RAB) (Snider et al., 1994) is a 38 item self report questionnaire which assesses high risk behavior for exposure to the HIV virus. The RAB yields drug, sex and total risk scores. It will be administered at baseline and the end of the randomized medication phase (Visits 1 and 40).
21. **Hamilton Anxiety Rating Scale** (Ham A) This instrument will be administered during baseline and at the end of the randomized medication phase (Visits 1 and 40) to assess changes in anxiety symptoms that occur during the trial.
22. **Hamilton Depression Rating Scale** (Ham D) (Nordgren 1995, Hamilton 1967). This instrument will be administered during baseline and again at the end of treatment to assess changes in depressive symptoms. This version of the Hamilton Depression Scale is based on the Hamilton Rating Scale for Depression (HRSD-24). Items 25 through 28 (Increased Appetite, Weight Gain, Hypersomnia, Social Withdrawal) have been added by the NIDA

Medications Development Division from various other scales believed to be pertinent to MDD research. These have not been validated. The additional items will be analyzed separately. This instrument will be administered at baseline and at the end of the randomized medication phase (Visits 1 and 40).

23. **Short Form-36 Health Status Questionnaire** (SF-36) (Jenkinson, 1994). The SF-36 is a 10-minute, 36-item self-report of the subject's quality of life. Eight health concepts are assessed: 1) limitations in physical activities; 2) limitations in social activities due to physical or emotional problems; 3) limitations in activities due to physical problems; 4) bodily pain; 5) general mental health; 6) limitations in activities due to emotional problems; 7) vitality; and 8) general health perceptions. The SF-36 will be given once at baseline, at end of treatment (week 14).
24. **Weight and Vital Signs** Body weight, temperature, pulse and blood pressure will be monitored weekly, and at the end of randomized medication phase (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40).

Laboratory Measurements

1. **Breathalyzer** (BAL) Blood alcohol levels will be estimated at each study visit (1-40) by breathalyzer.
2. **Carbon Monoxide** (CO) Expired carbon monoxide, a biomarker for very recent cigarette smoking will be assessed at each visit (1-40) by Bedfont CO monitor.
3. **Urine cotinine** will be measured at each study visit (1-40) using NicCheck urinary cotinine dipstick testing. Cotinine captures cigarette smoking within the past 48 hours.
4. **Electrocardiogram** is a standard 12-lead ECG recorded once during baseline and one time at the end of randomized medication phase by the nurse or physician. Any abnormal results are brought to the attention of the principal investigator or study physician (Visits 1, 40).
5. **Complete Blood Count and Blood Chemistry** will be collected once at baseline and once at the end of the randomized medication phase by the nurse or physician and sent to an off-site laboratory for examination. The tests include glucose, uric acid, BUN, creatinine, glom filt rate, BUN/creatinine ratio, sodium, potassium, osmolality, albumin, bilirubin, alkaline phosphatase, LDH, AST (SGOT), ALT (SGPT), GGT, cholesterol, triglycerides, HDL cholesterol, VLDL cholesterol, LDL cholesterol, T. cholesterol/HDL ratio, Estimated CHD risk, WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW and platelets. Any abnormal results are brought to the attention of the principal investigator or study physician (Visits 1 and 40).
6. **Urinalysis** will be collected once at baseline and once at the end of randomized medication phase by the nurse or physician and sent to an off-site laboratory for examination. The test includes color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin urobilinogen, and microscopic examination of urine sediment. Any abnormal results are brought to the attention of the principal investigator or study physician (Visits 1 and 40).
7. **Qualitative Benzoylecgonine Screens (UBT):** Qualitative urine benzoylecgonine levels will be obtained at each study visit using One Step Drug Screen Test Cards (Cliawaived) or tested at the Main Toxicology Laboratory at the Philadelphia VA Medical Center.
8. **Qualitative Urine Drug Screens (UDS):** Qualitative (emit) urine toxicology of benzodiazepines, barbiturates, amphetamines, and opiates will be done weekly during the baseline phase, the medication phase of the trial and once at the end of randomized

medication phase (Visits 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40) at the Main Toxicology Laboratory at the Philadelphia VA Medical Center.

9. **Urine Pregnancy Test** (UPT): A specimen will be collected once at baseline, every four weeks during the randomized medication phase, and once at the end of randomized medication. Samples will be tested at the Main Toxicology Laboratory of the Philadelphia VA Medical Center (Visits 1, 19, 40).

Screening: Subject will have three screening visits. The visits must be completed within a minimum of one week and a maximum of four weeks. The screening period is referred to as "Week 1".

Regular Evaluation Visits: Subjects will be in contact with the research staff three times weekly throughout the medication Phase of the study (weeks 2-13), preferably every Monday, Wednesday, and Friday (M,W,F). A few basic measures will be taken at each visit, UDS for BE, breathalyzer, TLFB, and adverse event recording. At the first evaluation visit each week, the following additional measures will be accomplished by research staff: Urine drug screen for benzodiazepines, barbiturates, opiates, marijuana, methadone, amphetamine, CSSA, Subject (CGIS), Treatment Services Review (TSR), Minnesota Cocaine Craving Scale (MCCS), and Cocaine Craving Questionnaire (CCQ). This will take about 45 minutes. At the first visit of week 7 and week 13, research staff will administer the Addiction Severity Index (ASI) (about 20 minutes) and obtain the Treatment Group prediction Form. Each subject will meet weekly with a nurse or physician for MM sessions to assess clinical status, monitor vital signs and weight, dispense study medications, pill count, monitor concomitant medications, monitor adverse events and provide Clinical Global Impressions (CGI) ratings. This will take about 15-30 minutes. The nurse or physician will also complete a Treatment Group Prediction Form at week 7 and visit 40.

The subject's individual therapist will complete the CGI weekly weeks 2-13 and complete the Treatment Group Prediction Form at week 7 and visit 40(about 3 minutes).

End of Medication Phase Evaluations: These will be done after the completion of Week 13, or at the completion of the trial in participants who are discontinued from the trial prematurely.

At this time, a nurse or physician will conduct the following procedures: vital signs and weight, physical exam, electrocardiogram, concomitant medications, adverse events, obtain blood samples for chemistry including liver function tests and CO2, CBC, obtain a urinalysis, CGI, pill count, and Treatment Group Prediction Form.

Research staff will conduct the following procedures: breathalyzer, CO, cotinine, ASI, TSR, CSSA, CCQ, SCL-90-R, RAB, BSCS, CGI, MCCS, TLFB, UDS, UBT, UPT, and Treatment Group Prediction Form. A clinically trained diagnostician will conduct the Ham A and Ham D. This entire visit will take about 120 minutes.

Psychosocial Treatment: Subjects will receive weekly psychotherapy from week 2 through week 13. This results in 12 individual, cognitive behavioral therapy (CBT) sessions, each lasting 50 minutes, for each subject.

CBT is based on general principles of social learning theory, which assume that disordered individuals have coping skill deficits that prevent them from managing high-risk situations. CBT utilizes direct practice, role playing and fine-tuning of new coping skills to achieve treatment goals.

The CBT we will use is based on relapse prevention principles. We are currently using, as part of another study, Project MATCH's CBT manual that Dr. Kathy Carroll has adapted for use in treating both cocaine and alcohol dependence (Kadden et al., 1992, Carroll et al., 1991, 1994). We will follow this manual in all procedures. We have had much experience with this manualized therapy as we have used it to treat over 300 cocaine and alcohol dependent subjects in two previous clinical trials.

CBT will be provided by a clinician who will receive training and day-to-day supervision from Margo Hendrickson, the TRC's Clinical Director. All CBT visits will be audiotaped and a minimum of two treatment sessions (an early and later session) will be rated for clinician adherence to the respective treatment principles and therapeutic alliance. Ms. Hendrickson is trained in CBT principles and is familiar with Dr. Carroll's manual. She will provide the adherence ratings for the audiotapes. We will use Dr. Carroll's adherence checklists, which are written based on general principles of CBT and can be used in both core and elective sessions. These tapes will also assist in the supervision provided to the clinician and reduce drift.

Subjects will also receive once weekly Medical Management (MM)—an intervention developed as part of NIAAA's COMBINE that provides advice and support from medical practitioners concomitantly with dispensing medications and checking safety and compliance. The main goal of the intervention is to increase medication compliance. All subjects will receive regularly scheduled manualized adherence enhancement therapy for cocaine dependence. The initial MM session is an hour; follow-up sessions last no more than 15-30 minutes.

After the initial MM visit, subjects will meet with their nurse for 15-30 minutes for a total of 12 visits, primarily to dispense varenicline and assess varenicline safety (adverse events), treatment adherence (pill counts and visit attendance), and drinking / cocaine use status. The content of each visit is fully outlined in the MM manual (see appendix) and is briefly outlined in the following tables.

Table 2. Medical Management (MM): Content of Initial Visit

- Review with participant their biopsychosocial status, using the Clinician Report from the MM manual.
- Discuss with participant the role of the MM clinician: Safety, Education, Support
- Educate participant about his/her cocaine disorder and about the medication, i.e., varenicline
- Record baseline safety information
- Discuss importance of medication adherence --develop a plan for medication adherence
- Encourage attendance at CBT therapy visits, MM visits and self-help support groups

Table 3. Medical Management (MM): Content of Follow-up Visits

- Brief check on medical functioning
- Determine participant status re: using cocaine? Medication taking?
- Give support and advice based on participant status

Nurse Recruitment and Training: The Nurse will be responsible for interacting clinically with the subjects. Training and supervision will focus on the clinical skills and pharmacological knowledge needed to manage individual cases within the parameters of MM. The training will also aim to impart a high level of personal responsibility for the welfare of study subjects.

6.1 Visit 1 (screening)

All screening procedures are to be completed prior to randomization (visits 1, 2, or 3). They may not necessarily be completed at the exact visit noted below.

Nurse or physician:

1. Informed consent and consent quiz
2. Medical history
3. Physical Exam (PE)
4. Vital signs weight (VITALS)
5. Electrocardiogram (EKG)
6. Concomitant medications (CONMEDS)
7. Adverse Events (AE)
8. CBC and blood chemistry including liver function tests (LFT) and CO2.
9. Urinalysis (UA)
10. Clinical Global Impression Scale, Observer (CGIO)
11. Supplemental questions
12. Clinical Institutes Withdrawal Scale for Alcohol Revised (CIWA AR)

Research staff

1. Breathalyzer (BAL)
2. CO
3. Cocaine Selective Severity Assessment (CSSA)
4. Treatment Services Review (TSR)
5. Minnesota Cocaine Craving Scale (MCCS)
6. Cocaine Craving Questionnaire (CCQ)
7. Fargerstrom Nicotine Tolerance Questionnaire (FNTQ)
8. Brief Substance Craving Scale (BSCS)
9. Multiple Choice Procedure (MCP)
10. Delay Discounting Questionnaire (DD)
11. Risk Assessment Battery (RAB)
12. Symptom Checklist-90-Revised (SCL-90-R)
13. Timeline Follow Back (TLFB)
14. Urine drug screen other than cocaine (UDS)
15. Urinary BE level (qualitative)
16. Cotinine
17. Clinical Global Impression Scale, Subject (CGIS)
18. Urine pregnancy test (UPT)(females)
19. Short Form Health Survey (SF-36)

6.2 Visit 2 (screening)

Research Staff

1. CSSA
2. BAL
3. TLFB

4. UBT
5. AE
6. CO
7. Cotinine

Diagnostician

1. Structured Clinical Interview for DSM-IV (SCID) / Mini International Neuropsychiatric Interview (MINI)
2. Hamilton Anxiety Rating Scale (HAM A)
3. Hamilton Depression Rating Scale (HAM D)

6.3 Visit 3 (screening)

Research Staff

1. CSSA
2. BAL
3. UBT
4. TLFB
5. Addiction Severity Index (ASI)
6. AE
7. CO
8. Cotinine

6.4 First visit of each study week during randomized medication phase: Visits 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37

All assessments may not be collected at the exact visits specified. Assessments completed weekly will be collected on either the first, second, or third visit of the week. Assessments not completed weekly must be completed within half of the time frame that exists before the next scheduled collection of the assessment.

Nurse or physician

1. Dispense study medications
2. Medical Management session (MM)
3. VITALS
4. CONMEDS
5. AE
6. CGIO
7. Pill count
8. Treatment Group Prediction Form visit 19

Research Staff

1. CCQ
2. CSSA
3. CGIS
4. TSR

5. MCCS
6. BSCS
7. MCP
8. DD
9. UDS
10. CO
11. Cotinine
12. UBT
13. BAL
14. TLFB
15. AE
16. ASI at visit 19
17. Treatment Group Prediction Form visit 19
18. UPT at visit 19 (females)
19. Any earned fishbowl draws completed and voucher earnings delivered

6.5 Second visit of each study week during randomized medication phase: Visit 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38

CBT Therapist

1. CBT Psychotherapy
2. CGIO
3. Treatment Group Prediction Form at visit 20

Research Staff

1. UBT
2. BAL
3. TLFB
4. AE
5. CO
6. Cotinine
7. Any earned fishbowl draws completed and voucher earnings delivered

6.6 Third visit of each study week during randomized medication phase: Visit 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39

Research Staff

1. UBT
2. CO
3. Cotinine
4. BAL
5. TLFB
6. AE
7. Any earned fishbowl draws completed and voucher earnings delivered

6.7 End of Randomized Medication Phase: Visit 40

Nurse or physician

1. PE
2. VITALS
3. EKG
4. CONMEDS
5. AE
6. CBC and blood chemistry including liver function tests (LFT) and CO2.
7. UA
8. CGIO
9. Pill count
10. Treatment Group Prediction Form

Research Staff

1. CCQ
2. CSSA
3. CGIS
4. TSR
5. MCCS
6. BSCS
7. MCP
8. DD
9. RAB
10. SCL-90-R
11. UDS
12. UBT
13. BAL
14. TLFB
15. ASI
16. Treatment Group Prediction Form (research technician and subject)
17. UPT(females)
18. Short Form Health Survey (SF-36)
19. CO
20. Cotinine

CBT Therapist

1. Treatment Group Prediction Form
2. CGIO

Diagnostician

1. HAM A
2. HAM D

7 Statistical Plan

7.1 Sample Size Determination

Power Analysis

Based on the results of our pilot trial (Plebani et al., 2011), we use the method described by Diggle et al. (1994) to estimate power, assuming a compound symmetry covariance structure. We assume a Type-I error level (Alpha level) of 0.05.

7.2 Statistical Methods

Data Analyses: The data analyses will be performed by Dr. Kevin Lynch, the CSA Statistician, and his staff. Prior to performing analyses, standard data screening/cleaning procedures will be applied (Tabachnik and Fidell, 2000). These procedures will (1) screen the data for data-entry errors, (2) check for outliers, (3) assess the extent and pattern of missing data, and (4) check that appropriate assumptions of Normality are met whenever necessary. Because of the size of the sample, it is unlikely that the randomization will result in significant imbalance of the distributions of demographic or other variables across the treatment groups. However, some additional covariates will be considered for inclusion in the analyses, to improve the precision of estimation for the treatment effects (Hauk et al., 1998). In particular, we will consider covariates describing levels of alcohol and cocaine use prior to the study. In all analyses, the assumptions underlying the application of all the statistical methods that are used will be examined, principally through the use of standardized residuals, influence diagnostics, and graphical displays.

Primary Hypotheses:

Hypothesis 1: The outcome of interest is cocaine use, measured with three-times-weekly urine benzoylecgonine (BE) levels and self-reports of use from the Time Line Follow Back, combined to yield daily use/no-use indicators for each study day. We will be examining both point prevalence and continuous cocaine abstinence. A generalized estimating equations (GEE) model will be used to model the effects of group and time on the log-odds of use across the treatment period.

The explanatory variables in these models will be a factor for group, and terms for time effects, and group by time interactions. In these models, we are interested in weekly rates of use, so time will be coded as weekly units, with up to seven daily indicators providing replications within a week. These models will provide valid estimates of the regression parameters (i.e. group and time effects) without requiring that the correlation between a subjects repeated urine drug screens is known. It is usually enough to specify a simple "working" correlation matrix, which need not agree with the true correlation matrix underlying the repeated measures. This provides a "robust" approach, but usually at the cost of larger sample sizes, and the lack of simple methods for comparing different models. Based on the work of Lipsitz,(Lipsitz et al., 1994), the sample size in this study will be more than adequate for the method to be valid. We will follow the recommendations of Pan and Connett (Pan and Connett, 2002) in selecting the working correlation matrix, and the recommendations of Pan (Pan, 2001a) in using an adjusted AIC statistic (his QIC statistic) to compare models. These analyses will be performed using PROC GENMOD in SAS.

Secondary Hypotheses:

Hypothesis 2 (effects of compliance with medication): The main analyses will be performed using an intent-to-treat (ITT) approach, so subjects will be analyzed according to their

assigned treatment, without reference to the level of treatment they actually receive. It is likely that some subjects will not comply with their assigned treatment, and that this non-compliance will be related to subject characteristics, and/or to unmeasured factors related to outcome. This non-compliance can diminish the extent to which the treatment groups are comparable with respect to measured and unmeasured variables. In this study, the placebo group will be unable to obtain varenicline, so non-compliance will probably result in underestimated treatment effects. We will gather information on compliance, and use it in further analyses to assess the sensitivity of the ITT analyses to the presence of non-compliance. The information will be obtained from weekly pill counts, on the basis of self-report and examination of blister packs.

Initially, we will use these sources to determine whether each subject has complied with their assigned medication for at least 80% of the trial. We will then include a binary variable indicating "80%" compliance in the analyses described above for Hypothesis 1, both as a main effect and as an interaction effect with varenicline group.

We will also use the sources described above to define variables representing compliance/non-compliance over each the 12 weeks of the treatment period. For the primary outcomes, we will perform extensions of instrumental variable regression analyses presented by Nagelkerke et al. (Nagelkerke et al., 2000). Here the instrumental variable is randomization and, under certain assumptions, will control for unmeasured bias when estimating the effect of varenicline relative to placebo in those who comply with their assigned treatment. These analyses will permit a more complete examination of the time-varying effects of compliance across the treatment period.

Hypothesis 3: The CCQ and MCC scales will provide weekly measures of cocaine craving. The scales provide a seven and a six-category Likert response, respectively, and it is likely that we will collapse some adjacent categories prior to the analyses, and regard the responses as ordinal. The analyses for these hypotheses will be perfectly analogous to those for Hypothesis 1, except that mixed-effects models for ordinal responses will be used (Hedeker and Mermelstein, 2000). These analyses will be performed using PROC NLMIXED in SAS.

Hypothesis 4: The CO and cotinine measures will be used to analyze dynamic changes in cigarette smoking, both in isolation and as they relate to cocaine use.

Other Analytic Issues:

Missing Data: For the longitudinal analyses described above, drop out from treatment and occasional missing daily use indicators will lead to incomplete data. The mixed effects and GEE models described above can make use of all available data provided by subjects, but the inferences drawn from them will be unaffected by the missing data only if the missing data can be regarded as ignorable, in the sense of Laird (Laird, 1988). In the current setting, this is implausible, and further analyses of the sensitivity of the mixed-effects and GEE models to the presence of missing data will be required. For the urine toxicology data, a simple approach, of frequent use in the current setting, is to assume that any missing urines are positive. While this is a reasonable starting point for analyses, it almost certainly overestimates the rates of use, and underestimates the variability about those rates, and further investigation through more formal analyses is required. We will use selection models to examine the effects of missing data (Kenward, 1998, Rotnitzky et al., 1998). We will explicitly model the probability of drop out at a time point as a function of baseline characteristics and responses at previous time points, using a logistic regression model, and incorporate the predicted probabilities into the main analysis. Any attempt to model the drop

out process requires us to make modeling assumptions about it, none of which can be tested on the observed data. While this was originally seen as a controversial aspect of the approach (Diggle and Kenward, 1994), it has become standard practice to perform the analyses under a range of different assumptions, and to assess the sensitivity of the results to them (Rotnitzky et al., 1998).

Additional Analyses: We will also collect and analyze some additional measures, of withdrawal severity, general clinical improvement (CGI), and external treatment (TSR). These variables are intended to provide a description of change in these areas across the course of the study. They will be used in analyses addressing possible mechanisms of treatment process, and will be included as time-varying covariates in the longitudinal analyses described above. Because we have no a priori hypotheses on their likely influence, and because there are selection issues regarding the interpretation of post-randomization change, we regard these analyses as exploratory and as hypothesis-generating for future studies.

7.3 *Subject Population(s) for Analysis*

- All-treated population: Any subject randomized into the study that received at least one dose of study drug

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose

or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment visit.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study personnel must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event electronic form. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor within 24 hours of the event. The investigator will keep a copy of an SAE report form on file at the study site. Report serious adverse events by phone and/or facsimile to:

Kyle M. Kampman, M.D. (Principal Investigator / Medical Director)
215 746 2764

At the time of the initial report, the following information should be provided:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

As information regarding the SAE becomes available, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will

assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.3.2 IRB Notification by Investigator

Reports of adverse events that are both unexpected and study drug related must be submitted to the IRB in real-time (weekly). These AEs will be recorded on the subject's AE Log and documentation of IRB notification will be kept in the regulatory binder. Reports of all serious adverse events (including follow-up information) that are unexpected and study drug related must be submitted to the IRB within 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the regulatory binder.

8.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

Integrity of the Blind: All research staff will be blind to the medication status until the end of the study. A statistician will work with the research pharmacist at HUP in setting up the urn randomization sequences, and will ensure that the codes linking subject's ID numbers to treatments are secured in an opaque envelope that will be maintained in a locked drawer in the research pharmacy. If a subject is prematurely discontinued from the trial, all attempts will be made to not break the blind. If an emergency necessitates that the blind be broken, only the pharmacist will have access to the blind to do so. He will be given the name of the staff who have authority to request that the blind be broken (Dr. Kampman or the TRC Doctor-On-Call). The HUP pharmacist can be reached 24 hours a day by beeper and can access a subject's code rapidly. If the study blind is broken for any subject this will be documented in the subject's medical chart.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The most significant risks to the subjects are those that would follow any breaches in confidentiality and the disclosure of clinical information. While we recognize the potential severity of these risks we also do not want to overstate this risk. Currently there are no known uses for information that may be obtained from this study.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The research data for this project will be gathered using the CSA's direct-entry data system, and will be stored on the DMU network. Interview data and self-report data are entered directly onto computers at the research sites, by research staff and study subjects respectively. Field validation (e.g. no out of range or otherwise invalid responses will be accepted) and form validation (e.g. logically impossible responses to different questions will not be accepted) are built into this entry process.

Research Staff will be present with the subject through the entire assessment, and will review each instrument as it is completed. On completion of this review, research staff will transmit the data (in 128-bit encrypted form) over the Internet to the DMU data servers. After a series of online reviews, the data is archived on the servers. No identifying information is stored on the DMU servers. Only certain members of the DMU staff have permission to modify the archived data. Audit logs record any modification to the original entry. Various levels of password protection

allow different members of the research team appropriate levels of access to the data. The various levels of access are decided by the PI, in consultation with Mr. Petro, DMU Director, prior to the initiation of the study. Mr. Petro will be responsible for working with the project staff to ensure the integrity of the data entry process, throughout the course of the study.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Purpose

The investigator will allocate adequate time for monitoring this study. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. The monitoring of a clinical trial is necessary to ensure the protection of the subject's rights, the safety of subjects enrolled in the trial and the integrity and quality of the resulting data. This monitoring section details the Case Report Form (CRF) and source data verification of efficacy and safety parameters, the frequency of monitoring visits, regulatory document review, drug accountability and compliance review. Monitoring will be conducted according to the University of Pennsylvania Sponsor-Investigator Standard Operating Procedures.

10.1.a Trial Management

Projected Timetable:

Each participant will be enrolled in the trial for 13 weeks. With an N of 200 participants, and projected enrollment of 4 participants per month, we expect to complete the study within 5 years (60 months). Below is the proposed timeline for the study:

Study months 1-3: (Hire and train personnel, submit regulatory documents, prepare for study initiation;
Study months 4-52: Recruit participants, collect data;
Study months 52-54: Data collection for last enrolled participant;
Study months 55-60: Data analysis and manuscript preparation.
Recruitment rate: **4-6** participants per month will be recruited, with a recruitment target of 60 subjects per year (36 subjects for Year 1).

TARGETED/PLANNED ENROLLMENT: Number of Subjects

Ethnic Category	Females	Males	Total
Hispanic or Latino	**10**	**30**	**40**
Not Hispanic or Latino	**40**	**120**	**160**
Ethnic Category: Total of All Subjects	**50**	**150**	**200**
Racial Categories			
American Indian/Alaska Native	**0**	**0**	**0**
Asian	**0**	**0**	**0**
Native Hawaiian or Other Pacific Islander	**0**	**0**	**0**
Black or African American	**38**	**113**	**151**
White	**12**	**37**	**49**
Racial Categories: Total of All Subjects	**50**	**150**	**200**

10.1.b Data Management and Analysis

Data Acquisition

Data will be collected by trained study staff with standardized forms using only a study number and initials to identify the participant. A code that links the participant to the study will be kept confidential by the study team in a password protected secure database. The clinical research coordinator and fellow staff members will be responsible for collecting and checking all clinical data. This includes ensuring that all fields are completed appropriately, that the clinical database is complete and accurate and all corrections are done according to GCPs. Any inconsistencies/deviations will be documented and reviewed by the PI.

All data collection is HIPAA compliant. The TRC supports the appropriate privacy of all clinical and research data collected as part of any study. We follow Penn's policy in the use and disclosure of protected health information in research in a manner that respects the patient's privacy in accordance with the "Privacy Rule" promulgated under the Health Insurance Portability and Accountability Act (HIPAA) and other applicable laws. All staff receive appropriate HIPAA training. All participants sign a HIPAA-authorization form, receive a copy of this form, and receive a notice of Penn's privacy practice. HIPAA signed forms are retained in locked file cabinets with participants' source documents.

Data analysis will be conducted by the Center statistician, Dr. Kevin G. Lynch, with assistance from the PI.

Data entry methods

A computerized data entry and management system will be developed during the initial project months by the Center's data management unit (DMU). All data will be entered into this web-based entry system by the research staff.

A closed and password protected data entry system has been designed so that only the responsible data entry person and the DMU supervisor can enter and/or edit data and this can be done only be using the programs and/or utilities available on the menu system. Data and user stamping are used to create an audit trail. Range checks, review screens, and various error trapping routines are built into the system as quality control procedures. All possible relevant

information on the forms is pre-coded and field-validated. All specific instructions and choices are provided for all data forms. All errors on source documents must be initialed and dated. The DMU director will be responsible for working with the project staff to ensure the integrity of the data entry process. The investigator or study research staff can request the data at any point during the study so that audits of the study's current data input can be conducted and the data's integrity assessed.

After entry of all data in the Case Report Forms, these source documents will be kept on location until study closeout at which point they may be moved to a secure long-term storage facility.

Mechanisms of Action:

In our pilot study, we found significant differences between the longitudinal time course of the vareniclinine and placebo groups on the MCP. In addition to the analyses on the CCQ and MCC scale described above, we will also test for longitudinal differences on the Cocaine Selective Severity Assessment (CSSA), and also on alcohol craving as measured by the Penn Alcohol Craving (PACS) (intensity, frequency and duration subscales). To examine whether change in any of these measures is related to change in cocaine use, we will run further analyses where these scales are included as time varying covariates in models for cocaine use. We will also perform cross-sectional and longitudinal mediation analyses (MacKinnon, 2008), using these scales as possible mediators.

10.1.c Quality Assurance Plan

Procedures in place to ensure the validity and integrity of the data

A closed and password protected data entry system has been designed so that only the responsible data entry person and the DMU supervisor can enter and/or edit data and this can be done only be using the programs and/or utilities available on the menu system. Data and user stamping are used to create an audit trail.

Procedures to guarantee the accuracy and completeness of the data collected

The clinical research coordinator and fellow staff members will be responsible for collecting and checking all clinical data. This includes ensuring that all fields are completed appropriately, that the clinical database is complete and accurate and all corrections are done according to GCPs. Range checks, review screens, and various error trapping routines are built into the system as quality control procedures. All possible relevant information on the forms is pre-coded and field-validated. All specific instructions and choices are provided for all data forms. All errors on source documents must be initialed and dated after correction.

10.1.d Study Monitoring Plan

Monitor Selection and Training

One primary monitor will be assigned for this trial and will be responsible to complete the monitoring process. The monitor will be a Research Coordinator who is independent

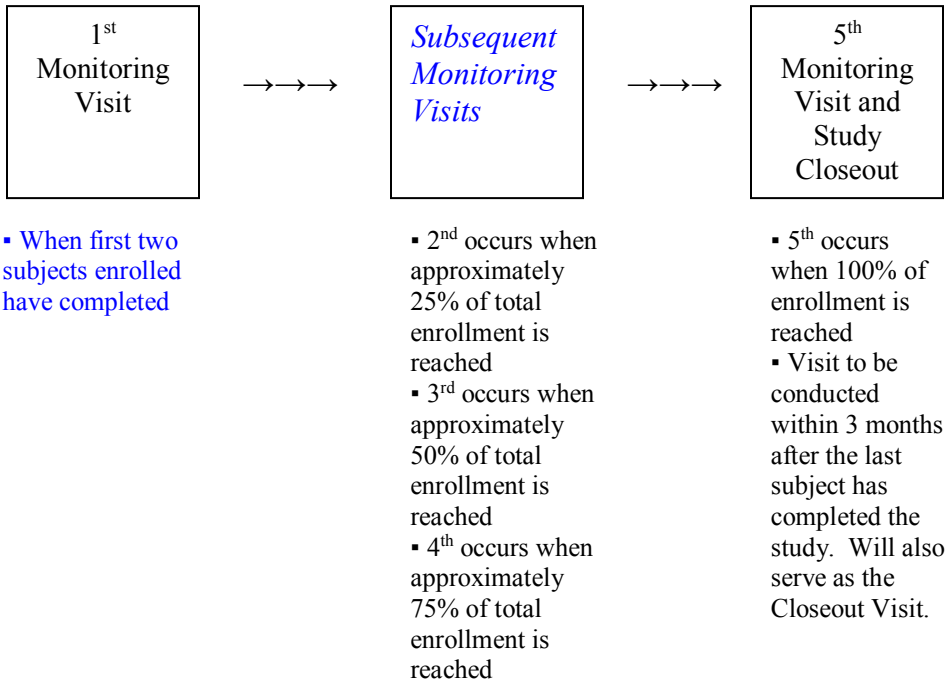
from the trial and the study team. A CV for the monitor will be obtained and updated annually. The CV will be kept on file in the Sponsor section of the Regulatory Binder to document the qualifications of the monitor. To train the independent Monitor, the Principal Investigator and the Research Coordinator actively overseeing this trial will schedule a monitoring training session to discuss the protocol, case report forms, the informed consent, and the monitoring plan. In addition a monitoring manual will be created, which includes the complete protocol with the approved informed consent form, approved CRF, and this monitoring plan.

Study Initiation

The Principal Investigator will be responsible for assuring through personal contact between the co-investigators, the monitor and the clinical staff that each clearly understands and accepts the obligations incurred in the undertaking of this clinical trial. The Principal Investigator will ensure that the clinical staff fully understand the nature of the protocol and the requirements for an adequate and well-controlled study; the obligation to conduct the clinical investigation in accordance with the applicable federal regulations; the obligation to obtain informed consent in accordance with 21 CFR Part 50; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated; and will ensure a continuing review of the study by the IRB in accordance with 21 CFR Part 56. A check list containing the elements of study initiation as described in the CFR and ICH GCPs will be completed by the study staff prior to the first the monitoring visit and placed in the Sponsor section of the Regulatory Binder.

Monitoring Visits

Monitoring Flow Diagram



Frequency

Enrollment will be complete when 200 subjects are enrolled into the trial. Enrollment for this study means when a participant is found to be eligible and is started on the study medication. Approximately 4 subjects will be enrolled per month. After the study initiation visit, further monitoring visits will be conducted periodically throughout the study as described below. (Note: The specific data to be reviewed at each visit is indicated in section 7.3.2)

- The first independent monitoring visit will occur when the first two subjects have completed the study.
- The second independent monitoring visit will occur when 25% of the subjects have been enrolled.
- A third independent monitoring visit will be conducted when approximately 50% of the subjects have been enrolled.
- A fourth independent monitoring visit will be conducted after 100% of the subjects have been enrolled. This visit may be conducted after the subjects have completed the study and can also serve as the close-out monitoring visit (as required by GCPs and described in section 7.6).

Data Review for Moderate Risk Study

The monitor will complete:

- The **Compliance Assessment Checklist,** developed by the University of Pennsylvania Office of Human Resources, will be used for monitoring the Regulatory Binders.
- The monitor will also ensure that the CRFs are being completed and finalized in the DMU in a timely manner.

All CRFs for the first 2 subjects will be 100% source data verified.

In addition, the CRF for one in every cohort of 5 subjects will be 100% source data verified.

If a greater than 10% error rate is noted during the data review, the monitor will source data verify 100% of the data on a larger sample at the following two monitoring visits.

Additional subjects/events to be reviewed**:**

a. All subjects who are discontinued from the protocol due to adverse events will be reviewed for key safety and efficacy data.
b. All subjects who are discontinued because they are “lost to follow-up” or for “other” reasons, their data will be reviewed for 100% source data verification.

The following variables will be 100% source data verified for *all* subjects enrolled in the study.

- Screening Consent (if applicable)
- Informed Consent
- Inclusion/Exclusion Criteria
- Drug Accountability
- Serious and Non-Serious Adverse Events
- Prohibited concomitant medications

Regulatory Documents Reviewed

The Regulatory Documents will be maintained in the Regulatory Binder. The Regulatory Binder will be reviewed by the monitor in an ongoing manner at the time of each monitoring visit. The monitor will review the regulatory binder for completeness and will assure that the CRFs are being completed in a timely manner.

Documentation of the Monitoring Visit

Monitoring Log

The monitor is required to sign and date the monitoring log documenting the dates of the monitoring visit. The Monitoring Log will be filed in the Regulatory Binder.

Monitoring Report

All monitoring visits will be documented on the Monitor's Report and Visit Checklist. The original report for each visit will be filed in the Sponsor section of the Regulatory Binder.

Close Out Visit

The monitor will conduct the Close Out Visit at the time of the third monitoring visit and within 3 months after the last patient has completed the study.

The following activities will be completed by the monitor to close out the study:

- Ensure all data has been reviewed and collected;
- Ensure all outstanding queries are answered;
- Confirm all Serious Adverse Events, MedWatch Reports and IND Safety Reports, if applicable, have been reported to the IRB(s), NIDA, DSMB and FDA (if applicable);
- Review the Regulatory documentation and Subject Files for completeness and compliance with GCP and all applicable federal regulations;
- Ensure initial and revised 1572 forms were submitted to the IRB (if applicable);
- Ensure all protocol violations were submitted to the IRB;
- Ensure that all continuing review reports were submitted to the IRB;
- Perform drug accountability and destroy any unused drug and
- Review requirements for record retention with the investigator and the clinical staff.

Compliance Monitoring Review

Good Clinical Practice oversight monitoring is conducted for randomly selected studies by the Office of Human Research (such as Informed Consent Monitoring or Monitoring Plan implementation). In addition, studies may be randomly selected and reviewed by other designated offices in the School of Medicine for compliance aspects.

Medical Monitoring

Patient safety will be monitored continuously by the Principal Investigator or the designated, qualified Medical Monitor. Additionally, the DSMB, as noted below, will provide guidance and input on an annual or as-needed basis. The Principal Investigator has the front-line responsibility for identifying potential adverse events experienced by study participants, adjusting the intervention accordingly and reporting the experience. The Sponsor/Investigator is responsible for tracking these reports and relaying them as required to the FDA, IRBs and other investigators.

The potential risks of this study include adverse reactions to varenicline, potential adverse interactions between varenicline and cocaine and the small risk incurred by venipuncture. In prior research with varenicline for cocaine dependence conducted here and elsewhere there have been no reported SAEs from varenicline, and the side effects have not required withdrawal of therapy; thus, preliminary data suggest minimal potential risk of varenicline treatment for cocaine dependent subjects. Subjects are asked about AEs at each study visit. Any reported AEs are assessed by the Nurse Practitioner or Study Doctor and followed until resolution.

Data Safety Monitoring Board (DSMB)

Members and Affiliation

A safety monitoring board has been established at the Center for the Studies of Addiction with the following purpose (according to NIDA guidelines): to assure that the safety of study subjects is protected while the scientific goals of the ongoing studies are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies either when significant benefits or risks have been uncovered or when it appears that a clinical trial cannot be concluded successfully. The DSMB consists of:

- David Oslin, M.D., chair, a faculty member within the Department of Psychiatry at the University of Pennsylvania.
- Kevin Lynch, Ph.D. (senior statistician),
- David Metzger, Ph.D. and
- Daniel Weintraub, M.D., who are faculty members of the University of Pennsylvania School of Medicine, Department of Psychiatry,
- Deb Dunbar, MSN, CRNP and
- Cynthia Clark, PhD, MSN, CRNP, who are medical professionals for the University of Pennsylvania Center for Studies of Addiction.

Frequency of the DSMB

This study will be reviewed by the DSMB on an annual basis (unless more frequent meetings are deemed necessary). Safety data will be reviewed annually by the Data Safety Monitoring Board. A Data Safety Monitoring Board report will be issued to the NIDA project officer with the annual progress report.

Conflicts of Interest

All board members meet NIDA requirements regarding background and experience, and none will have ethical conflicts, including financial interest related to study outcome. Individuals invited to serve on the board disclose any potential conflicts in writing.

Protection of confidentiality

The DSMB is changed with the same confidentiality requirements as all other personnel involved in the study conduct.

Monitoring activities (initial and ongoing study review)

The DSMB reviews the study prior to study start, and again annually at DSMB meetings.

Content of the DSMB Report

An annual data safety monitoring report will be submitted to the NIDA project officer and will include, but may not be limited to, a synopsis of the trial, socio-demographic characteristics of subjects accrued, retention and disposition of subjects, quality assurance issues regulatory issues, and reports of AEs/SAEs.

When the current study is reviewed, the meeting will open with a report on the trial status, followed by a closed session under the direction of Dr. Oslin. Issues related to recruitment, subject safety and efficacy, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues) are assessed. Following each DSMB meeting, Dr. Oslin will make recommendations, and a final report (edited by all Board members) will be prepared and submitted to the NIDA PO, the Penn IRB, and (if required) the FDA according to each bodies reporting requirements.

Drug Accountability

Study drug for this trial consists of 2.0 mg of varenicline and matching placebo. Study drug will be supplied by Pfizer or purchased and will be stored at the University of Pennsylvania's Investigational Drug Services located at 3600 Spruce Street, ground floor of the Maloney Building, Philadelphia Pa 19104. The study drug needed for patient visits will be picked up on a weekly basis from the IDS. All used and unused blister packs will be returned to the IDS upon completion of the study. Once the monitoring of final drug accountability has taken place, all unused medication will returned to Pfizer or destroyed. The monitor will perform 100% drug accountability in an ongoing manner at the time of each monitoring visit. The monitor will confirm the receipt, use and return of drug.

Trial Efficacy

Efficacy analyses will be conducted at the trial end. There are no plans for interim analyses.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents,

data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment 1 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

The National Institute on Drug Abuse is funding this protocol.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

Subjects will be financially compensated for travel and completing assessments. They will receive $5 for each visit for visits 1-3 ($15 total), a maximum of 438 voucher draws for attendance for visits 4-39 and $25.00 for visit 28. In addition, they will receive $5.00 for each medication pack they return. Maximum total compensation available for study participation is $900: $60 for

compliance, $15 for visits 1-3, $25 for final visit, and a maximum of $800 for attendance, prorated if the subject discontinues treatment or the study ends earlier than planned. Because compensation is based on fishbowl draws, the average payment earned will be closer to $300. Subjects will receive a maximum of $162 for travel in payments of $2 (last visit) or $4.

The schedule of voucher draws for attendance is shown in Table 2 below.

Table2

Attendance Voucher Draw Schedule

Week	1			2			3			4			5			6			7		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Draws				5	5	5	6	6	6	7	7	7	8	8	8	9	9	9	10	10	10
Bonus						5			5			5			5			5			5
Total Draws				5	5	10	6	6	11	7	7	12	8	8	13	9	9	14	10	10	15

Week	8			9			10			11			12			13			14		
Visit	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40		
Draws	11	11	11	12	12	12	13	13	13	14	14	14	15	15	15	16	16	16			
Bonus			5			5			5			5			5			5			
Total Draws	11	11	16	12	12	17	13	13	18	14	14	19	15	15	20	16	16	21			

Total Draws: 438

The fishbowl will be filled with the following tokens as shown in Table 3 below:

Number of tokens	Value
1	$50
2	$25
30	$5
267	$1
200	"Good job"

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 Reference

Appel, P. W., Hoffman, J. H., Blane, H. T., Frank, B., Oldak, R. and Burke, M., 2001. Comparison of self-report and hair analysis in detecting cocaine use in a homeless/transient sample. Journal of Psychoactive Drugs, 33, 47-55.

Arinami, T., et al., A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Human Molecular Genetics., 1997. 6: p. 577 - 582.

Berrettini, W., et al., Human mu opioid receptor gene polymorphisms and vulnerability to substance abuse. Addiction Biology, 1997. 2: p. 303 - 308.

Carroll, K.M., Rounsaville, B.J., Gawin, F.H. (1991): A comparative trial of psychotherapies for ambulatory cocaine abusers: relapse prevention and interpersonal psychotherapy. Am. J. Drug and alcohol Abuse. 17: 229-247.

Carroll, K., Rounsaville, B.J., Gordon, L.T., Nich, C., Jatlow, P., Bisighini, R.M., Gawin, F.H. (1994): Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. Archives of General Psychiatry. 51: 177-187.

Center for Disease Control (CDC). (1986): Prevention and Control of Influenza. MMWR-Morbidity and Mortality Weekly Report. 35:317-326.

Cichon, S., et al., Detection of four polymorphic sites in the human dopamine D1 receptor gene (DRD1). Human Molecular Genetics, 1994. 3: p. 209.

Cone, E. J. and Dickerson, S. L., 1992. Efficacy of urinalysis in monitoring heroin and cocaine abuse patterns: implications in clinical trials for treatment of drug dependence. In (Ed, Jain, R. B.) Statistical Issues in Clinical Trials for Treatment of Opiate Dependence. US Department of Health and Human Services, Rockville MD, pp. 46-57.

Derogatis, L.R. (1977): SCL 90, Administration, scoring and procedures. Manual of Cliical Psychometrics research.

Diggle, P. J. and Kenward, M. G., 1994. Informative dropout in longitudinal data analysis (with Discussion). Applied Statistics, 43, 43-93.

Ehrman, R.N., Robbins, S.J., Childress, A.R., O'Brien, C.P. (1992); Conditioned responses to cocaine -related stimuli in cocaine abuse patients. Psychopharmacology. 107: 523-529.

First,M.B., Spitzer, R.L., Gibbon, M, Williams,J.B.W. Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, Version 2.0). Biometrics Research Department New York State Psychiatric Institute. New York, New York 10032.

Gelernter, J., H. Kranzler, and J. Cubells, Genetics of two mu opioid receptor gene (OPRM1) exon 1 polymorphisms: population studies, and allele frequencies in alcohol- and drug-dependent subjects. Molecular Psychiatry, 1999. 4: p. 476 - 483.Gonzales, D., Rennard, S.I., Nides, M., Oncken, C., et al. (2006). Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release buproprion and placebo for smoking cessation. JAMA. 296(1): 47-55.

Guy, W. (Ed.) (1976) Assessment Manual for Psychopharmacology: Publication ADM 76-338., US Department of Health Education and Welfare, Washington, DC.

Halikas, J. A., Kuhn, K. L., Crosby, R., Carlson, G. and Crea, F., 1991. The measurement of craving in cocaine patients using the Minnesota Cocaine Craving Scale. Comprehensive Psychiatry, 32, 22-27.

Hamilton, M. (1967): Development of a rating scale for primary depressive illness. British Hournal of Social and clinical Psychology. 6: 278-296.

Hauk, W. W., Anderson, S. and Marcus, S. M., 1998. Should we adjust for covariatesin nonlinear regression analyses of randomized trials? Controlled Clinical Trials, 19, 249-256.

Hedeker, D., Gibbons, R. D. and Waternaux, C., 1999. Sample size estimation for longitudinal designs with attrition: comparing time-related contrasts between two groups. Journal of Educational and Behavioral Statistics, 24, 70-93.

Hedeker, D. and Mermelstein, R., 2000. Analysis of longitudinal substance use outcomes using ordinal random-effects regression models. Addiction, 95, S381-S394.

Hser, Y., 1997. Self-reported drug use: results of selected empirical investigations of validity. In (Eds, Harrison, L. and Hughes, A.) The Validity of Self-reported Drug Use: Improving the Accuracy of Survey Estimates. US Department of Health and Human Services, Rockville, MD, pp. 320-343.

Hser, Y. I., Maglione, M. and Boyle, K., 1999. Validity of Self-report of drug use among STD patients, ER patients, and arrestees. American Journal on Drug and Alcohol Abuse, 25, 81-91.

Jenkinson, C., Wright, L., Coulter, A, 1994. Criterion validity and reliability of the SF-36 in a population sample. Quality of Life Research, 3**,** 7-12.

Johnson, B.A. (2006). New weapons to curb smoking: No mor excuses to delay treatment. Archives of Internal Medicine. 166: 1547-1550.

Jufer, R. A., Wstadik, A., Walsh, S. L., Levine, B. S. and Cone, E. J., 2000. Elimination of cocaine and metabolites in plasma, saliva, and urine following repeated oral administration to human volunteers. Journal of Analytical Toxicology, 24, 467-477.

Kadden, R., Carroll, K. M., Donovan, D., Cooney, N., Monti, P., Abrams, D., Litt, M. and Hester, R.,1992 Cognitive Behavioral Coping Skills Manual., U.S. Government Printing Office, Washington, DC.

Kampman, K.M., Leiderman, D., Holmes, T., LoCastro, J., Bloch, D.A. et al. (2005). Cocaine rapid efficacy screening trials (CREST): lessons learned. Addiction. 100 (suppl. 1): 102-110.

Kampman, K.M., Volpicelli, J.R., McGinnis, D.E., Alterman, A.I., Weinrieb, R.M., D'Angelo, L., Epperson, L.E. (1998a): Reliability and Validity of the cocaine selective severity assessment. Addictive Behaviors. 23: 449-461.

Kelley, A.E. (2002). Nicotinic receptors: Addiction's smoking gun? Nature Medicine 8(5): 447-449.

Kenward, M. G., 1998. Selection models for repeated measurements with non-random dropout: an illustration of sensitivity. Statistics in Medicine, 17, 2723-2732.

Koob, G. F., 1992. Neural mechanisms of drug reinforcement. Annals of the New York Academy of Sciences, 654, 171-191.

Lachman, H., et al., Human catechol-O-methyl transferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics, 1996. 6: 243 - 250.

Laird, N. M., 1988. Missing data in longitudinal studies. Statistics in Medicine, 7, 305-315.

Lahiri, D. and B. Schnabel, DNA isolation by a rapid method from human blood samples: effects of MgCl2, EDTA, storage time, and temperature on DNA yield and quality. Biochemical Genetics, 1993. 31: p. 321- 328.

Lannfelt, L., et al., Amino acid substitution in the dopamine D3 receptor as a useful polymorphism for investigating psychiatric disorders. Psychiatric Genetics, 1992. 2: p. 249 - 256.

Lichter, J., et al., A hypervariable segment in the human dopamine D4 receptor gene. Human Molecular Genetics., 1993. 2: p. 767 - 773.

Lipsitz, S. R., Fitzmaurice, G. M., Orav, E. J. and Laird, N. M., 1994. Performance of generalized estimating equations in practical situations. Biometrics, 50, 270-278.

McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., Argeriou, M. (1992): The Fifth Edition of the Addiction Severity Index. Journal of Substance Abuse Treatment. 9: 199-213.

McLellan, A.T., Alterman, A.I., Metzger, D.S., Grissom, G.R., Wooody, G.E., Luborsky, L., O'Brien, C.P. (1994): Similarity of outcome predictors across opiate, cocaine, and alcohol treatments: role of treatment services. Journal of Consulting Clinical Psychology. 62: 1141-1158.

Mihalak, K.B., Carroll, F.I., & Luetje, C.W. (2006).Varenicline is a partial agonist at α4β2 and a full agonist at α7 neuronal nicotinic receptors. Molecular Pharmacology. 70(3):801-5.

Morral, A. R., McCAffrey, D. and Iguchi, M. Y., 2000. Hardcore drug users claim to be occasional users: drug use frequency underreporting. Drug Alcohol Depend, 57, 193-202.

Nagelkerke, N., Fidler, V., Bernsen, R. and Borgdorff, M., 2000. Estimating treatment effects in randomized clinical trials in the presence of noncompliance. Statistics in Medicine, 19, 1849-1864.

Nestler, E., Molecular neurobiology of drug addiction. Neuropsychopharmacology, 1994. 11: p. 77 - 87.

Nides, M., Oncken, C., Gonzales, D., Rennard, S.I., et al. (2006). Smoking cessation with varenicline, a selective α4β2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and buproprion- controlled trail with 1-year follow-up. Archives of Internal Medicine. 166: 1561-1568.

Nordgren, J. C. (1995): Instruments for Assessing Depression in Adults in Handbook of Depression, Second Edition, Edited by E. Edward Beckham and William R. Leber, The Guilford Press, New York.

Oncken, C., Gonzales, D., Nides, M., Rennard, S., Watsky, E., et al. (2006). Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, fo smoking cessation. Archives of Internal Medicine. 166: 1571-1577.

Pan, W., 2001a. Model selection in estimating equations Biometrics, 57, 529-534.

Pan, W., 2001b. Sample size and power calculations with correlated binary data. Controlled Clinical Trials, 22, 211-227.

Pan, W. and Connett, J. E., 2002. Selecting the working correlation structure in generalized estimating equations with application to the Lung health Study. Statistica Sinica, 12, 475-490.

Panagis, G., Kastellakis, A., Spyraki, C. & Nomikos, G. (2000). Effects of methyllycaconitine (MLA), an α7 nicotine receptor antagonist, on nicotine- and cocaine-induced potentiation of barin stimulation reward. Psychopharmacology. 149: 388-396.

Preston, K. L., Epstein, D. H., Cone, E. J., Wtsadik, A. T., Huestis, M. A. and Moolchan, E. T., 2002. Urinary Excretion of cocaine metabolites in chronic cocaine users during cessation. Journal of Analytical Toxicology, 26, 393-400.

Preston, K., Silverman, K., Schuster, C. and Cone, E., 1997a. Assessment of cocaine use with quantitative urinalysis and estimation of new uses Addiction, 92, 717-727.

Preston, K. L., Silverman, K., Schuster, C. R. and Cone, E. J., 1997b. Comparison of self-reported drug use with quantitative and qualitative urinalysis for assessment of drug use in treatment In (Eds, Harrison, L. and Hiughes, A.) The Validity of Self-reported Drug Use: Improving

the Accuracy of Survey Estimates. Us Department of health and Human Services, Rockville MD, pp. 130-145.

Schoffelmeer, A.N.M., De Vries, T.J., Wardeh, G., van de Ven, H.W.M. & Vanderschuren, L.J.M.J. (2002). Psychostimulant-induced behavioral sensitization depends on nicotinic receptor activation. Journal of Neuroscience. 22(8); 3269-3276.

Sobell, L., Sobell, M. (1992): Timeline Follow Back: A technique for assessing self-reported alcohol consumption, in Measuring Alcohol consumnption, Allen, L.A., Editor. The Humana Press.

Sobell, L.C. Sobell,M.B. (1995) Alcohol Timeline Follow Back Users' Manual. Toronto, Canada: Addiction Research Foundation.

Sommer, S., J. Sobell, and L. Heston, A common exonic polymorphism in the human D5 dopamine receptor gene. Human Genetics, 1993. 96: p. 633 - 634.

Somoza, E., Dyrenforth, S., Goldsmith, J., Mezinskis, J., and Cohen, M. (1995): In search of a Universal Drug Craving Scale. Paper presented at the Annual Meeting of the American Psychiatric Association, May 20-25, , Miami, Florida.

Snider, E., Navaline, H., Petro, C., Tobin, D., Metzger, D., Alterman, A., Woody, G. (1994): An Automated Version of the Risk Assessment Battery (RAB): Reliability, Validity, and Patient Acceptance. NIDA Research Monograph 153.

Tabachnik, B. and Fidell, L. S., 2000 Using multivariate statistics., Allyn and Bacon, Boston.

Tiffany, S T., Singleton, E, Haertzen, C.A., Henningfield, J.E. (1993): The Development of a Cocaine Craving Questionnaire. Drug and Alcohol Dependence. 34: 19-28.

Tonstad, S., Tonnesen, P., Hajek, P., Williams, K.E., Billing, C.B. & Reeves, K.R. (2006). Effect of maintenance therapy with varenicline on smoking cessation. JAMA. 296(1): 64-70.

Vandenbergh, D., et al., Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics., 1992. 14: p. 1104 - 1106.

Wei, J., C. Ramchand, and G. Hemmings, Possible control of dopamine beta-dydroxylase via a codominant mechanism associated with the polymorphic GT repeat at its gene locus in healthy individuals. Human Genetics, 1997. 99: p. 52 - 55.

15 Attachments

1. Consent Form
2. Monitoring Plan
3. Study Procedures Flowchart/Table
4. Varenicline prescribing information