NIDA CTN Protocol: CTN-0046

Smoking-Cessation and Stimulant Treatment (S-CAST): Evaluation of the Impact of Concurrent Outpatient Smoking-Cessation and Stimulant Treatment on Stimulant-Dependence Outcomes

Version: 5.0
Date: October 12, 2011

CONTACT INFORMATION

Lead Investigator:	**Theresa Winhusen, Ph.D.** **Ohio Valley Node** **University of Cincinnati College of Medicine**
Co-Lead Investigator:	**Eugene Somoza, M.D., Ph.D.** **Ohio Valley Node** **University of Cincinnati College of Medicine**
CCTN Protocol Coordinators:	**Udi Ghitza, Ph.D. and Carmen Rosa, M.S.** **Center for the Clinical Trials Network (CCTN)** **National Institute on Drug Abuse**
Project Implementation Director:	**Frankie Kropp, M.S.** **Ohio Valley Node** **University of Cincinnati College of Medicine**

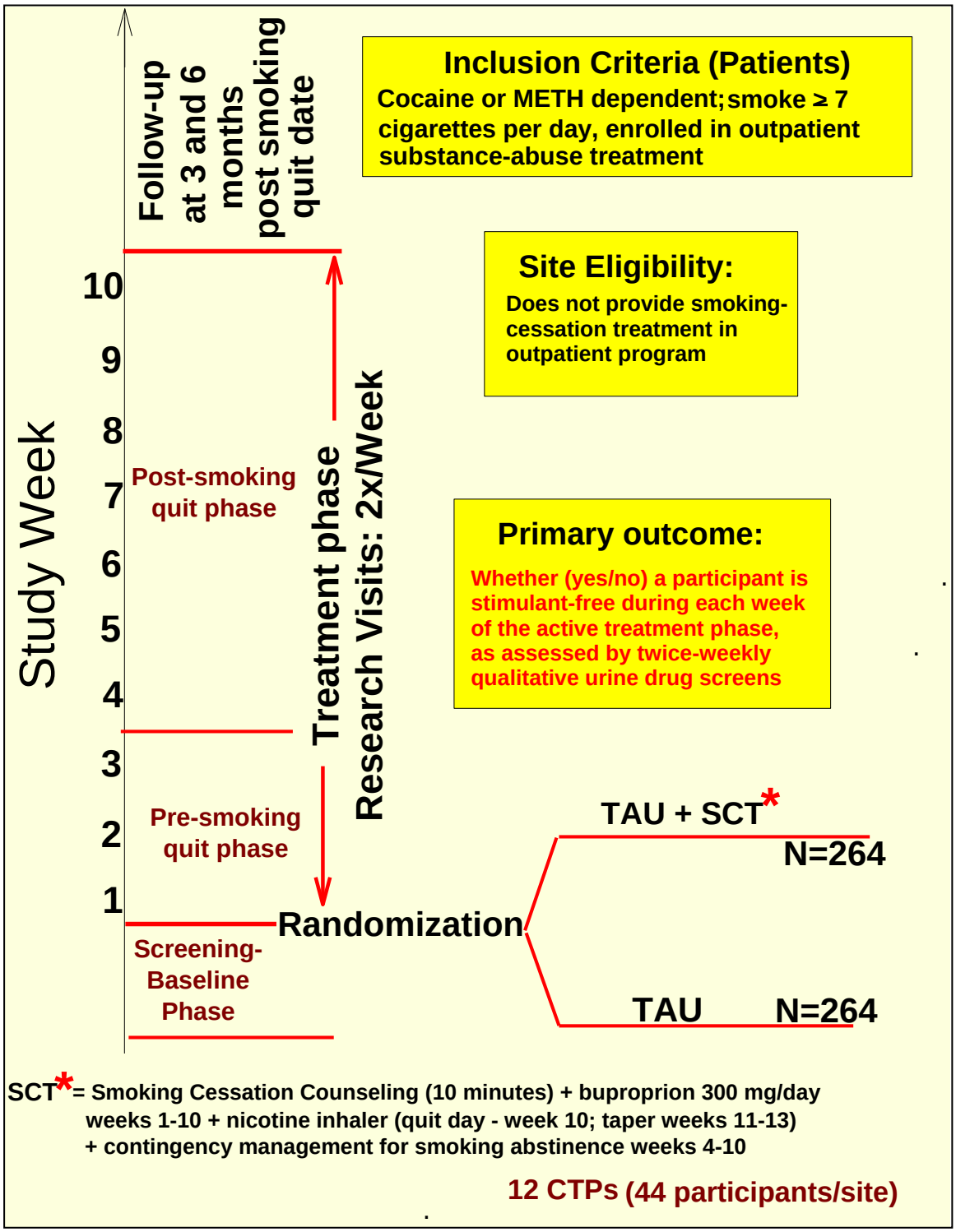
TABLE OF CONTENTS

1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BSCS	Brief Substance Craving Scale
CO	Carbon Monoxide
cpd	Cigarettes per day
CRF	Case report form
CDMC	Centralized Data Management Center
CCC	Clinical Coordinating Center
CTN	Clinical Trials Network
CTP	Community treatment program
CIDI	Composite International Diagnostic Interview
CM	Contingency management
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision
FTND	Fagerström Test for Nicotine Dependence
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
IRB	Institutional review board
ITT	Intent-to-Treat
LI	Lead Investigator
LN	Lead Node
MC	Medical Clinician
MSO	Medical safety officer
METH	Methamphetamine
NIDA	National Institute on Drug Abuse
QA	Quality Assurance
PI	Principal Investigator
PSQI	Pittsburgh Sleep Quality Index
RAB	Risk Assessment Battery
RA	Research assistant
SCT	Smoking-cessation Treatment
TLFB	Time-line follow-back
TOT	Training of Trainers
TAU	Treatment as Usual
UDS	Urine drug screen
USPHS	U.S. Public Health Service
XL	Extended-release

2.0 STUDY SCHEMA

Figure 1: Study Schema



3.0 STUDY SYNOPSIS

STUDY OBJECTIVES. The primary objective of this study is to evaluate the impact of substance-abuse treatment as usual plus smoking-cessation treatment (TAU+SCT), relative to substance-abuse treatment as usual (TAU), on drug-abuse outcomes. Specifically, this study will evaluate whether concurrent smoking-cessation treatment improves, worsens, or has no effect on stimulant-use outcomes in smokers who are in outpatient substance-abuse treatment for cocaine or methamphetamine dependence. Secondary objectives include evaluating: 1. the impact of TAU+SCT, relative to TAU, on other drug-abuse outcomes; 2. the efficacy of TAU+SCT, relative to TAU, in improving smoking outcomes; and 3. whether achieving complete smoking abstinence is associated with improved stimulant use outcomes.

STUDY DESIGN. This is a 10-week, intent-to-treat, 2-group randomized controlled trial with follow-up visits at 3 and 6 months post-smoking quit date. Eligible participants will be randomized to the TAU+SCT or TAU arm. Participants randomized to the TAU+SCT arm will have a target quit smoking day at the end of study week 3. Randomization strata include study site and baseline urine drug screen (UDS) results (stimulant-negative vs. positive).

STUDY POPULATION. Approximately 528 participants, recruited from approximately 12 community treatment programs (CTPs), will be randomized into the study. CTPs that do not provide smoking-cessation treatment in their outpatient programs are eligible to participate. Each CTP will enroll between approximately 15 and 100 participants, with a target of 44. The study population will include individuals who smoke at least 7 cigarettes per day, wish to stop smoking, meet DSM-IV-TR criteria for cocaine and/or methamphetamine dependence, and are enrolled in outpatient (including intensive outpatient) substance-abuse treatment. Participants meeting DSM-IV-TR criteria for current alcohol or sedative dependence will be excluded; participants receiving methadone or buprenorphine will be excluded.

TREATMENTS. Participants randomized to TAU will participate in treatment as typically provided by the CTP. Participants randomized to the TAU+SCT arm will receive individual smoking-cessation counseling consisting of approximately one ten-minute counseling session per week during study weeks 1 through 10. In addition, all TAU+SCT participants will receive extended-release (XL) bupropion (300 mg/day) and, during the post-quit treatment phase, nicotine inhaler (6-16 cartridges per day ad libitum). Finally, all TAU+SCT participants will receive contingency management in which drawings for prizes are given for smoking abstinence as assessed by carbon monoxide (CO) levels during the post-quit phase of the trial (i.e., weeks 4-10).

ASSESSMENTS. Drug-abuse outcomes include stimulant use as assessed by UDS results and self-report of stimulant use, other substance use as assessed by UDS and self-report of substance use (i.e., alcohol and/or illicit drugs), HIV risk behavior, and substance-abuse treatment attendance. Smoking-related efficacy assessments include continuous abstinence during study weeks 6-9, point prevalence abstinence, breath carbon monoxide (CO) levels, and cigarettes per day. Safety measures include vitals, adverse events (AEs), and mood measures.

PRIMARY ANALYSIS. The primary analysis will evaluate the impact of smoking treatment (i.e., TAU+SCT vs. TAU) on the percentage of participants who are stimulant-free, defined by the results of twice-weekly UDS results confirmed by self-report of no illicit stimulant use, during the weeks of the active treatment phase.

4.0 BACKGROUND AND RATIONALE

4.1 Background

Each year, cigarette smoking accounts for an estimated 438,000 deaths and $92 billion in productivity losses in the United States (Centers for Disease Control and Prevention, 2005). The prevalence of smoking in illicit drug abusers is 49 – 98%, a rate substantially higher than the 19.8% smoking prevalence in the general population (Schroeder, 2009). A link between cigarette smoking and non-nicotine stimulant abuse has been established in both clinical and laboratory studies. The results from clinical studies suggest that the rate of smoking in cocaine abusers is 75-80% (Budney et al., 1993; Sees and Clark, 1993; Gorelick et al., 1997) and that smoking cigarettes is associated with more severe addiction, including more frequent cocaine use, a greater likelihood of injecting or smoking cocaine, and more severe employment and legal difficulties (Roll et al., 1996). A recent outpatient study in methamphetamine (METH) dependent individuals reported that 65% of the participants were current cigarette smokers (Shoptaw et al., 2008b). Human laboratory studies have found that cocaine administration increases the rate of cigarette smoking (Nemeth-Coslett et al., 1986; Roll et al., 1997) and that mecamylamine, a nicotine antagonist, reduces cue-induced cocaine craving (Reid et al., 1999).

Despite the pervasiveness of smoking in cocaine/ METH abusers, and the deadly consequences of smoking in addicted individuals (Hurt et al., 1996), smoking-cessation treatment is typically not provided in community substance-abuse treatment programs. Failure to provide smoking-cessation treatment concurrently with substance-abuse treatment stems, in part, from concern that smoking cessation might impact negatively on non-nicotine substance use outcomes (Ziedonis et al., 2006). Prochaska et al. (2004) completed a meta-analysis of nine studies in which the impact of smoking-cessation treatment on non-nicotine drug/alcohol abstinence was assessed; the findings suggest that smoking-cessation treatment can actually improve substance use outcomes. However, it is important to note that the nine studies analyzed included mainly alcohol-dependent, and, to a lesser extent, methadone-maintained participants, and did not include outpatient cocaine/METH abusers and, thus, the impact of smoking-cessation treatment in this population was not addressed. A CTN study conducted by Reid et al. (2008) evaluated smoking-cessation treatment provided with outpatient substance-abuse treatment, relative to outpatient substance-abuse treatment alone, on smoking and non-nicotine substance use outcomes; the study found no significant treatment group difference on non-nicotine substance use outcomes including treatment retention and abstinence. The Reid et al. (2008) study sample was primarily comprised of methadone-maintained participants (80%) and, thus, the impact of smoking-cessation treatment on substance-abuse outcomes in cocaine/METH abusers was not addressed. One small smoking-cessation study (n=20; Wiseman et al., 2005) has been conducted in cocaine abusers in outpatient treatment but the investigators reported only on smoking outcomes, and, thus, the impact of the smoking intervention on non-nicotine substance-abuse outcomes was not addressed.

The present study will fill a gap in the research literature by evaluating the impact of substance-abuse treatment as usual plus smoking-cessation treatment (TAU+SCT), relative to substance-abuse treatment as usual (TAU), on drug-abuse outcomes in smokers who are in outpatient substance-abuse treatment for cocaine/METH dependence. The SCT utilized will follow the recommendations of the U.S. Public Health Service (USPHS) Clinical Practice Guideline (Fiore et al., 2008) by using a combination of effective pharmacologic and psychosocial approaches for smoking cessation. Specifically, bupropion extended-release (XL), nicotine inhaler, brief individual counseling, and contingency management (CM) will be used; the rationale for each treatment component is provided below.

4.2 Rationale for Selecting Bupropion Extended-Release (XL) and Nicotine Inhaler as the Study Medications

4.2.1 Safety and Efficacy of Bupropion

The USPHS Clinical Practice Guideline recommends that both effective pharmacologic and psychosocial approaches be used in smoking-cessation treatment (Fiore et al., 2008). The present trial will be conducted with cocaine/METH-dependent smokers and with study sites that may be relatively new to research and which may have relatively minimal medical services; consequently, the medication utilized for the present trial should be a treatment whose efficacy for smoking-cessation is established and which has a well known safety profile. Bupropion SR clearly meets both criteria. In terms of efficacy, bupropion SR is a first-line pharmacological treatment for smoking cessation with FDA approval for this indication (Fiore et al., 2008). For safety, bupropion SR has been subject to hundreds of clinical trials, as well as prescription use since 1996 and, thus, its safety profile is well known. Specifically, bupropion SR was originally approved by the FDA in 1996 for the treatment of depression and marketed under the trade name of Wellbutrin SR®. In 1997, buproprion SR was approved as a smoking-cessation treatment and marketed under the trade name Zyban®. In addition, buproprion SR has been evaluated as a treatment for adult ADHD (Reimherr et al., 2005) and, of particular import for the present trial, as a treatment for cocaine dependence (Margolin et al., 1995; Poling et al., 2006; Shoptaw et al., 2008a) and methamphetamine dependence (Elkashef et al., 2008; Shoptaw et al., 2008b) and, thus, its safety for use in stimulant-dependent populations has been evaluated.

Three randomized, placebo-controlled clinical trials have evaluated the safety and efficacy of bupropion SR in the treatment of cocaine dependence. A trial conducted by Margolin et al. (1995) did not find an overall beneficial effect for buproprion SR in reducing cocaine use in cocaine-dependent methadone-maintained participants but did find a significant medication effect for cocaine use in the subsample of participants who were depressed at baseline (i.e., Hamilton Depression Rating Scale>12). In this trial, there were no significant differences between placebo and bupropion SR in the number of participants discontinued from medication or with a medication dose reduction due to adverse events (AEs); the most commonly reported side-effect in the bupropion SR group was agitation (reported by 9.5% of participants). A second trial evaluating the efficacy of bupropion SR in reducing cocaine use in cocaine-dependent methadone-maintained participants found that bupropion SR significantly reduced cocaine use when combined with contingency management for clean urines but not when combined with vouchers given for providing urines regardless of whether they were "clean" for opiates/cocaine (Poling et al., 2006). The authors did not report any medication discontinuation for this trial and, thus, bupropion SR seems to have been well tolerated. A third trial evaluating bupropion SR for cocaine, conducted with individuals meeting DSM-IV criteria for cocaine abuse/dependence, found no significant medication effect on cocaine use (Shoptaw et al., 2008a). However, given the small sample size (N=70) and poor completion rate (19% in bupropion SR and 15% in placebo), this may represent a Type-II error. The safety data reported from this trial suggest that bupropion SR was well tolerated. Specifically, there were no serious AEs and the AEs for which significant group differences were reported were headache, which occurred more frequently in the bupropion SR participants, and body aches/pain, which occurred more frequently in the placebo participants (Shoptaw et al., 2008a).

Two randomized, placebo-controlled clinical trials have evaluated the safety and efficacy of bupropion SR in the treatment of methamphetamine dependence. A trial conducted by Elkashef et al. (2008) did not find an overall beneficial effect for buproprion SR in reducing methamphetamine use in methamphetamine-dependent participants but did find a significant medication effect in the subsample of participants with relatively low baseline methamphetamine use, most of whom were male. The safety assessments from this trial revealed that bupropion SR did not result in significant ECG or vital signs changes and that the AE rate

did not differ significantly between the bupropion SR and placebo groups (Elkashef et al., 2008). A second trial evaluating bupropion SR for methamphetamine dependence found no significant effect of bupropion SR on methamphetamine use in pre-planned analyses but did find a medication effect on methamphetamine use in the subsample of light methamphetamine users in post-hoc analyses (Shoptaw et al., 2008b). In this trial, 65% of the participants were smokers and bupropion SR, relative to placebo, significantly decreased the number of cigarettes per day despite smoking reduction not being a focus of the trial (Shoptaw et al., 2008b). The safety results from the trial suggest that bupropion SR was well tolerated, with no treatment group differences in the occurrence of AEs; the most common AEs reported were headache and nasal congestion/upper respiratory infection, which occurred at equal rates in the bupropion SR and placebo participants (Shoptaw et al., 2008b).

The prior bupropion SR clinical trials in stimulant abusing/dependent samples suggest that this medication will be generally well-tolerated by the present study sample. One concern associated with bupropion SR is the required twice-daily dosing, which might translate into problematic medication compliance. The bupropion SR trials discussed above utilized various measures of medication compliance but, overall, suggest that medication compliance has been good. In the Margolin et al. (1995) study, medication compliance, as assessed via six blood draws, revealed that only 2 of 74 (2.72%) participants had 3 blood draws with no detectable bupropion/ metabolite levels while 13 of 74 (17.56%) participants had at least one blood draw with no detectable levels. In the Poling et al. (2006) study, participants were given the morning bupropion SR dose at the clinic and compliance with taking the evening dose was not assessed. In the Shoptaw studies (2008a, 2008b), pill count was used to assess medication compliance. In the cocaine dependence trial, bupropion SR participants took approximately 79% of their medication doses compared to 75% compliance in the placebo participants (Shoptaw et al., 2008a). In the methamphetamine dependence trial, bupropion SR participants took approximately 85% of their medication doses compared to 92% compliance in the placebo participants (Shoptaw et al., 2008a). Finally, in the Elkashef et al. (2008) trial, medication compliance, assessed via pill count, revealed that participants in both groups took an average of 1.73, out of an expected 2.0, pills per day. However, there is evidence to suggest that compliance with taking extended-release bupropion (XL) is significantly better than compliance with taking bupropion SR (Stang et al., 2007) and the bioequivalence of bupropion XL and SR has been established. Consequently, bupropion XL will be utilized in the present trial.

4.2.2 Rationale for Selecting Nicotine Inhaler

Five forms of nicotine replacement therapy (NRT; gum, patch, nasal spray, inhaler, and lozenge) are FDA approved as smoking-cessation aids, with approval of the first NRT, nicotine gum, received in 1981. Past research with drug-abusing participants, typically methadone-maintained participants, suggests that NRT is not a particularly effective smoking cessation treatment for this population. Specifically, the smoking abstinence rates in methadone-maintained participants treated with the nicotine patch were reported as 8.5% for 3-month point-prevalence abstinence in a study by Stein et al. (2006), and as less than 20% during the active treatment phase in a study conducted by Shoptaw et al (2002). Moreover, in the CTN study conducted by Reid et al. (2008), which utilized the nicotine patch as the pharmacological treatment, smoking abstinence rates were 11% during the active treatment phase and approximately 5% at the 13- and 26-week follow-up visits. Consequently, NRT was not selected for use as a monotherapy for the present trial. However, data suggest that NRT used in combination with bupropion can significantly improve smoking cessation outcomes (Fiore et al., 2008). The nicotine inhaler, which consists of a mouthpiece and nicotine cartridges, is of interest in this regard in that a recent trial revealed significantly higher smoking abstinence rates in the buproprion SR plus nicotine inhaler condition relative to either bupropion SR or nicotine inhaler alone (Croghan et al., 2007). The good side-effect and tolerability profile of NRT (Fiore et al., 2008), combined with the results of the recent bupropion SR plus nicotine inhaler trial (Croghan et al., 2007), led to the decision to utilize the nicotine inhaler in the present trial.

4.2.3 Rationale for Not Selecting Varenicline

Varenicline, a partial agonist for the α4β2 nicotinic acetylcholine receptor, has been FDA approved for smoking cessation treatment since 2006. There is evidence to suggest that varenicline may be a more effective smoking cessation treatment than bupropion SR (Gonzales et al., 2006; Jorenby et al., 2006), which makes it an attractive candidate for the present trial. However, post-marketing research suggests that varenicline can be associated with significant psychiatric adverse events, including suicidal behavior (Kuehn, 2009). Moreover, an outpatient trial of varenicline with stimulant-dependent smokers has yet to be completed and, thus, the safety issues associated with the use of varenicline in this population have yet to be delineated. As noted above, the present trial will be conducted with study sites that may be relatively new to research and which may have relatively minimal medical services. Consequently, the lack of safety data for varenicline in the stimulant-dependent population makes it a poor candidate for the present trial from a safety perspective.

4.3 Rationale for Smoking-cessation Counseling – Smoke Free and Living It©

The USPHS Clinical Practice Guideline recommends that both effective pharmacologic and psychosocial approaches be used in smoking-cessation treatment (Fiore et al., 2008). In considering smoking-cessation counseling approaches for use in outpatient substance-abuse treatment, the results of a CTN smoking-cessation trial conducted with individuals in outpatient substance-abuse treatment suggest that the use of a group treatment could be associated with poor treatment attendance and could make study recruitment infeasible (Reid et al., 2008). Smoke Free and Living It©, a brief, individualized smoking-cessation counseling program designed to provide education, problem-solving skills, and social support, was developed by the Mayo Clinic Nicotine Research Program for use in clinical trials. This program was used successfully in a prior CTN smoking-cessation trial, CTN-0029 (*A pilot study of osmotic-release methylphenidate in initiating and maintaining abstinence in smokers with attention deficit hyperactivity disorder*). Specifically, the interventionists trained to implement this counseling program demonstrated a high level of treatment adherence during the course of the trial (95.7%) and the study participants were highly compliant with the treatment, attending an average of 9.3 (SD=2.8) of 11 possible sessions. In addition, the counselors' rating of participant compliance with the treatment, based on the participants' completion of homework assignments and session participation, was an average of 4.1 (SD=0.7) of a possible maximum of 5.0.

4.4 Rationale for Contingency Management Intervention

Contingency management (CM), in which clients receive some form of reward contingent upon a desired behavior, such as providing drug-free urines, attending treatment, or taking medication, is one of the most effective psychosocial treatments for substance use disorders (Dutra et al., 2008). In a meta-analytic evaluation of the effectiveness of CM for tobacco use, 11 studies were included in the analysis, which yielded an estimated effect size of d=.31 (Prendergast et al., 2006); this is considered to be a medium effect size (Cohen et al., 1988). One of the 11 studies evaluated the effectiveness of CM for smoking cessation in illicit drug users; this study, completed by Shoptaw et al. (2002) in methadone-maintained participants, found that contingency management nearly doubled the smoking abstinence rate during the active treatment phase although this advantage was not maintained at the 6- and 12-month follow-up visits (Shoptaw et al., 2002). More recently, a small study (n=20) evaluating the efficacy of CM in reducing carbon monoxide (CO) levels to ≤8 ppm in cocaine-abusing smokers in outpatient treatment found a significantly greater CO reduction in the contingent, relative to the non-contingent, groups (Wiseman et al., 2005). In the present trial, CM, which should serve to significantly increase smoking abstinence during the active treatment phase, is

being used in conjunction with bupropion XL+ nicotine inhaler and smoking-cessation counseling, which are effective in increasing long-term smoking abstinence.

5.0 STUDY OBJECTIVES

5.1 Primary Objective

1. To evaluate the initial impact of TAU+SCT, relative to TAU, on stimulant use outcomes in cocaine/METH-dependent individuals in outpatient substance-abuse treatment.

5.2 Secondary Objectives

1. To evaluate the longer-term impact (through 6-month follow-up) of TAU+SCT, relative to TAU, on stimulant use outcomes in cocaine/METH-dependent individuals in outpatient substance-abuse treatment.

2. To evaluate the initial impact of TAU+SCT, relative to TAU, on other drug-abuse outcomes in cocaine/METH-dependent individuals in outpatient substance-abuse treatment.

3. To evaluate the longer-term impact (through 6-month follow-up) of TAU+SCT, relative to TAU, on other drug-abuse outcomes in cocaine/METH-dependent individuals in outpatient substance-abuse treatment.

4. To evaluate the initial efficacy of TAU+SCT, relative to TAU, in improving smoking outcomes in cocaine/METH-dependent individuals in outpatient substance-abuse treatment.

5. To evaluate the longer-term efficacy (through 6-month follow-up) of TAU+SCT, relative to TAU, in improving smoking outcomes in cocaine/METH-dependent individuals in outpatient substance-abuse treatment.

6. To evaluate whether achieving continuous smoking abstinence during study weeks 6-9 is associated with improved stimulant use outcomes in cocaine/METH-dependent individuals in outpatient substance-abuse treatment.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a 10-week, intent-to-treat, 2-group randomized controlled trial with follow-up visits at 3 and 6 months post-smoking quit date. As noted above, the present study will address a significant gap in the research literature by evaluating the impact of concurrent smoking-cessation treatment and substance-abuse treatment in stimulant-dependent individuals. Eligible participants will be randomized to the TAU+SCT or TAU arms. Participants randomized to the TAU+SCT arm will have a target quit smoking day at the end of study week 3. The primary outcome measure is whether (yes/no) a participant is stimulant-free during each week of the active treatment phase, as assessed by twice-weekly qualitative UDS (see section 6.5.1 for details). Secondary outcomes include drug-free UDS results, self-report of drug/alcohol use, substance-abuse treatment attendance, HIV risk behavior, point-prevalence abstinence for smoking, continuous abstinence for smoking during study weeks 6-9, breath carbon monoxide (CO) levels, and cigarettes per day (cpd). Safety measures will include vital signs, adverse events (AEs), and mood measures.

6.2 Number of Sites and Participants

Approximately 528 participants will be randomized into this study. Approximately 12 sites will participate, with each site enrolling between approximately 15 and 100 participants, with a target of 44. Patients who are entering/in substance abuse treatment at the participating sites, smoke, and are likely to meet DSM-IV-TR criteria for cocaine/METH dependence and other study requirements will be recruited for the study. Participants may be recruited from a variety of other sources as well, including advertising. Recruitment advertisements will be approved by the site's Institutional Review Board (IRB). An attempt will be made to randomize approximately 50% female participants. In addition, efforts will be made to recruit a study sample that reflects, or exceeds, the proportion of minorities in the community where the site is located. Recruitment of a sample with adequate representation of particular racial/ethnic groups and of women should be readily attainable given the typical racial/ethnic and gender composition of stimulant-dependent individuals entering treatment. For example, in an on-going CTN trial with stimulant abusers, of the first 190 participants randomized, approximately 51% were female, 5% were Hispanic, 44% were Caucasian and 41% were African-American.

6.3 Study Implementation

6.3.1 Staged Implementation

This study will be implemented in two stages. The first stage will consist of initiating the study at approximately six sites. Initiating the trial in a subset of sites will allow an evaluation of study feasibility and study procedures prior to full-scale implementation. For example, we are assuming that the randomization rate per site will be approximately 2.5 participants per month. If the experience with the initial six sites indicates that this assumption is optimistic, then the protocol will need to be adjusted (e.g., increasing the number of sites or extending the recruitment period). It is estimated that the first stage will entail approximately six months of randomization at the sites initiated in stage one. In stage two, the remaining study sites will be initiated.

6.3.2 Study Duration

Once all sites are initiated, enrollment is expected to take place over a period of approximately 15 months.

6.4 Site and Participant Selection

6.4.1 Site Selection

6.4.1.1 Site Characteristics

Participating sites should:

1. have access to a medical clinician (e.g., R.N., P.A., M.D., etc.; the degree and licensing requirements depend on the regulations of the state in which the site is located), to perform medical assessments (e.g., medical history, concomitant medications, etc.) to determine participant eligibility, to regulate the medication dose appropriately, and to advise about possible untoward interactions between the study medications and other medications the study participant may be taking

2. have access to, or the ability to contract with, a pharmacy/pharmacist (or other appropriately qualified entity based on local/state regulations) to store/dispense study medications

3. be able to provide after-hours clinical back-up for study-related emergencies

4. have access to, or the ability to contract with, a phlebotomist or other appropriate professional, to complete blood draws

Participating sites should not:

1. provide smoking-cessation treatment as part of the outpatient (including intensive outpatient) treatment program from which study participants would be recruited; programs that only provide information about smoking cessation and referrals, but do not provide treatment with counseling and/or pharmacological interventions, are eligible to participate.

6.4.1.2 Rationale for Site Selection

The site eligibility criteria outlined in section 6.4.1.1 consist of the minimal staffing that is required in order to safely and effectively conduct a medication trial. Since the design of the present trial requires a treatment as usual group in which smoking-cessation treatment is not provided, sites that provide smoking-cessation treatment in outpatient programming as described above are not eligible for participation.

6.4.2 Participant Selection

6.4.2.1 Inclusion Criteria

Potential participants must:

1. be 18 years of age or older

2. be able to understand the study, and having understood, provide written informed consent in English

3. meet DSM-IV-TR diagnostic criteria for current (within the last 12 months) dependence for cocaine or methamphetamine

4. have smoked cigarettes for at least 3 months, currently smoking $\geq$ 7 cigarettes/day, and have a measured exhaled CO level > 8 ppm

5. have an interest in quitting smoking and a willingness to comply with all study procedures and medication instructions

6. be enrolled in outpatient/intensive outpatient treatment at a participating CTP and scheduled to attend at least one treatment session per week for at least 10 weeks after randomization

7. if female and of child bearing potential, agree to use one of the following methods of birth control:
    - oral contraceptives
    - contraceptive patch
    - barrier (diaphragm or condom)
    - intrauterine contraceptive system
    - levonorgestrel implant
    - medroxyprogesterone acetate contraceptive injection
    - complete abstinence from sexual intercourse
    - hormonal vaginal contraceptive ring

6.4.2.2 Exclusion Criteria

Potential participants must not:

1. meet DSM-IV-TR diagnostic criteria for current (within the past month) dependence for alcohol or sedatives or have a physiological dependence on alcohol or sedatives requiring medical detoxification

2. have an Axis-I psychiatric condition that, in the judgment of the study medical clinician (MC), would make study participation unsafe or which would make treatment compliance difficult

3. meet DSM-IV-TR criteria for current (within the last 12 months) bipolar disorder or current (within the last 12 months) or lifetime anorexia nervosa or bulimia

4. be seeking/receiving treatment for opiate-agonist replacement therapy (e.g., methadone, buprenorphine), naltrexone, or for detoxification only

5. have a history of a seizure disorder

6. have experienced a closed head trauma with >30 minutes loss of consciousness within the past 12 months

7. have a potentially life-threatening or progressive medical illness other than addiction that may compromise participant safety or study conduct including, but not limited to:
    - uncontrolled hypertension (i.e., blood pressure readings ≥ 140/90 on two clinic visits; Chobanian et al. 2003),
    - known coronary artery disease including myocardial infarction or angina, or an EKG with significant conduction abnormality
    - AIDS according to the current CDC criteria for AIDS
    - liver function tests greater than 3X upper limit of normal
    - serum creatinine greater than 2 mg/dL
    - diabetes treated with hypoglycaemics or insulin

8. use/have used other smoking-cessation counseling programs or medication treatments currently, or within the last 30 days

9. have a known or suspected hypersensitivity to bupropion, nicotine, or menthol (the nicotine inhaler contains menthol)

10. be pregnant or breastfeeding

11. have used any of the following medications within 14 days of randomization: monoamine oxidase (MAO) inhibitors, antimalarials, tramadol, theophylline, systemic steroids, quinolones, bupropion, any investigational drug, or any drug with known potential for toxicity to a major organ system (e.g., isoniazid, methotrexate) and/or have used sedating antihistamines within 7 days of randomization.

12. be taking any medications which, in the judgment of the study medical clinician (MC), may produce interactions with bupropion XL that are sufficiently dangerous so as to exclude the patient from participating in the study. Alternatively, the MC, with consultation with the patient and his or her

physician, may elect to withdraw the patient from the problem medications before randomization. Some of the possible interactions are discussed in section 8.8.

13. be anyone who, in the judgment of the investigator, would not be expected to complete the study protocol (e.g., due to relocation from the clinic area, probable incarceration, etc.)

14. have used electronic cigarettes or tobacco products, other than cigarettes, in the week before consent

15. be a significant suicidal/homicidal risk

16. be seeking and likely to enter residential/inpatient treatment within 10 weeks

17. have all stimulant-positive UDS results during screening/baseline

6.4.2.3 Rationale for Eligibility Criteria

The rationale for each inclusion and exclusion criterion is provided in Table 1.

Table 1: Rationale for Study Eligibility Criteria

Criterion#	Criterion Description	Criterion Rationale
I1	18 years of age or older	Definition of Study Sample (adults)
I2	Understand study/give consent	GCP Requirement
I3	DSM-IV-TR Diagnosis of cocaine/METH dependence	Definition of Study Sample (Cocaine/ METH dependent)
I4	Smoking requirements	Definition of Study Sample (Smoker)
I5	Wants to quit smoking, willing to comply with study procedures	To help ensure that the participant will provide useful data
I6	Enrolled in outpatient/intensive outpatient treatment	Required by study design (i.e., for TAU)
I7	Agree to birth-control	Safety of bupropion during pregnancy has not been established
E1	Meet DSM-IV-TR criteria for alcohol/sedatives, need for medical detoxification	Safety – excess use of alcohol/sedatives increases risk of seizures; bupropion contraindicated in abrupt withdrawal from alcohol/sedatives
E2	Psychiatric condition making participation unsafe/difficult	Safety
E3	Meet DSM-IV-TR criteria for bipolar, anorexia, bulimia	Safety-bupropion can trigger mania in bipolar disorder, increase risk of seizure in anorexia/bulimia
E4	Seek/receive treatment – opiate agonist, naltrexone, detox	Study Definition (outpatient stimulant dependence treatment)
E5	Seizure disorder	Safety–bupropion can increase seizure risk
E6	History of closed head trauma	Safety – can increase seizure risk
E7	Life-threatening or progressive illness	Safety
E8	Use of other smoking-cessation	Will interfere with the study objectives

Criterion#	Criterion Description	Criterion Rationale
	treatments	
E9	Hypersensitivity to bupropion, nicotine, menthol	Safety
E10	Pregnancy or lactation	Safety of bupropion during pregnancy not established; bupropion and metabolites expressed in human breast milk
E11	Listed medications within 14/7 days of randomization	Safety – medications listed either contraindicated or can increase the risk of seizure when used with bupropion
E12	Taking medications with possible interactions with bupropion	Safety
E13	Unlikely to complete the study	To help ensure that the participant will provide useful data
E14	Use tobacco products other than cigarettes	Would interfere with study objectives
E15	Significant Suicide/Homicide risk	Safety
E16	Seek treatment for residential/inpt	Study Definition (outpatient stimulant dependence treatment)
E17	All stimulant-positive UDS results	Heavy users unlikely to complete study

6.5 Outcome Measures

6.5.1 Primary Outcome Measure – Stimulant-free Weeks

The primary outcome measure is whether (yes/no) a participant is stimulant-free during each week of the active treatment phase, as assessed by qualitative urine drug screen (UDS). At the group level, this outcome translates into the percentage of participants in each study arm who are stimulant-free during each week of the active treatment phase. This outcome was selected as primary since it is an objective measure of a critical stimulant-dependence outcome: stimulant use. During the active treatment phase, participants ideally will be scheduled to provide two urine samples per week on nonconsecutive days. A rapid UDS system that screens for drugs of abuse including cocaine, methamphetamine, amphetamine, opioids, benzodiazepines, and marijuana will be used to analyze the urine samples. Urine samples will be collected using temperature monitoring and the validity of urine samples will be checked with the use of a commercially available adulterant test. In cases where the temperature reading/adulterant test indicates a non-valid sample, an attempt will be made to obtain a second urine sample. The strategies that will be employed for handing missing data are outlined in section 11.3.1.

6.5.2 Secondary Outcome Measures

6.5.2.1 Drug-abuse Outcomes

The impact of TAU+SCT, relative to TAU, on drug-abuse outcomes will be evaluated with the following assessments:

1. **Stimulant-free UDS Results at Follow-up**

A UDS will be obtained at the 3- and 6-month post-quit follow-up visits. The treatment groups will be compared on the percentage of participants providing a stimulant-free UDS coupled with self-report of no illicit stimulant use at each of these visits.

2. Drug-free UDS Results

This outcome measure is the percentage of drug-free weeks/UDS results for three time-periods: the active treatment phase, and the 3- and 6-month post-quit follow-up visits. The outcome during the active treatment phase is the percentage of participants who are drug-free during each week, as assessed by qualitative UDS. A drug-free week is defined as a week in which both urine samples test negative for drugs of abuse and the participant self-reports no illicit drug use. A drug-positive week is defined as a week in which at least one urine sample tests positive for an illicit drug or during which the participant self-reports illicit drug use. Missing urine samples during the active treatment phase will be treated as described in section 11.3.1. At the 3- and 6-month post-quit follow-up visits the treatment groups will be compared on the percentage of participants providing a drug-free UDS coupled with self-report of no illicit drug use at each of these visits.

3. Timeline Follow-back (TLFB)

The Timeline Follow-back (TLFB) procedure (Sobell and Sobell, 1992; Fals-Stewart, 2000) will be used to assess the participants' self-reported use of substances for each day of the study. Outcomes derived from this assessment will include the number of stimulant-use days and the number of substance-use (i.e., alcohol and/or illicit use) days during the active treatment phase. Substance-use days is a key outcome measure in that abstinence from all substances, including alcohol, is the treatment goal for many CTPs and, thus, it is important to assess the degree to which participants achieve this abstinence goal. For the follow-up periods, stimulant-use and substance-use days will be assessed for the 28 days prior to the follow-up visit.

4. Substance-abuse Treatment Attendance

The CTN smoking cessation trial conducted by Reid et al. (2008) found that, in the non-methadone-maintenance sites, there was a significant decrease in substance-abuse treatment attendance in the SCT, relative to TAU, participants; fortunately, this decrease occurred only during the time-period in which the smoking-cessation treatment was provided, with an increase back to pre-randomization levels once the SCT was concluded. In the present trial, participant compliance with substance-abuse treatment attendance will be evaluated by assessing the ratio of the number of outpatient (including intensive outpatient) treatment hours attended to the number of hours scheduled. Attendance of the research assessment visits, smoking-cessation counseling sessions, and contingency management sessions will not be scored as substance-abuse treatment attendance. Determination of attendance will be based on the clinic's records of treatment attendance.

5. ASI-Lite

The ASI-Lite is derived from the Fifth Edition of the ASI (McLellan et al., 1992), a structured clinical interview that yields scores for seven areas of functioning typically impacted by addiction, including medical status, employment status, drug use, alcohol use, family status, legal status, and psychiatric status. The ASI-Lite will be completed according to the schedule outlined in Table 2.

6. Risk Assessment Battery (RAB)

Multiple studies have established an association between stimulant use and increased sexual risk behavior (Booth et al., 2000; Lejuez et al., 2005; McCoy et al., 2004). Effective drug-abuse treatment, which decreases stimulant use, decreases sexual risk behavior (National Institute on Drug Abuse, 2006). The Risk Assessment Battery (RAB) (Navaline et al., 1994) is a self-administered assessment of the participant's engagement in activities that increase the likelihood of contracting HIV. Several scores including drug risk, sex risk, total risk, and scale score can be derived from the RAB. The RAB will be completed according to the schedule outlined in Table 2.

7. Brief Substance Craving Scale (BSCS)

A potentially important factor in stimulant dependence is craving, which might drive the individual to seek and use stimulants regardless of the potential negative consequences. Cocaine/METH craving will be assessed with the Brief Substance Craving Scale (BSCS; Mezinskis et al., 1998) according to the schedule outlined in Table 2. The BSCS instructs the participant to use a five-point scale to rate the intensity, frequency, and length of time spent craving during the past 24 hours; these scores will be added together to yield a total craving score.

6.5.2.2 Smoking Outcomes

The impact of TAU+SCT, relative to TAU, on smoking outcomes will be evaluated with the following assessments:

1. Carbon Monoxide (CO) level

CO in each participant's breath will be tested using a standard calibrated CO gas-monitoring device connected to a disposable mouthpiece. During the active treatment phase, participants ideally will be scheduled to provide CO samples for two visits each week, occurring on nonconsecutive days. CO will ideally be assessed twice during each study visit. Expired CO also will be assessed at the 3- and 6-month post-quit follow-up visits.

2. Point-Prevalence Abstinence

Point-prevalence abstinence is defined as not smoking in the previous seven days based on self-report and confirmed with a Carbon Monoxide (CO) level ≤8 ppm (Hurt et al., 2003). Self-report of cigarette use (measured by TLFB) and expired CO will be obtained as outlined in Table 2. Point-prevalence abstinence will be assessed during both the active treatment phase and the 3- and 6-month post-quit follow-up visits.

3. Four Week Continuous Abstinence

In the present study, the smoking quit date will occur during study week 3. A combination of daily self-reported smoking data and weekly CO levels will be used to determine continuous abstinence during post-quit days 15 – 42. This time-frame was selected based on the recommendation that a two-week post-quit grace period be included in smoking-cessation studies during which time smokers can smoke without it being counted as a treatment failure (Hughes et al., 2003). The use of a 4-week abstinence period is consistent with FDA standards for approving smoking-cessation medications (Hughes et al., 2003). Continuous abstinence will be defined as no self-reported smoking on any of the days during this four-week period AND no positive CO level (>8 ppm) measurement during the same period AND at least one CO assessment per week. Because a positive CO level almost always indicates smoking on either the day of the measurement or the previous day, smoking during the post-grace period will be indicated by a positive CO level measured on any of the post-quit days 16-42. (A positive value on day 15 might be due to smoking on day 14, which is within the grace period.) In order to have no missing CO week measurements, the following conditions must be met: at least four CO measurements must be obtained during this period; the first one may be no later than post-quit day 23, and no subsequent measurement may fall more than 13 days after the previous measurement.

4. Initial Quit

Achieving an initial quit is defined as a self-report of <u>no</u> smoking for 24 hours or more (Hughes et al., 2003). In the present protocol, if the participant meets this criterion at any time during the first two weeks following the smoking quit date (as determined by TLFB) then s/he will be scored as having achieved an initial quit.

5. Cigarettes per Day (CPD)

The TLFB assessment will be used to evaluate the number of CPD that the participant reports using throughout the study as outlined in Table 2.

6. Non-cigarette Tobacco Use

Participant use of non-cigarette tobacco products will be assessed on the TLFB as outlined in Table 2.

6.5.3 Safety Measures

1. Adverse Events (AEs)

AEs will be assessed by study staff as outlined in Table 2. If an AE requires medical attention, it should be reported to a study medical clinician immediately.

2. The Hospital Anxiety and Depression Scale (HADS)

A potential side-effect of bupropion XL is anxiety (see section 8.7) and smoking cessation can be associated with symptoms of nicotine withdrawal, which includes depressed mood. In addition to AE assessments, the potential increase in depression and anxiety will be assessed with the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). The HADS is a brief, validated instrument that screens for both depression and anxiety (Bjelland et al. 2002) and will be completed following the schedule outlined in Table 2. Participants who score in the range for possible depression (total depression score of 8 or higher) or anxiety (total anxiety score of 8 or higher) should be assessed by a qualified clinician before leaving the clinic. If a participant is assessed and, at subsequent visits, continues to have the same elevated score then the need for reassessment is at the discretion of a qualified clinician; a subsequent increase in the HADS score would require assessment by a qualified clinician.

3. Suicide and Homicide Screening Form

Smoking cessation can be associated with symptoms of nicotine withdrawal, which includes depressed mood. The Suicide and Homicide Screening Form is a structured, reliable interview modified from the Psychiatric Research Interview for Substance and Mental Disorders- PRISM (Hasin, et al. 1996). This form will be completed by study staff according to the schedule outlined in Table 2. Participants reporting current suicidal/homicidal intent should be assessed by a qualified clinician.

4. Pregnancy Test and Birth Control Assessment

A urine pregnancy test designed to measure human chorionic gonodotropin hormone will be completed on study day 1, prior to randomization, and during study weeks 5 and 10. All female participants will be tested except women who have a documented hysterectomy. During screening/baseline, female participants' use of birth control and breastfeeding status will be assessed.

5. Prior/Concomitant Medications

All medications taken by the participant for the 30 days prior to screening/baseline, during screening/baseline, and during the active study will be documented on a Prior/Concomitant Medications assessment (see Table 2). All medications taken by the participant while in the study should ideally be pre-approved by the medical clinician whenever possible to avoid interactions with the study drug.

6. Vital Signs and Weight

Vital signs, including blood pressure and heart rate, will be assessed according to the schedule in Table 2. In addition, the participant's weight will be recorded during screening/baseline and at the week-5 and week-10 study visits. Vital signs will be assessed by a trained staff member, either manually or by using a digital blood pressure monitor calibrated within the past twelve months and ideally approved by the Lead Investigator. If the blood pressure is abnormally high or low, it will be repeated one more time approximately 5 minutes later using the same technique. These readings will then be averaged.

7. The Pittsburgh Sleep Quality Index (PSQI)

A potential side-effect of bupropion XL is insomnia (see section 8.7) and smoking cessation can be associated with symptoms of nicotine withdrawal, which includes insomnia. In addition to AE assessments, the potential increase in insomnia will be assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a relatively brief, validated instrument that measures sleep quality. The PSQI will be completed following the schedule outlined in Table 2.

6.5.4 Other Measures

1. Demographics

This assessment will include questions about the participant's ethnicity, age, and sex.

2. CIDI

The Composite International Diagnostic Interview (http://www.hcp.med.harvard.edu/wmhcidi/about.php) (WHO CIDI) will be administered during screening/baseline by a RA who has been trained in the proper administration of this instrument. In addition, each interviewer will undergo a certification check, in which the administration of the instrument is rated by a CIDI trainer. In addition, at least once during the active trial a re-certification check will be completed; interviewers found to be performing below criteria will be provided with additional training as needed.

3. Medical History and Addendum

A medical history will be performed by a MC certified to perform this. In addition, the MC will complete a Medical History Addendum form that includes questions specific to assessing participant eligibility/safety for the present protocol. Any history relevant to cardiac functioning will be provided to the cardiologist responsible for reviewing the participant's ECG.

4. Physical Exam

Performance of a physical exam during screening/baseline will be done at each site by a MC certified to perform physical exams.

5. Smoking History Survey

The Smoking History Survey is a modified version of the Mayo Nicotine Dependence Center Patient Questionnaire (1991) and is administered by the RA. It asks participants how many CPD they smoke, at what age they started smoking, number of years smoking, how many times they have attempted to quit (including methods), when the last quit attempt occurred, their longest period of cigarette abstinence, and if there are other smokers in their household. Information on other non-cigarette tobacco products will also be noted.

6. Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND) is a brief self-administered assessment of cigarette use patterns (Heatherton et al., 1991). The FTND yields a single overall dependence score and is a standard measure in smoking-cessation trials.

7. Thoughts about Abstinence

Motivation and perceived self-efficacy to change substance use behavior could be impacted by the smoking cessation attempt in the TAU+SCT group. The Thoughts about Abstinence assessment (Hall et al., 1991), which assesses desire to quit, expected success in quitting and estimated difficulty in avoiding relapse, will be completed for alcohol, illicit drugs, and cigarettes, following the schedule outlined in Table 2.

8. Withdrawal Scale for Tobacco (WST)

The WST is a modified version of the Minnesota Withdrawal Scale (Hughes et al, 1991; Hatsukami et al, 1997; Hughes and Hatsukami, 1986). The WST is a self-report questionnaire which asks participants to rate 8 items of withdrawal on a scale from 0=None to 4=Severe. A total score is then computed from the responses to these 8 items. In addition, the 8 items are also examined separately.

9. Medication Compliance

Medication Compliance will be assessed through pill and cartridge counts and self-report according to the schedule provided in Table 2.

10. Smoking Cessation Counseling Compliance

For the TAU+SCT participants, compliance with smoking cessation counseling will be assessed through the number of counseling sessions that the participant attends and completion of homework assignments/session participation.

11. Non-study Smoking Cessation Treatment

For all participants, the use of any non-study smoking cessation treatment, including self-help materials, will be assessed.

12. Study Questionnaire

The Study Questionnaire is a self-report assessment of the relationship between smoking and stimulant use as perceived by the participant. The data from this assessment will be utilized in exploratory analyses.

13. Blood Chemistries

During screening/baseline, blood will be collected in serum separation evacuated venous blood collection tubes. Quantitative analysis will be performed, which will include the following analytes: glucose, creatinine, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), and blood urea nitrogen (BUN). A prescription topical numbing cream may be offered to all participants prior to the blood draw.

14. Hepatitis Screen

Participants with ALT or AST >2 times normal will be offered the opportunity to have a hepatitis test performed. This test is not requisite for study participation. Blood will be collected in a serum separation evacuated venous blood collection tube (e.g., Vacutainer^{TM}) and serum separated according to standard

procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C virus antibody.

15. ECG

Twelve-lead electrocardiograms will be performed during screening/baseline according to standard procedures. Ventricular rate (bpm), PR (ms), QRS (ms) and QTc (ms) will be reported on the ECG readouts. The results will be reviewed by a board-certified cardiologist for interpretation and for a clinical judgment about whether the participant is eligible for the study based on the ECG results.

16. Substance Abuse Treatment Status

The Substance Abuse Treatment Status form will be used to assess study candidate's status on study inclusion/exclusion criteria related to substance abuse treatment (e.g., enrolled in outpatient/IOP treatment, etc.). In addition, information regarding pressure to attend treatment, which can be related to substance use outcome, will be assessed.

6.6 Randomization Plan

Eligible participants will be randomized in a 1:1 ratio to the TAU+SCT and TAU arms. The randomization process will be performed by computer at a centralized location. Randomization will be stratified by site and by whether a stimulant-positive UDS result was obtained during baseline/ screening (yes/no). The block size chosen will be adequate to ensure approximate treatment balance. The number in each treatment group will never differ by more than a factor of KB/2 where B is the block size and K is the number of strata.

6.7 Study Treatments

6.7.1 Treatment as Usual + Smoking Cessation Treatment

The four components of the smoking cessation treatment, bupropion XL+ nicotine inhaler, counseling, and contingency management, are described in sections 8.0, 9.0, and 10.0, respectively. Participants randomized to the TAU+ SCT group will be eligible to receive SCT for the full 10 weeks of the SCT intervention irrespective of their concurrent level of participation in drug abuse treatment.

6.7.2 Treatment as Usual

Participants randomized to TAU will participate in substance abuse treatment as typically provided by the CTP. It should be noted that the participants will be recruited from outpatient substance abuse treatment programs that do not provide smoking cessation treatment services on site (see section 6.4.1.1). Participants randomized to TAU in the present trial will, thus, not be deprived of smoking cessation treatment to which they would otherwise have access. Participants in the TAU condition may seek smoking cessation treatment during the course of the trial and any smoking treatment received will be monitored. At the end of the week 28 follow-up visit, the TAU participants will be offered a referral to a specific smoking cessation treatment. An attempt will be made to contact TAU participants who fail to complete the week 28 follow-up visit and a referral to smoking cessation treatment will be offered if the participant is successfully contacted. The specific referral provided will be determined on an individual site basis but will include, at minimum, information about the Smoking Quitline for the state in which the participant resides.

7.0 STUDY PROCEDURES

7.1 Study Overview

Table 2 provides an overview of the participant procedures and assessments.

Table 2 Overview of Study Assessments and Procedures

Assessment/ Procedure	Time Est (Min)	Scrn/ Base	Active Treatment Phase										FU	
			1	2	3	4	5	6	7	8	9	10	16	28
Bupropion XL	5		X	X	X	X	X	X	X	X	X	X		
Smoking Cessat. Counseling	10		X	X	X	X	X	X	X	X	X	X		
Nicotine Inhaler	5				X	X	X	X	X	X	X	X		
Contingency Management	15					2X	2X	2X	2X	2X	2X	2X		
Screening Assessments														
Informed Consent	30	X*												
Demographics	5	X*												
Smoking History Survey	10	X*												
CIDI	90	X*												
Blood chemistry	2	X*												
Birth Control Assessment	2	X*												
ECG	15	X*												
Medical History & Addendum	15	X*												
Substance Abuse Tx Status	5	X*												
Physical Exam	20	X*												
Safety Assessments														
Vital Signs	5	X+	X	X	X	X	X	X	X	X	X	X		
Weight	1	X*					X					X		
Urine Pregnancy Test	2		X*				X					X		
Adverse Events	5	X*	X	X	X	X	X	X	X	X	X	X		
Prior/Concom Meds	5	X*	X	X	X	X	X	X	X	X	X	X		
HADS	2	X*	X	X	X	X	X	X	X	X	X	X		
Pittsburgh Sleep Quality Index	5	X*					X					X		
PRISM -Suicide and Homicide	5	X*					X					X		
Efficacy Assessments														
Urine for UDS	2	X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X
ASI-Lite	45	X*												
ASI-Lite Follow-up	30											X	X	X
Timeline Follow-Back	10	X*	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X
Risk Assessment Battery	15	X*										X	X	X
BSCS	2	X*	X	X	X	X	X	X	X	X	X	X	X	X
CO level	2	X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X
Other Assessments														
Fagerström (FTND)	2	X*										X	X	X
Locator Information	5-10	X*										X	X	
Study Questionnaire	5	X*												

Assessment/ Procedure	Time Est (Min)	Scrn/ Base	Active Treatment Phase										FU	
			1	2	3	4	5	6	7	8	9	10	16	28
Thoughts about Abstinence	6	X*										X		
Withdrawal Scale Tobacco	1	X*				X	X	X	X	X	X	X		
Compliance – Medication	5			X	X	X	X	X	X	X	X	X		
Non-study Smoking Tx	1		X	X	X	X	X	X	X	X	X	X	X	X
Assessment Time Est. (min) ♣		340♠	40	43	43	44	57	44	44	44	44	115	69	64
Administrative Forms														
Study Eligibility	15	X*												
Randomization	5	X*												
Treatment Tracking Form	10		X	X	X	X	X	X	X	X	X	X		
Compliance – Smk Counseling	2		X	X	X	X	X	X	X	X	X	X		
CM Tracking Form	5					2X	2X	2X	2X	2X	2X	2X		
End of Treatment Status	5											X		

Notes: "X*" = once during screening/baseline; "X^{+}"=at each screening/baseline visit; "X" represents a procedure or assessment performed once per Week; "2X" represents a procedure or assessment performed twice per Week. ♣The estimates provided for the active treatment weeks reflect the total amount of time for the week (i.e., for the two visits combined). ♠ Screening/baseline will ideally be completed in three visits, with the average time per visit being approximately 113 minutes.

7.2 Participant Recruitment and Consent

Interested candidates who have been determined by telephone or face-to-face interview to smoke 7 or more CPD, want to quit smoking, are likely to meet the diagnostic criteria for cocaine/METH dependence and other study requirements, and are in (or soon to enroll in) outpatient substance-abuse treatment are invited to receive an explanation of the study purpose and requirements. If still interested after receiving a face-to-face explanation of the study, the candidate is given an opportunity to review, inquire about, and sign the informed consent form.

Any participant who has difficulty understanding the information contained in the consent form is asked to review the misunderstood portion(s) of the consent and discuss them with a research staff member until he or she shows complete understanding of the information and may thus give full consent. Research staff members work closely with the study candidates in an effort to help them understand the requirements of their participation. Persons with literacy problems are assisted to the extent possible. Any participant who is unable to demonstrate understanding of the information contained in the informed consent is excluded from study participation.

7.3 Screening/Baseline

After signing the informed consent form, the study participant proceeds through the screening/baseline phase. Ideally, the screening/baseline procedures will be completed in three visits, but they can be completed in fewer visits or more visits if necessary, with the restriction that randomization can, at the earliest, occur on the seventh day after consent and that at least three screening/baseline UDS results, collected on non-consecutive days, are obtained. Ideally, the screening/baseline procedures will be completed within a two-week time-frame but the allowable time for completion is within 30 days of signing consent. Under certain circumstances a participant will be allowed to re-consent and repeat the screening/baseline procedures if he or she was unable to complete the screening/baseline procedures within the 30-day time-frame. Participants who meet study eligibility and complete screening/baseline as outlined above will be randomly assigned to the TAU+SCT or TAU condition.

7.4 Active Treatment Phase

The active treatment phase is 10 weeks in duration. During this time, participants in both treatment conditions will participate in the substance-abuse treatment typically offered by the CTP. Participants randomized to the TAU+SCT arm will receive individual smoking-cessation counseling consisting of approximately one ten-minute counseling session per week during study weeks 1 through 10. In addition, all TAU+SCT participants will receive bupropion XL (300 mg/day) and, during the post-quit treatment phase, the nicotine inhaler (6-16 cartridges per day ad libitum). Finally, all TAU+SCT participants will receive contingency management in which drawings for prizes are given for smoking abstinence as assessed by carbon monoxide (CO) levels during the post-quit phase of the trial (i.e., weeks 4-10). The TAU+SCT participants will have a target quit smoking day at the end of study week 3. Following the final week 10 visit, TAU+SCT participants will be provided with a 3-day bupropion XL dose taper, in which 150 mg is taken once per day and with a 3 week nicotine inhaler taper. Participants in both conditions will meet with study staff twice weekly to complete study assessments as outlined in Table 2, with the constraint that visits ideally occur on nonconsecutive days.

7.5 Follow-up

The follow-up visits will be conducted at approximately study weeks 16 and 28. The measures to be collected during this visit are delineated in Table 2. There will be a 21-day timeframe in which to complete each follow-up visit.

7.6 Medication and Trial Discontinuation

7.6.1 Medication Discontinuation

An investigator may discontinue a participant's medication if he or she deems it clinically appropriate or, at the discretion of the investigator, for any of the reasons listed below.

1. significant side effects that are likely to have been caused by the study medication
2. serious or unexpected AEs which would make further study medication dosing not in the participant's best interest
3. inability or unwillingness of the participant to comply with the study protocol
4. serious intercurrent illness

A participant may discontinue medication anytime s/he wishes. Although the participant may withdraw entirely from the study whenever s/he wishes, s/he will be strongly encouraged to continue attending visits at which safety measures are scheduled to be assessed. TAU+SCT participants who wish to discontinue from study medication early or to withdraw from the study will have their medication discontinued. Any participant who discontinues the study prematurely, regardless of the reason, will be requested to return for a final visit during week 10 to perform the necessary procedures listed in Table-2 and to obtain data for end of study/early termination. Whenever a study participant stops coming to the clinic without notification, staff will make a concerted effort to contact the participant (or the designated contact person if the participant cannot be contacted) to assure that they have had no untoward effects from study participation.

Study participants withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Participants will be asked to sign a general consent for the release of information to the referred health care provider. Study staff may request transportation for emergency treatment of a participant if medically appropriate (e.g., for acutely psychotic or suicidal participants).

7.6.2 Stopping Guidelines

If a participant experiences a seizure while on bupropion XL, he or she will be immediately discontinued from the study medication and will not be eligible to restart on the study medication. Participants who develop elevations of blood pressure >145/95 or heart rate >100 on two consecutive research visits, will be considered as developing clinically significant elevations of blood pressure provided no other contributing causes can be identified other than the study medication. Participants who fail to re-establish normotensive blood pressure readings or normal heart rates, will be evaluated for initiating or readjusting antihypertensive therapy, or have their dose of buproprion XL adjusted downward if necessary to re-establish normotensive blood pressure readings/ normal heart rate, or will be withdrawn from the study medication after a discussion with the study safety officer. Participants with blood pressure ≥ 165/115 will be seen immediately by qualified medical staff, will have their dose of bupropion XL adjusted downward, or will be withdrawn from the study medication after a discussion with the study safety officer, and will be evaluated for initiating or readjusting antihypertensive therapy. Participants who develop chest pain or shortness of breath on exertion or upon using stimulants during the study will be evaluated by the MC who may order an ECG and follow it up, if necessary, with an exercise test. Any new onset of a clinically significant conduction abnormality or arrhythmia will be discussed with a study cardiologist for a decision on lowering the dose of buproprion XL or withdrawal from the study medication.

7.6.3 Trial Discontinuation

The study sponsor has the right to discontinue the investigation at any time.

7.7 Participant Reimbursement

Participants will be reimbursed for their transportation, inconvenience, and time. This reimbursement will be in the form of retail scrip or vouchers. It is recommended that participants receive a total of $75 for completing screening/baseline. During the active treatment phase, there are two visits per week, one of which is fairly short, comprised of the TLFB, assessing CO level, and collecting urine for the UDS. The other visit during the week will be longer and will include the assessments outlined in Table 2. The recommended reimbursement schedule for these visits is outlined in Table 3. Since the week 10 visit will be substantially longer than all of the other visits, it is recommended that participants be reimbursed a total of $50 for that visit, as outlined in Table 3. In addition, since the 3- and 6-month follow-up visits are also longer visits, it is recommended that participants be reimbursed a total of $40 as outlined in Table 3. Using the recommended schedule, a participant could be reimbursed a maximum of $580. However, participant reimbursement might vary across study sites to take into account local IRB guidelines, as well as special circumstances and geographic differences across sites. The Lead Node should be informed of any changes in level of participant reimbursement.

Table 3: Reimbursement schedule for research visits

Visit	Transportation ($)	Valid urine/CO sample ($)	Assessment ($)	Total per Visit ($)	Total # of Visits	Grand Totals ($)
Screening/baseline						75
Longer visits wks 1-9	10	5	10	25	9	225
Shorter visits wks 1-10	10	5	0	15	10	150
Longer visit week 10	10	5	35	50	1	50
3- and 6-month FU visits	10	5	25	40	2	80
Total						$ 580

8.0 STUDY MEDICATIONS

8.1 Bupropion XL

Bupropion hydrochloride XL 150 mg (for dose escalation and taper) and 300 mg tablets, manufactured by GlaxoSmithKline, will be used in the present trial. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. The structure of bupropion XL closely resembles that of diethylpropion and it is related to phenylethylamines. Its molecular formula is $C_{13}H_{18}ClNO$•HCl and its molecular weight is 276.2.

8.2 Nicotine Inhaler

The nicotine inhalation system, NICOTROL® inhaler, will be utilized. The nicotine inhaler consists of a plastic mouthpiece and cartridges containing 10 mg of nicotine, of which 4 mg is delivered, and the inactive component menthol. Proper use of the inhaler involves a shallow "puffing" technique in which the vapor is drawn into the mouth and held for buccal absorption. At temperatures between 15 °C (59 degrees F) and 30°C (86 °F), the inhaler will deliver approximately 13 micrograms nicotine per puff. Intensive puffing of the inhaler over 20 minutes releases the 4 mg of the nicotine content of each cartridge. The recommended dosing is 6-16 cartridges per day ad libitum.

8.3 Dispensing Study Medication

Starting in study week 1 and continuing through study week 9, bupropion XL will be dispensed weekly to the TAU+SCT participants for daily self-administration. At the week 10 visit, TAU+SCT participants will be provided with a 3-day bupropion XL dose taper, in which 150 mg is taken once per day. Starting in study week 3 and continuing through study week 9, nicotine cartridges will be dispensed weekly to the TAU+SCT participants for daily self-administration. During week 10, the TAU+SCT participants will receive nicotine cartridges for the 3 week taper.

8.4 Storage

Study medication will be stored in compliance with state law and institutional policy.

8.5 Record of Administration

Drug-accountability records including perpetual inventory, will be maintained at all times. These will include a record of the number of bupropion tablets and nicotine cartridges transferred between areas of the study site (from pharmacy to clinic and back, for example), and those dispensed to and returned by an individual participant.

8.6 Used/Unused Supplies

Empty, partially used, and unused bottles of study medication and used and unused nicotine cartridges will be returned to the pharmacy (or other appropriately qualified entity based on local/state regulations) and logged into a perpetual inventory of study drug returned. The study staff will accurately maintain study drug accountability records.

8.7 Side Effects of Bupropion XL

The most commonly observed AEs (i.e., at a rate of >5% of that for placebo) associated with bupropion in smoking-cessation trials are insomnia and dry mouth. The AEs most commonly resulting in medication discontinuation include nervous system disturbances (3.4%), most of which were tremors, and skin disorders (2.4%). Side-effects occurring in up to 10-12% of people include: dizziness and an irritated or runny nose. Side-effects occurring in 4-9% of people include: nausea, trouble concentrating, constipation, joint pain, unusual dreams, muscle pain, diarrhea, nervousness, and anxiety. Some other side-effects of bupropion

(occurring in 1 -3 % of people) include: loss of appetite, changes in taste, abdominal pain, coughing, sore throat, neck pain, increased appetite, shakiness (tremors), drowsiness, bronchitis, dry skin, canker sores, sinus infections or irritation, bloody nose, hot flashes, high blood pressure, changes in thought patterns, and ringing of the ears (tinnitus). Less common but potentially serious side-effects include: seizures; suicidal thoughts or behavior; agitation, or panic attacks; hostility or aggressiveness; engaging in unusual or dangerous activities; mania, hallucinations; delusions; paranoia; a rapid heart rate; chest palpitations; and signs of an allergic reaction, including: unexplained rash, hives, itching, unexplained swelling, wheezing, and difficulty breathing or swallowing. Beginning in July 2009, the FDA is requiring a boxed warning on bupropion outlining the risk of changes in behavior, depressed mood, hostility, and suicidal ideation. **Note**: Using alcohol in combination with bupropion XL can increase the risk of seizure. Thus, participants taking bupropion should minimize, or if possible, avoid alcohol use.

8.8 Side Effects of Nicotine Inhaler

The most commonly reported AEs include heartburn, coughing, runny nose, and nausea. Irritation in the mouth and throat is common but is generally mild and declines with repeated usage.

8.9 Concomitant Medications

Any medication (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study ideally must be approved by the investigator. The following medications should be used only after careful consideration by the medical clinician.

1. Sympathomimetics (because of possible synergistic increases in blood pressure with bupropion)

2. Medications known to affect the CYP2B6 isoenzyme (bupropion is metabolized by CYP2B6):
   - orphenadrine,
   - cyclophosphamide,
   - ifosfamide,
   - ticlopidine,
   - clopidogrel

3. Levodopa or amantadine (there is some clinical data to suggest a greater incidence of neuropsychiatric adverse events in patients receiving bupropion concurrently with these medications)

4. Drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide) should be used with caution since bupropion and its main metabolite, hydroxybupropion, inhibit the CYP2D6 pathway. The use of bupropion XL with such medications might necessitate that a lower dose of the CYP2D6-metabolized medication be used.

8.10 Treatment Plan

8.10.1 Bupropion XL

Study participants randomly assigned to the TAU+SCT condition will be prescribed 150 mg/day of bupropion XL for study days 1-3 and then 300 mg/day of bupropion XL for study days 4 – the final visit of study week 10. At the final study week 10 visit, the TAU+SCT participants will be provided with a 3-day bupropion XL dose taper, in which 150 mg is taken once per day. Bupropion XL tablets will be dispensed weekly as described in section 8.3. This procedure will provide enough extra medication that the participants

will not run out of medication if they should miss a visit. Participants will be instructed on how to take the study medication during each week, and they will be instructed to return empty bottles or any unused medication on a weekly basis.

8.10.2 Nicotine Inhaler

Study participants randomly assigned to the TAU+SCT condition will be prescribed 6-16 nicotine cartridges per day ad libitum starting with the smoking quit date (study day 20) through week 10. During week 10, participants will be provided with a 3 week taper in which a maximum of 12 cartridges per day is taken in the first week, a maximum of 8 cartridges per day is taken in the second week, and a maximum of 4 cartridges per day is taken in the third week.

9.0 SMOKING-CESSATION COUNSELING

9.1 Introduction

The U.S. Public Health Service (USPHS) Clinical Practice Guideline recommends that smoking-cessation interventions should include counseling and behavioral therapy as this specifically results in higher tobacco abstinence rates (Fiore et al., 2008). Consistent with the guideline, participants enrolled in the present study will receive brief, individualized counseling with the aim of providing them with problem-solving skills, education, and social support as part of treatment. The "Smoke Free and Living It©" manual has been developed and used extensively in research by the Mayo Clinic Nicotine Research Center (Nicotine Research Program Staff. Smoke-Free and Living It. Mayo Foundation for Medical Education and Research - Nicotine Dependence Center - Research Program).

9.2 Overview of "Smoke Free and Living It©"

Since 1998, the "Smoke Free and Living It©" manual has been used in large scale, multi-center, multi-country trials, including a CTN trial, as an adjunct to medication in helping smokers abstain from smoking. It serves both as a self-help manual and the basis for brief counseling, based on the USPHS guideline. An interventionist guide accompanies the patient manual that will assist the interventionist in the delivery of each counseling topic. In the present trial, the "Smoke Free and Living It©" counseling will consist of an approximately 10-minute weekly session administered by a trained interventionist during study weeks 1-10. Although this therapy is in the form of a manual, the intention is to cover the material in a sequence that best meets the need of a given participant. Table 4 lists the modules from "Smoke-free and Living It©" along with the study week during which they typically will be implemented.

Table 4: Typical Time-line for Administering Psychosocial Treatment Modules

Study Week	Treatment Module*	Administered by
1	Nicotine Addiction/Congratulations and Contract	MC/Site PI
2	Making not smoking easier	Interventionist
3	Benefits of quitting smoking/Day Before Quit Day	Interventionist
4-8	Withdrawal	Interventionist
	Triggers/Rewarding yourself for not smoking	Interventionist
	Managing Stress	Interventionist
	Rationalizations	Interventionist
	Weight Management/Exercise	Interventionist
9	Stopping Study Medication	Interventionist
10	Self Image/Focus on the Future	Interventionist

*Treatment Modules can be completed in the order listed or rearranged to best meet the needs of a given participant

9.3 Interventionist Selection

Interventionist Selection Criteria:

- A minimum of a bachelor's degree, preferably in a behavioral science (e.g., psychology, sociology, etc.), or equivalent experience
- willing to learn and implement the "Smoke Free and Living It©" counseling program
- willing to have counseling sessions video-recorded and then reviewed by a Site Trainer and/or a Mayo Clinic staff member

9.4 Interventionist training and supervision

9.4.1 Training Model

The present study will utilize a "training of trainers" (TOT) model for training the interventionists.

9.4.2 Interventionist Training

TOT Training – Site Trainers will attend a training provided by staff from the Mayo Clinic Nicotine Research Program. This approximately twelve-hour training will include the interventionist training and the training required to serve as a Site Trainer. This training will include a lecture format, review of video examples of counseling sessions, and role playing exercises.

Interventionist Training – Interventionists will be trained by certified Trainers, either from a participating node or the Mayo Clinic Nicotine Research Program. This approximately four hour training will include a lecture format, review of video examples of counseling sessions, and role-playing exercises. The last step will involve the trainer observing staff administering mock counseling sessions for certification (see below).

9.4.3 Site Trainer and Interventionist Certification

Site Trainers – The Site Trainer will complete a mock counseling session, which will be rated by a qualified staff member from the Mayo Clinic Nicotine Research Program. To be certified, the Site Trainer will be scored on the following criteria:

- Familiarity with each of the intervention topics
- Ability to effectively guide study participant through key points in the 10 minute time allowed
- Ability to make and maintain eye contact
- Ability to listen
- Ability to identify individual needs and provide the appropriate intervention
- Ability to remain non-judgmental and encouraging
- Ability to recognize the opportunity for teaching vs the need to allow for more interaction and discussion remaining within the 10 minute time allowed

The rater will use a three (3) point scale (1-Meets expectations, 2-Needs improvement, 3-Expectations not met and additional training required) that will determine if the staff member meets each criterion.

If a Site Trainer does not meet 6 out of 7 of the established criteria, more time must be allowed for additional training. This would include watching recorded sessions and doing practice sessions with other staff. Another mock counseling session would need to be completed by the Site Trainer for certification.

In addition, the Site Trainer must demonstrate reasonable inter-rater agreement with Mayo staff and thus, will rate at least one session that has been rated by Mayo staff. To be certified, the Site Trainer's ratings must be in perfect agreement with those of the Mayo staff for at least six of the seven items rated. Site Trainers who fail to be certified on the first certification session will receive additional training and will complete an additional certification session(s); a Site Trainer who is unable to meet the inter-rater agreement criterion will not be allowed to supervise the Interventionist(s).

Interventionist – The Interventionist will complete a mock counseling session, which will be rated by a certified Trainer. To be certified, the Interventionist will be scored on the following criteria:

- Familiarity with each of the intervention topics
- Ability to effectively guide study participant through key points in the 10 minute time allowed
- Ability to make and maintain eye contact
- Ability to listen
- Ability to identify individual needs and provide the appropriate intervention
- Ability to remain non-judgmental and encouraging
- Ability to recognize the opportunity for teaching vs the need to allow for more interaction and discussion remaining within the 10 minute time allowed

The rater will use a three (3) point scale (1-Meets expectations, 2-Needs improvement, 3-Expectations not met and additional training required) that will determine if the staff member meets each criterion.

If an Interventionist does not meet 6 out of 7 of the established criteria, more time must be allowed for additional training. This would include watching recorded sessions and doing practice sessions with other staff. Another mock counseling session would need to be completed by the Interventionist for certification.

9.4.4 Ongoing Interventionist Supervision and Training

A certified Site Trainer will have primary responsibility for supervising the interventionists' "Smoke Free and Living It©" counseling. It is expected that the Site Trainer will rate one video-recorded session per interventionist, on an approximately per month basis, contingent upon the interventionist having active cases to review. The Site Trainer will then provide feedback, and if needed, additional training, to each interventionist.

9.4.5 Quality Control of Counseling Administered

Quality control checks will include the rating of a randomly selected video-recorded session by a certified Site Trainer on an approximately monthly basis, contingent upon the Interventionist having active cases. If an interventionist falls below criterion for certification (see section 9.4.3) additional supervision will be provided. If an interventionist falls below criterion on three consecutive sessions then the interventionist will need to repeat the certification process (see section 9.4.3) prior to being assigned any additional study participants.

In addition, video-recorded sessions will be independently rated by Mayo Clinic staff to determine inter-rater agreement. For Site Trainers who originally met the inter-rater agreement certification criterion on their first certification tape (see section 9.4.3), the independent rating by Mayo Clinic staff will occur approximately 6 months after the Site Trainer's original certification. For Site Trainers who originally failed to meet the inter-rater agreement certification criterion on their first certification tape (see section 9.4.3), the independent rating by Mayo Clinic staff will occur approximately 3 months after the Site Trainer's original certification. For the independent rating assessments, if the Site Trainer's ratings are in perfect agreement with those of the Mayo staff for at least six of the seven items rated, then the next independent rating by Mayo staff will

occur approximately 6 months later. Otherwise, the Site Trainer will: 1. receive additional training, 2. have another tape independently rated by the Mayo staff, and 3. have an independent rating by Mayo staff approximately 3 months later. The video-records of the sessions will be destroyed within 6-months post database lock.

10.0 CONTINGENCY MANAGEMENT (CM)

The CM procedure utilized in early research typically followed the reinforcement schedule developed by Higgins et al. (1994) in which participants received vouchers for goods/services of escalating value based on maintaining a target behavior (e.g., drug-free urines, treatment attendance, etc.). While highly effective, this voucher-based procedure has been criticized as being more costly than most CTPs can afford, which led to the development of an intermittent reinforcement approach in which participants earn chances to draw for prizes based on maintaining a target behavior (Petry et al., 2000). This prize-based approach has been found to be effective in a number of studies, including a CTN study, CTN-0006, in which it was found to significantly increase treatment retention and negative urine drug screens in stimulant abusers (Petry et al., 2005).

In the present study, prize-based CM will be used to reinforce negative CO (i.e., CO < 4 ppm) results during the post-quit phase. The CO cut-off of < 4 ppm is consistent with research findings that the use of 2-3 ppm produces the most accurate identification of smoking abstinence whereas 8-10 ppm, which has been traditionally used to verify abstinence, can result in smokers being classified as abstinent (Javors et al., 2005; Cropsey et al., 2006). Participants can begin to earn abstinence incentives at the level of the study week whenever they submit a qualifying sample; this will encourage late quitters to continue to try to quit smoking throughout the active treatment phase. As outlined in Table 5, participants who start abstaining at week 4 and continue to abstain will receive a bonus draw for each negative CO sample starting in week 5. The number of draws will be reset to 4 whenever a participant submits a sample that indicates smoke exposure or if they have an unexcused missing CO sample. After two consecutive negative CO samples are again submitted, the third consecutive qualifying sample will reinstate the participant to receiving the number of draws associated with that study week. The bonus draw for achieving abstinence at week 4 will not be reinstated post-lapse. The maximum number of draws that can be earned is 110.

The composition of the container from which participants will draw for prizes will hold 500 chips, each worth a particular reward value: 250 chips will be worth $0 and will state “Good Job,” 149 chips will be worth $1 and will state “Small,” 50 chips will be worth $10 and will state “Medium,” 50 chips will be worth $20 and will state “Large” and 1 chip will be worth $80 - $100 and will be marked as “Jumbo.” Prizes for each corresponding amount will be maintained in a locked cabinet at each study site. In past studies, $1 prizes have included snacks, toiletries and fast-food gift certificates; $10 prizes might include retail gift certificates, DVDs, and earphones; $20 prizes have included retail gift certificates, home goods (e.g., pots, dishes) and telephones; and jumbo prizes have included televisions and DVD players. Based on the proportion of each type of chip in the container, the average value of each draw will be $3.46; thus, participants earning the maximum number of draws (110) will earn approximately $380 in prizes.

Table 5: Number of Prize Drawings per Week as a function of Negative CO levels

Study Week	Intervention Visit	Number draws for negative CO	Bonus for negative CO since week 4	Max Draw/Sample
4	1	4	0	4
4	2	4	0	4
5	3	5	1	6
5	4	5	1	6
6	5	6	1	7
6	6	6	1	7
7	7	7	1	8
7	8	7	1	8
8	9	8	1	9
8	10	8	1	9
9	11	9	1	10
9	12	9	1	10
10	13	10	1	11
10	14	10	1	11
Total				**110**

11.0 ANALYTICAL PLAN

11.1 Statistical Hypotheses

11.1.1 Primary Hypothesis

The primary hypothesis is that a significantly greater percentage of TAU+SCT, relative to TAU, participants will be stimulant-free during the weeks of the active treatment phase (see section 6.5.1).

11.1.2 Secondary Hypotheses

It is also hypothesized that:

1. A significantly greater percentage of TAU+SCT, relative to TAU, participants will provide a stimulant-free UDS result at the 3 and 6-month post-quit follow-up visits (see section 6.5.2.1).

2. TAU+SCT, relative to TAU, participants will have better drug-abuse outcomes during the active treatment phase including:

   - a significantly greater percentage of participants with drug-free weeks (see section 6.5.2.1);
   - significantly fewer stimulant-use and substance-use (i.e., alcohol and/or illicit drug use) days as assessed by the TLFB;
   - better compliance with substance-abuse treatment defined by a greater proportion of scheduled hours attended;
   - significantly greater decrease in ASI-Lite composite scores between baseline and end of treatment;
   - significantly greater decrease between baseline and end of treatment in sexual risky behavior as assessed by the sex risk scale of the RAB;
   - significantly greater reduction in cocaine/METH craving as measured by the BSCS from baseline through the end of the active treatment phase

3. TAU+SCT, relative to TAU, participants will have better drug-abuse outcomes at the 3- and 6-month post-quit follow-up visits including:
    - a significantly higher percentage of participants with drug-free urines at the 3- and 6-month follow-up visits (see section 6.5.2.1);
    - significantly fewer stimulant-use and substance-use (i.e., alcohol and/or illicit drug use) days as assessed by the TLFB at the 3- and 6-month follow-up visits (see section 6.5.2.1);
    - significantly lower ASI-Lite composite scores at the 3- and 6-month follow-up visits;
    - significantly lower RAB sex risk scale score at the 3- and 6-month follow-up visits;
    - significantly lower cocaine/METH craving as assessed by the BSCS at the 3- and 6-month follow-up visits

4. TAU+SCT, relative to TAU, participants will have better smoking outcomes during the active treatment phase including:
    - higher rates of point-prevalence abstinence (see section 6.5.2.2) at the week 10 assessment
    - higher rates of continuous smoking abstinence (see section 6.5.2.2) during post-quit days 15-42
    - a lower number of CPD during study weeks 4-9

5. TAU+SCT, relative to TAU, participants will have better smoking outcomes at the 3- and 6-month post-quit follow-up visits including:
    - higher rates of point-prevalence abstinence (see section 6.5.2.2) at the 3- and 6-month follow-up visits
    - a lower number of CPD during the prior 28 days at the 3- and 6-month follow-up visits

6. Participants who achieve continuous smoking abstinence during post-quit days 15 – 42, relative to participants who do not, will have better stimulant-use outcomes including:
    - a significantly greater percentage of participants with stimulant-free weeks (see section 6.5.1 for the definition of stimulant-free weeks) during study weeks 4-10 of the active treatment phase;
    - a significantly greater percentage of participants with stimulant-free urines at 3- and 6-month follow-up visits

11.2 Intent-to-Treat Participant Population

The intent-to-treat population is defined as the participants who are randomized to treatment.

11.3 Analysis Plan

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat (ITT) population. While there is every intention to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency, and some adjustments may be required to meet constraints posed by the structure of the data. Constraints such as non-linearity, non-normality, etc. may lead to different but more appropriate approaches to analysis.

All statistical tests will be conducted at the 5% Type I error rate (two-sided). When multiple tests are conducted, the chance of finding a significant difference in one of the tests, when in fact no difference exists, is greater than the stated Type I error rate. The investigators are aware of the multiple testing issues and will interpret results with caution and use confidence intervals where possible.

11.3.1 Primary Outcome

The primary hypothesis is that a significantly greater percentage of TAU+SCT, relative to TAU, participants will be stimulant-free during the weeks of the active treatment phase. For each participant, a stimulant-free week is defined as a week in which both urine samples test negative for stimulants and the participant self-reports no illicit stimulant use. A stimulant-positive week is defined as a week in which at least one urine sample tests positive for a stimulant or during which the participant self-reports illicit stimulant use. However, in the analysis of data from any clinical trial, strategies must be employed for handling missing data. In this trial, data for a week in which both urine samples are missing and the participant self-reports no illicit stimulant use will be treated as missing. For a week in which one stimulant-free UDS is produced, the second urine sample is missing, and the participant self-reports no illicit stimulant use or the self-report data are missing will be treated as negative (Table 6).

Data will be analyzed using a generalized linear mixed model (GLMM) for repeated-measures analysis (Brown and Prescott, 1999). Suppose Y represents the vector of observed response data, X and Z the fixed and random effects design matrices, and α and β be the vectors of fixed and random effects, respectively. Then, the GLMM model formulation assumes that

$$E(Y|\beta) = g^{-1}(X\alpha + Z\beta),$$

where $E(Y|\beta)$ is the expected value of Y conditional on the random effects vector, g^{-1} is the inverse link function, and $X\alpha + Z\beta$ is the linear predictor. The response variable Y will be modeled using the logit link function, i.e., $g(\mu) = \log(\mu / (1 - \mu))$. Fixed effects will include treatment group and week, while random effects will include site. SAS Proc GLIMMIX will be used to fit the model as follows:

```
proc glimmix;
class site treatment;
model Y = treatment week treatment*week / dist=binary link=logit covb solution;
random intercept / subject=site;
random _residual_/subject=patientid type=cs;
run;
```

The model formulation implies the same treatment effect in each site. The effect of the intervention on change in response from baseline will be addressed by the treatment by week interaction parameter. Due to the possibility that CTPs may differ in their success at helping participants become/remain stimulant-free, each regression model will adjust for site effects. Site will be included in the GLMM model as a random effect based on the participation of 12 CTPs. Assumptions of linearity will be examined by adding a restricted cubic spline to represent nonlinearity (Harrell, 2001). Assumptions for the covariance structure that provides the best fit to the data will be analyzed using the COVTEST statement under SAS Proc GLIMMIX. Since GLMM inference is only valid if data are missing at random (MAR), logistic regression analyses will be conducted to identify patterns of attrition and to determine if there is differential attrition by treatment condition. A binary indicator variable for missing data will be regressed on treatment assignment and other covariates. Variables that are associated with attrition at or below the α=0.10 level of significance will be included in subsequent analyses where the assumption of data missing at random (conditional on covariates) is required (Verbeke and Molenberghs, 2000).

If the random effects model unexpectedly fails to converge, then a general estimating equation (GEE) approach will be employed treating site as a fixed effect. If this model is utilized, then missing data (see Table 6) will be imputed using standard multiple imputation procedures, since GEE inference is only valid if data are missing completely at random (MCAR). SAS Proc MI will be used to create five complete data sets

using multiple imputation. Each data set subsequently be analyzed using SAS Proc GENMOD (the GEE procedure), and the results combined using SAS Proc MIANALYZE.

Table 6: Stimulant-use assignment for study week as a function of TLFB and UDS result

Urine Drug Screen - Stimulant result		Time Line Follow Back (TLFB)			
Result	**Result**	**At least one positive day**	**All days negative**	**Some days negative, some missing**	**All days missing**
-	-	+	-	-	-
+	-	+	+	+	+
+	+	+	+	+	+
+	0	+	+	+	+
0	0	+	Missing	Missing	Missing
-	0	+	-	-	-

Note: ’0’=missing, ‘+’=positive and ‘-‘=negative

11.3.2 Secondary Outcome

Several secondary analyses that will further elucidate the efficacy of TAU+SCT, compared to TAU, for treating smokers in outpatient substance-abuse treatment for cocaine or methamphetamine dependence have been included in this study. For all repeated measures mixed model and generalized linear mixed model (GLMM) analyses, the response variable will be modeled using the appropriate link function. The effect of the intervention on change in response from baseline will be addressed by the treatment by week interaction parameter. Each model will adjust for possible site differences by including site as a random effect. The SAS procedure MIXED will be used for continuous variables, while GLIMMIX will be used for binary data. Before modeling is commenced, assumptions of linearity and covariance structure will be examined.

1. Stimulant-free/Drug-free UDS

GLMM analyses will be conducted to compare the percentage of TAU+SCT, relative to TAU, participants who have stimulant-free and drug-free UDS at the 3- and 6-month follow-up visits. Imputation methods used for the primary endpoint analysis will also be used for the 3- and 6-month models.

2. Drug-free Weeks

GLMM analysis will be conducted to compare the percentage of TAU+SCT, relative to TAU, participants who have drug-free weeks during the active treatment phase. Imputation methods used for the primary endpoint analysis will also be used for the analysis of drug-free weeks.

3. Stimulant-use and Substance-use Days

A repeated measures mixed model analysis will be conducted to compare the stimulant-use and substance-use days reported during the active treatment phase as a function of treatment group. A mixed model analysis will also be conducted to compare the stimulant-use and substance-use days reported for the 28 days prior to the 3 and 6-month follow-up visits as a function of treatment group.

4. Ratio of treatment hours attended to hours scheduled

The ratio of the number of outpatient (including intensive outpatient) substance-abuse treatment hours attended to the number of hours scheduled during the active treatment phase will be analyzed using a GLMM

analysis with the log of the number of scheduled hours and the type of patient (intensive outpatient or outpatient) as covariates.

For a number of the remaining secondary outcomes, the effect of TAU+SCT, relative to TAU, is considered for both the active phase and follow-up phase. For these outcomes, a reference is made to controlling for baseline values. In the context of these analyses, the 'baseline value' for the active phase is the value of the outcome prior to randomization. If the analyses reveal a significant treatment effect during the active phase, then the 'baseline value' for the follow-up phase will be the outcome prior to randomization; this analysis will evaluate whether the effect observed during the active treatment phase is maintained through follow-up. If the analyses reveal no significant treatment effect during the active phase, then the 'baseline value' for the follow-up phase will be the value of the outcome measured at the end of the active phase; this analysis will evaluate whether a treatment effect becomes evident over a longer period of time (i.e., a "sleeper" effect).

5. The ASI- Lite

The seven areas of functioning measured by the ASI- Lite (medical status, employment status, drug use, alcohol use, family status, legal status, psychiatric status) will be assessed at baseline, the end of the active treatment phase and at the 3- and 6-month follow-up visits. These data will be analyzed using a repeated measures mixed model with group, time, time X group interaction and baseline values controlled as noted above. Significance of Group is declared if the joint effect of the Group and Group X time interaction (as defined by a change in log-likelihood) was significant ($p<0.05$). These 7 tests will be performed without adjustment for multiple testing.

6. Sexual Risky Behavior as assessed by the RAB

The sex risk scale of the RAB, which produces a score ranging from 0-28, will be assessed at baseline, the end of the active treatment phase and at the 3- and 6-month follow-up visits. The sex risk score data will be analyzed using a repeated measures mixed model with group, time, time X group interaction and baseline values controlled as noted above. Significance of Group is declared if the joint effect of the Group and Group X time interaction (as defined by a change in log-likelihood) is significant ($p<0.05$).

7. Cocaine/METH craving as assessed by the BSCS

The BSCS craving score, which ranges from 0-12, is assessed weekly during the active treatment phase and at the 3- and 6-month follow-up visits. These data will be analyzed using a repeated measures mixed model.

8. Smoking Point-Prevalence Abstinence

GLMM analyses including site and treatment group will be used to model rates of achieving point prevalence abstinence as assessed at the week 10 visit of the active treatment phase and at the 3- and 6-month follow-up visits.

9. Continuous Smoking Abstinence

GLMM analyses including site and treatment group will be used to model rates of achieving continuous smoking abstinence during post-quit days 15-42.

10. Cigarettes per Day (CPD)

Given the smoking quit date's likely substantial impact on CPD, analyses for CPD during the active treatment phase will be conducted for the pre-quit and post-quit phases as well as for the entire treatment phase, with the treatment x week interaction effect for study weeks 4-9 being the effect of interest. A

repeated measures mixed model analysis will be conducted to compare the CPD reported for the 28 days prior to the 3 and 6-month follow-up visits as a function of treatment group.

11. Participants with Continuous Smoking Abstinence

The primary outcome analysis will be modified to compare the percentage of participants who achieve continuous smoking abstinence, relative to those who do not, on stimulant-free weeks during study weeks 4-10 of the active treatment phase. In addition, GLMM analyses will also be conducted to compare the percentage of participants who achieve continuous smoking abstinence, relative to those who do not, on stimulant-free UDS at the 3- and 6-month follow-up visits.

11.3.3 Safety Analyses

1. Adverse events

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group. The incidence of adverse events and serious adverse events by type will be compared between treatment arms using either Fisher's Exact mid-p-value or Chi-Square analysis as appropriate; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, body system, and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available.

2. Vital Signs

Repeated measures mixed models will be used to compare the treatment groups on blood pressure and heart rate from screening/baseline through study week 10.

3. The Hospital Anxiety and Depression Scale (HADS)

Repeated measures mixed models will be used to compare the treatment groups on depression and anxiety symptoms, as measured by the HADS, from screening/baseline through study week 10.

4. The Pittsburgh Sleep Quality Index (PSQI)

A repeated measures mixed model will be used to compare the treatment groups on the PSQI from screening/baseline through study week 10.

11.3.4 Missing Data

Logistic regression analyses will be conducted to identify patterns of attrition and to determine if there is differential attrition by treatment condition. A binary indicator variable for missing data will be regressed on treatment assignment and other covariates. Variables that are associated with attrition at or below the α=0.10 level of significance will be included in subsequent analyses where the assumption of data missing at random (conditional on covariates) is required.

For the primary outcome measure, whether (yes/no) a participant is stimulant-free during each week of the active treatment phase, missing data will be addressed as described in section 11.3.1. For the smoking outcome measures, missing smoking self-report/CO data will be treated as positive for smoking.

For all other outcome measures, and as a supplementary sensitivity analysis for the outcome measures above, a model to predict the existence of missing data based on the baseline covariates will be examined. Any baseline covariate that is related to the occurrence of missing data will be added to the list of control covariates for the hypothesis test. To minimize any impact of attrition on the test of hypotheses, intent-to-treat analyses will be conducted for all hypotheses. The GLMM analysis described in section 11.3.1 allows a missing at random assumption (Dang, Mazumdar and Houck, 2008). With these methods, if data are MAR, weeks with missing outcome may be ignored, and will therefore not be imputed. If the random effects model (GLMM) unexpectedly fails to converge, a general estimating equation (GEE) approach treating site as a fixed effect will be used. If this model is utilized, then missing data will be multiply imputed using standard multiple imputation procedures, since GEE inference is only valid if data are missing completely at random (MCAR).

11.4 Sample Size Estimate

The minimum sample size required to achieve 80% power using an alpha level of 0.05 (two-sided) and a 1:1 randomization ratio was computed based on a repeated measures study design that takes into account that the data are binary and can be correlated across repeated measurements (Rochon, 1998). We assumed a compound symmetry covariance structure to be conservative (correlation between 2 successive time points does not change over time), as well as a maximum correlation between any 2 time points of 0.65. The higher the assumed correlation between time points, referred to as phi, the less information that we gain from successive measurements, thus requiring a larger sample size. The assumption of 0.65 for the present study is based on the phi calculated for the stimulant UDS results from the subgroup of cocaine dependent participants in CTN-0009, a study that evaluated the impact of concurrently providing smoking-cessation treatment with substance-abuse treatment.

The probability of stimulant-free urines in the TAU group is another key assumption in determining sample size. A review of the stimulant UDS results for cocaine-dependent participants from three prior CTN studies, CTN-0009, CTN-0015 (Seeking Safety for women with PTSD and substance-use disorders), and CTN-0006 (Contingency management for stimulant abusers) produced probabilities ranging from 0.55 to 0.75, with the lower probabilities (i.e., 0.55) requiring larger sample sizes. Based on these prior studies, we assumed a probability of 0.6 for stimulant-free urines in the TAU group. A final key consideration in calculating sample size is the size of the group difference to be detected. The present study has been powered to detect the lower limit of a clinically meaningful effect. Specifically, this study will detect a group difference if the probability of stimulant-free urines in the TAU+SCT group is at least 0.7.

The sample size yielded from the assumptions outlined above is 528, with 264 in each treatment group. As described in section 11.6, an interim analysis to evaluate the accuracy of the assumptions made in calculating this sample size will be conducted, with an adjustment made to the sample size if needed.

11.5 Descriptive Statistics

Summaries of the characteristics of the participant population in both treatment arms at screening/baseline will be prepared for the intent-to-treat participants. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatments and for major subgroups.

11.6 Interim Analyses

In coordination with the centralized Data and Statistics center (DSC), an interim check of the primary outcome measure for the control group (event rates, covariance and correlation matrices) will be conducted to assess the adequacy of the projected study sample size since this parameter is being estimated from limited

repeated measures data and involves several key assumptions that impact the required sample size. The analysis will be conducted when approximately 250 participants (about 125 in the control arm) have been enrolled and have completed the active treatment phase of the study. No interim analyses other than the check for the control group summary statistics to determine sample size adequacy are proposed for the trial. Specifically, an interim analysis to examine whether there is overwhelming evidence that one treatment is better or worse than the other (e.g., TAU+SCT is significantly better than TAU for stimulant use outcome) is determined to be unnecessary for the present protocol. This determination is primarily based on the fact that the outcome of interest, stimulant use, would only be indirectly impacted by the experimental treatment. Thus, while we expect to find a statistically and clinically significant treatment effect at the end of the study, we do not expect to find a large enough treatment effect to warrant an interim efficacy analysis. In addition, the results of five prior randomized placebo-controlled clinical trials of bupropion in stimulant abusers suggest that the potential for harm to the participants is minimal and, thus, an interim analysis to assess for potential harm is unnecessary.

A DSMB will monitor the progress of the present trial. An interim analysis could be performed to assess efficacy, futility, or safety if requested by the DSMB or NIDA. Trial monitoring guidelines for early stopping based on overwhelming benefit might be based on the Haybittle-Peto boundary, which requires $p<.001$ to stop a trial early (Pocock, 2005). The monitoring guidance for early stopping for lack of benefit or for futility might be based upon an approach of conditional probability (Jennison and Turnbull, 2000). Additional safety interim looks will be performed (without formal testing being performed) per the DSMB's request.

11.7 Minority/Gender Analyses

In accordance with NIH guidelines, repeated measures mixed model and GLMM analyses will be completed to determine whether treatment response was significantly affected by participant minority/gender status using an interaction term for treatment, time and minority/gender as appropriate.

11.8 Post-hoc Analyses

In addition to the analyses described above, a number of post-hoc analyses will be completed. Some examples of possible analyses include an exploration of participant screening/baseline variables that are predictive of treatment outcome, site characteristics associated with treatment outcome, and the impact that using different CO cut-off levels (e.g., 8 ppm vs. 4 ppm) has on the smoking outcome measures.

12.0 REPORTING AND MONITORING

Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

Regulatory Files
The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for the regulatory documents compliance prior to study initiation, throughout the study, as well as at the study closure.

12.1 Informed consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. Each study site must have the study informed consent approved by their IRB(s). A copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the lead node (LN) prior to the site initiation visit. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

Prior to signing the informed consent form, research staff who are knowledgeable about the study will explain the study to the potential participant and provide the participant with a copy of the consent to read. If the participant is interested in participating in the study, a researcher who is authorized to obtain informed consent by the PI and if applicable by the IRB, will review each section of the informed consent form in detail, answer any of the participant's questions, and determine if the participant comprehends the information provided by administering the comprehension tool. The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document. The consent must be properly executed and complete to be valid. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Persons delegated by the PI to obtain informed consent must be listed on the Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

In order to ensure that potential study participants understand the research study, a comprehension "quiz" (referred to as a comprehension tool) may be administered to potential participants prior to the informed consent being signed. If the potential participant misses an item on the quiz, the research staff will re-review that information to ensure understanding of study procedures and may have the person re-take the consent quiz prior to signing the informed consent document. The content of the quiz may be modified per local IRB requirements.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty.

Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

Investigator Assurances

Each community treatment program site (CTP) must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

12.2 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol must comply with their Institution's policy regarding conflict of interest.

12.3 Clinical monitoring

Investigators will host periodic visits by NIDA contract monitors who will ensure all study procedures are conducted and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), and corresponding source documents for each participant.
Qualified node personnel (Node Protocol Managers and/or QA monitors) will provide site management for each site during the trial. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will verify that study procedures are properly followed and that site staffs are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

12.4 Study documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include <u>all</u> recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

12.5 Safety Monitoring

12.5.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

12.5.2 Protocol Violations Reporting and Management

A protocol deviation is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, deviation versus violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The decision about whether a departure from the protocol will be designated as a protocol deviation or a protocol violation will be made by the protocol's Lead Investigator in conjunction with the CCC. The consequences will be specified and participating sites should be informed.

All protocol violations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Violations CRF. Additionally, each site is responsible for tracking and reporting to their IRB as required. Protocol deviations will be noted by participating sites and reported to their IRBs as required. The CCC and the Data and Statistics Center and the Lead Investigator must be contacted immediately if an unqualified/ ineligible participant is randomized into the study.

12.5.3 Confidentiality

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

12.5.4 Adverse Events (AEs)

The Lead Investigator (LI) may appoint a Study Clinician (MD, PhD, or PI) for this study, who will review or provide consultation for each Serious Adverse Event (SAE) as needed. These reviews will include an

assessment of the possible relatedness of the event to the study intervention or other study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary. The medical monitor will determine which safety events require expedited reporting to NIDA, the DSMB and regulatory authorities. The study staff will be trained to monitor for and report adverse events and Serious Adverse Events.

Each of the CTPs has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each CTP will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

12.5.4.1 Definitions of Adverse Event and Serious Adverse Event

Standard definitions for adverse events and serious adverse events, their identification, characterization regarding severity and relationship to therapy and processing are described in Appendix A.

12.5.4.2 Reportable Serious Adverse Events

For the present study, the following SAEs will not be recorded in the data system nor reported to IRBs.

- Admission to a hospital/surgery center for preplanned/elective surgeries;
- Admission to a hospital for scheduled labor and delivery

13.0 DATA MANAGEMENT AND PROCEDURES

13.1 Design and Development

This protocol will utilize a centralized Data and Statistics center (DSC). The DSC will be responsible for the development of the case report forms (CRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Ideally, a web-based distributed data entry model will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

13.1.1 Site Responsibilities

The data management responsibilities of each individual CTP will be specified by the DSC.

13.1.2 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities, 2) provide final CRFs for the collection of all data required by the study, 3) provide data dictionaries for each CRF that will comprehensively define each data element, 4) conduct ongoing data validation and cleaning activities on study data from all participating CTPs through database lock.

13.2 Data Acquisition and Entry

Completed forms and electronic data will be entered into the data management system in accordance with the CRF Completion Guidelines established by the DSC. Only authorized individuals shall have access to electronic CRFs.

13.3 Data Editing

Data will be entered into the DSC automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated and distributed to treatment programs for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the DSC automated data acquisition and management system. Data status reports ideally will be issued monthly to assist the site, the corresponding RRTC (node) and the lead investigator to monitor the site's progress in responding to queries.

13.4 Data Transfer/Lock

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

13.5 Data Training

The training plan for CTP staff includes provisions for training on assessments, CRF completion guidelines, and computerized systems.

13.6 Data QA

To address the issue of data quality, the DSC will follow a standard data monitoring plan. An acceptable data quality level prior to any database lock will be given as part of the data management plan. Data quality summaries will be made available during the course of the study.

14.0 PUBLICATIONS AND OTHER RIGHTS

Protocol development and implementation in the NIDA CTN is a collaborative process. The publication plan for the current protocol will comply with the CTN Publications Subcommittee's guidance on publications. Individuals making substantive contributions to the protocol development and implementation will have opportunities to participate in publications. Other contributors will also be acknowledged.

15.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____

INVESTIGATOR (S)

• I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of participants.
• I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
• I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.
• I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.
• I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human participants.
• I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

Typed Name	Signature	Date
_____	_____	_____
Principal Investigator		
_____	_____	_____
Sub-Investigator		
_____	_____	_____
Sub-Investigator		
_____	_____	_____
Sub-Investigator		

16.0 REFERENCES

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The Validity of the Hospital Axiety and Depression Scale: An Updated Literature Review. *J Psychosom Res.* 2002;52:69-77.

Booth R.E., Kwiatkowski C.F., Chitwood, D.D. Sex related HIV risk behaviors: differential risk among injection drug users, crack smokers and injection drug users who smoke crack. *Drug Alcohol Depend*. 2000; 58: 219-226.

Brown, H. and Prescott, P. *Applied Mixed Models in Medicine*. John Wiley & Sons Ltd., 1999.

Budney AJ, Higgins ST, Hughes JR, Bickel WK. Nicotine and caffeine use in cocaine-dependent individuals. *J Subst Abuse*. 1993; 5: 117-130.

Buysse,D.J., Reynolds,C.F., Monk,T.H., Berman,S.R., & Kupfer,D.J. (1989). The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research, 28(2), 193-213.

Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 1997-2001. MMWR Morb Mortal Wkly Rep. 2005; 54:625-628.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA*. 2003; 289: 2560–2572.

Cohen, J. Statistical Power Analysis of the Behavioral Sciences. Lawrence Erlbaum Associates, Hillsdale NJ; 1988.

Croghan IV, Hurt RD, Dakhil SR, Croghan GA, Sloan JA, Novotny PJ, Rowland KM, Bernath A, Loots ML, Le-Lindqwister NA, Tschetter LK, Garneau SC, Flynn KA, Ebbert LP, Wender DB, Loprinzi CL. Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. *Mayo Clin Proc.* 2007;82(2):186-195.

Cropsey KL, Eldridge GD, Weaver MF, Villalobos GC, Stitzer ML. Expired carbon monoxide levels in self-reported smokers and nonsmokers in prison. *Nicotine Tob Res*. 2006; 8(5):653-9.

Dang Q, Mazumdar S, Houck PR. Sample size and power calculations based on generalized linear mixed models with correlated binary outcomes. *Computer methods and programs in biomedicine* 2008; 91: 122–127

DiClemente, C.C., & Hughes, S.O. Stages of change profiles in alcoholism treatment. *J Subst Abuse.* 1990; 2, 217-235.

Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008; 165: 179-187.

Elkashef AM, Rawson RA, Anderson AL, Li SH, Holmes T, Smith EV, Chiang N, Kahn R, Vocci F, Ling W, Pearce VJ, McCann M, Campbell J, Gorodetzky C, Haning W, Carlton B, Mawhinney J, Weis D.

Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacol*. 2008; 33: 1162-1170.

Fals-Stewart, W., O'Farrell, T.J., Freitas, T.T., McFarlin, .SK., Rutigliano, P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. J *Consult Clin Psychol*. 2000; 68, 134-44.

Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an α4β2 nicotinic acetylcholine receptor Partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA.* 2006;293(1):47-55.

Gorelick DA, Simmons MS, Carriero N, Tashkin DP. Characteristics of smoked drug use among cocaine smokers. *Am J Addiction*. 1997; 6: 237-245.

Hall, S., Havassy, B., Wasserman, D. Effects of commitment to abstinence, positive moods, stress, and coping on relapse to cocaine use. J *Consult Clin Psychol.* 1991; 59, 526-532.

Harrell, F. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and*

Survival Analysis. Springer, 2001.

Hasin DS, Trautman KD, Miele GM, Samet S, Smith M, Endicott J. Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry*. 1996; 153(9):1195-201.

Hatsukami DK, Grillo M, Pentel PR, Oncken C and Bliss R. Safety of cotinine in humans: Physiologic, subjective, and cognitive effects. *Pharmacol Biochem Behav.* 1997; 57(4): 643-650.

Heatherton T, Kozlowski L, Freckler R, Fagerstrom K. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *Brit. J. Addiction.* 1991; 86, 1119-1127.

Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. Incentives improve outcome in outpatient treatment of cocaine dependence. *Arch. Gen. Psychiatry*. 1994; 51:568-576.

Hughes J R and Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch. Gen. Psychiatry.* 1986; 43: 289-294.

Hughes JR, Gust SW, Skoog K, Keenan RM and Fenwick JW. Symptoms of tobacco withdrawal: A replication and extension. *Arch Gen Psychiatry.* 1991; 48:52-59.

Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tob Res.* 2003; 5:603

Hurt RD, Krook JE, Croghan IT, Loprinzi CL, Sloan JA, Novotny PJ, Kardinal CG, Knost JA, Tirona MT, Addo F, Morton RF, Michalak JC, Schaefer PL, Porter PA, Stella PJ. Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. *J Clin Oncol.* 2003;21(5):914-20.

Hurt RD, Offord KP, Croghan IT, Gomez-Dahl L, Kottke TE, Morse RM, Melton J. Mortality following inpatient addictions treatment. *JAMA*. 1996; 275: 1097-1103.

Javors MA, Hatch JP, Lamb RJ. Cut-off levels for breath carbon monoxide as a marker for cigarette smoking. *Addiction*. 2005;100(2):159-67.

Jennison CJ, Turnbull BW. *Group Sequential Methods with Applications to Clinical Trials*. Chapman & Hall/CRC, 2000.

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):56-63.

Kuehn BM. Studies linking smoking-cessation drug with suicide risk spark concerns. *JAMA*. 2009;301(10):1007-1008.

Lejuez C.W., Bornovalova M.A., Daughters S.B., Curtin J.J. Differences in impulsivity and sexual risk behavior among inner-city crack/cocaine users and heroin users. *Drug Alcohol Depend*. 2005; 77: 169-175.

Margolin A, Kosten TR, Avants SK, Wilkins J, Ling W, Beckson M, Arndt IO, Cornfish J, Ascher JA, Li SH, Bridge P. A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depen.* 1995; 40: 125-131.

McCoy C.B., Lai S., Metsch L.R., Messiah S.E., Zhao W. Injection drug use and crack cocaine smoking: independent and dual risk behaviors for HIV infections. A*nn Epidemiol*. 2004; 14: 535– 542.

McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argerious, M. The fifth edition of the Addiction Severity Index. *J Subst Abuse Treat.* 1992; 9, 199-213.

Mezinskis J, Dyrenforth S, Goldsmith J, Cohen M, and Somoza E. Craving and withdrawal symptoms for various drugs of abuse. *Psychiatric Annals.* 1998; 28:577-583.

National Institute on Drug Abuse. NIDA Research Report - HIV/AIDS, 2006. NIH Publication No. 06-576. US Department of Health and Human Services, National Institutes of Health, 2006.

Navaline H.A., Snider E.C., Petro C.J., Tobin D., Metzger D., Alterman A.I., & Woody G.E. Preparations for AIDS vaccine trials. An automated version of the Risk Assessment Battery (RAB): enhancing the assessment of risk behaviors. *AIDS Res Hum Retrov*. 1994; 10, S281-S283.

Nemeth-Coslett R, Henningfield JE, Katz J, Goldberg S. Effect of cocaine on rate of cigarette smoking. *Pharmacol Biochem Behav*. 1986; 25: 303.

Pantalon, M.V., Nich, C., Frankforter, T., & Carroll, K.M The URICA as a measure of motivation to change among treatment-seeking individuals with concurrent alcohol and cocaine problems. *Psychol Addict Behav*. 2002; 16, 299-307.

Petry NM, Martin, B, Cooney, JL, Kranzler, HR. Give them prizes, and they will come: contingency management for treatment of alcohol dependence. *J Consult Clin Psychol*. 2000; 68: 250-257.

Petry NM, Peirce JM, Stitzer ML, Blaine J, Roll JM, Cohen A, Obert J, Killeen T, Saladin ME, Cowell M, Kirby KC, Sterling R, Royer-Malvestuto C, Hamilton J, Booth RE, Macdonald M, Liebert M, Rader L, Burns R, DiMaria J, Copersino M, Stabile PQ, Kolodner K, Li R. Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs. *Arch Gen Psychiatry*. 2005; 62: 1148-1156.

Pocock SJ. When (Not) to Stop a Clinical Trial for Benefit. *JAMA*. 2005; 294 (17): 2228-2230.

Poling J, Oliveto A, Petry N, Sofuoglu M, Gonsai K, Gonzalez G, Martell B, Kosten TR. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Arch Gen Psychiatry*. 2006; 63: 219-228.

Prendergast ML, Hall EA, Roll J, Warda U. Use of vouchers to reinforce abstinence and positive behaviors among clients in a drug court treatment program. *J Subst Abuse Treat*. 2008; 35: 125-136.

Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation with individuals in substance abuse treatment or recovery. *J Consult Clin Psych*. 2004; 72(6): 1144-1156.

Reid M, Mickalian J, Delucchi K, Berger SP. A nicotine antagonist, mecamylamine, reduces cue-induced craving in cocaine-dependent subjects. *Neuropsychopharmacol*. 1999; 20 (3): 297-307.

Reid MS, Fallon B, Sonne S, Flammino F, Nunes EV, Jiang H, Kourniotis E, Lima J, Brady R, Burgess C, Arfken C, Pihlgren E, Giordano L, Starosta A, Robinson J, Rotrosen J. Smoking cessation treatment in community-based substance abuse rehabilitation programs. *J Subst Abuse Treat*. 2008; 35: 68-77.

Reimherr FW, Hedges DW, Strong RE, Marchant BK, Williams ED. Bupropion SR in adults with ADHD: a short-term, placebo-controlled trial. *Neuropsychiatr Dis Treat*. 2005; 1(3): 245-251.

Rochon, J. Application of GEE Procedures for Sample Size Calculations in Repeated Measures Experiments. *Statistics in Medicine*. 1998; 17:1643-1658.

Roll JM, Higgins ST, Budney AJ, Bickel WK, Badger GJ. A comparison of cocaine-dependent cigarette smokers and non-smokers on demographic, drug use and other characteristics. *Drug Alcohol Depen*.1996; 40: 195-201.

Roll JM, Higgins ST, Tidey J. Cocaine use can increase cigarette smoking: evidence from laboratory and naturalistic settings. *Exp Clin Psychopharm*. 1997; 5(3): 263-268.

Schroeder SA. A 51-Year-Old woman with bipolar disorder who wants to quit smoking. JAMA. 2009; 301 (5): 522-231.

Sees KL, Clark HW. When to being smoking cessation in substance abusers. *J Subst Abuse Treat*. 1993; 10: 189-195.

Shoptaw S, Heinzerling KG, Rotheram-Fuller E, Hao UH, Wang PC, Bholat MA, Ling W. Bupropion hydrochloride versus placebo, in combination with cognitive behavioral therapy, for the treatment of cocaine abuse/dependence. *J Addict Dis*. 2008a; 27(1): 13-23.

Shoptaw S, Henzerling KG, Rotherman-Fuller E, Steward T, Wang J, Swanson AN, De La Garza R, Newton T, Ling W. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug Alcohol Depen*. 2008b; 96: 222-232.

Shoptaw S, Rotheram-Fuller E, Yang X, Frosch D, Nahom D, Jarvik ME, Rawson RA, Ling W. Smoking cessation in methadone maintenance. *Addiction*. 2002; 97: 1317-1328.

Sobell LC, Sobell MB. Timeline follow back: A technique for assessing self-reported ethanol consumption. In J. Allen & R. Lit-ten (Eds.), *Techniques to Assess Alcohol Consumption.* Pp 19-28. New Jersey: Humana Press, Inc; 1992.

Stang P, Young S, Hogue S. Better Patient Persistence With Once-Daily Bupropion Compared With Twice-Daily Bupropion. *Am J Ther.* 2007;14:20-24.

Stein MD, Weinstock MC, Herman DS, Anderson BJ, Anthony JL, Niaura R. a smoking cessation intervention for the methadone-maintained. *Addiction*. 2006;101:599-607.

Verbeke, G. and Molenberghs G. *Linear Mixed Models for Longitudinal Data*. Springer, 2000.

Wiseman EJ, Williams DK, McMillan DE. Effectiveness of payment for reduced carbon monoxide levels and noncontingent payments on smoking behaviors in cocaine-abusing outpatients wearing nicotine or placebo patches. *Exp Clin Psychopharm*. 2005; 13(2): 102-110.

Ziedonis DM, Guydish J, Williams J, Steinberg M, Foulds J. Barriers and solutions to addressing tobacco dependence in addiction treatment programs. *Alcohol Res Health*. 2006; 29(3): 228-235

Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67:361–70.

17.0 APPENDIX A

17.1 Definition of Adverse Event and Serious Adverse Event

Adverse Event: An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered study-related or clinically significant. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. A thorough history during the eligibility assessment phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. The AE form is used to capture reportable AEs (as defined in the protocol) and also used to record follow-up information for unresolved events reported on previous visits. A study investigator will identify and characterize each AE, and follow appropriate reporting procedures.

Serious Adverse Event (SAE): A serious adverse event is defined as any untoward physical or psychological occurrence during the study that suggests a significant hazard, side effect, or precaution will be defined as an SAE. This includes, but may not be limited to any of the following events:

- Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported.
- Life threatening: Any adverse therapy experience that places the participant or participants, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more serious form, might have caused death).
- In-patient hospitalization or prolongation of existing
- Persistent or significant disability or incapacity,
- Congenital anomaly/birth defect.
- An event that required intervention to prevent one of the above outcomes.

Unexpected Adverse Event: Any adverse therapeutic experience, the specificity or severity of which is not consistent with the investigator brochure or the package insert. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy: Pregnancies that occur on study (i.e., conception between randomization and study day 121) will be captured on a pregnancy CRF and not separately reported as an AE or SAE.

Laboratory Results: Laboratory results will be captured on specific laboratory CRFs. Those results that are considered clinically significant will also be reported as an AE.

Eliciting and Monitoring Adverse Events: Qualified research staff will elicit participant reporting of reportable AEs/SAEs at study assessment visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last active treatment visit. The research staff will obtain as much information as possible about the reportable AE/SAE to complete the AE/SAE forms and will consult with designated staff as warranted. Reportable SAEs will be reported as indicated below. A study investigator will review reportable AEs for seriousness, severity, and relatedness weekly. Appropriate site staff will review all reportable AE documentation and verify accuracy of assessments at least once weekly when the participant attends the CTP to ensure that all of these AEs are appropriately reported and to identify any unreported AEs that require reporting. Reportable AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization even beyond the end of the study. Each participating site's Protocol PI is responsible for study oversight, including ensuring human research subject

protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Protocol monitors from the Clinical Coordinating Center (CCC) and local node staff will review the study sites and study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable SAEs are being followed appropriately by the research staff. The node staff or CCC monitor will ensure that any unreported or unidentified reportable SAEs discovered during visits are promptly reported by the site to the Safety Monitor, NIDA, the Node or Protocol PI or designee, the lead investigator for the study and the IRB per local IRB requirements and will be reported on the monitoring report. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or SAEs are discovered, to ensure future identification and timely reporting by the site. The NIDA CTN DSMB will also review data related to safety monitoring for this trial periodically at regularly scheduled meetings.

17.2 Assessment of Severity and Relatedness

Qualified research staff will review each reportable AE for seriousness, relatedness, and severity at each study assessment visit designated to collect AEs. The severity of the experience refers to the intensity of the event. The relatedness of the event refers to causality of the event to the study intervention. Relatedness requires an assessment of temporal relationships, underlying diseases or other causative factors and plausibility.

Severity: Severity grades are assigned by the study site to indicate the severity of adverse experiences. Adverse events severity grade definitions are provided below:

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/ therapy intervention required, hospitalization or hospice care probable
Grade 5	Death	

Relatedness: Relationship to therapy is defined as:

- Definitely related: An adverse event that follows a temporal sequence from administration of the test intervention and/or procedure; follows a known response pattern to the test intervention and/or procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the test intervention and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

- Probably related: An adverse event that follows a reasonable temporal sequence from administration of the test intervention and/or procedure; follows a known response pattern to the test intervention and/or

procedure and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.

- Possibly related: An adverse event that follows a reasonable temporal sequence from administration of the test intervention and/or procedure and follows a known response pattern to the test intervention and/or procedure, but could have been produced by the participant's clinical state or by other therapies.

- Unrelated: An adverse event that does not follow a reasonable temporal sequence after administration of the test intervention and/or procedure; and most likely is explained by the participant's clinical disease state or by other therapies.

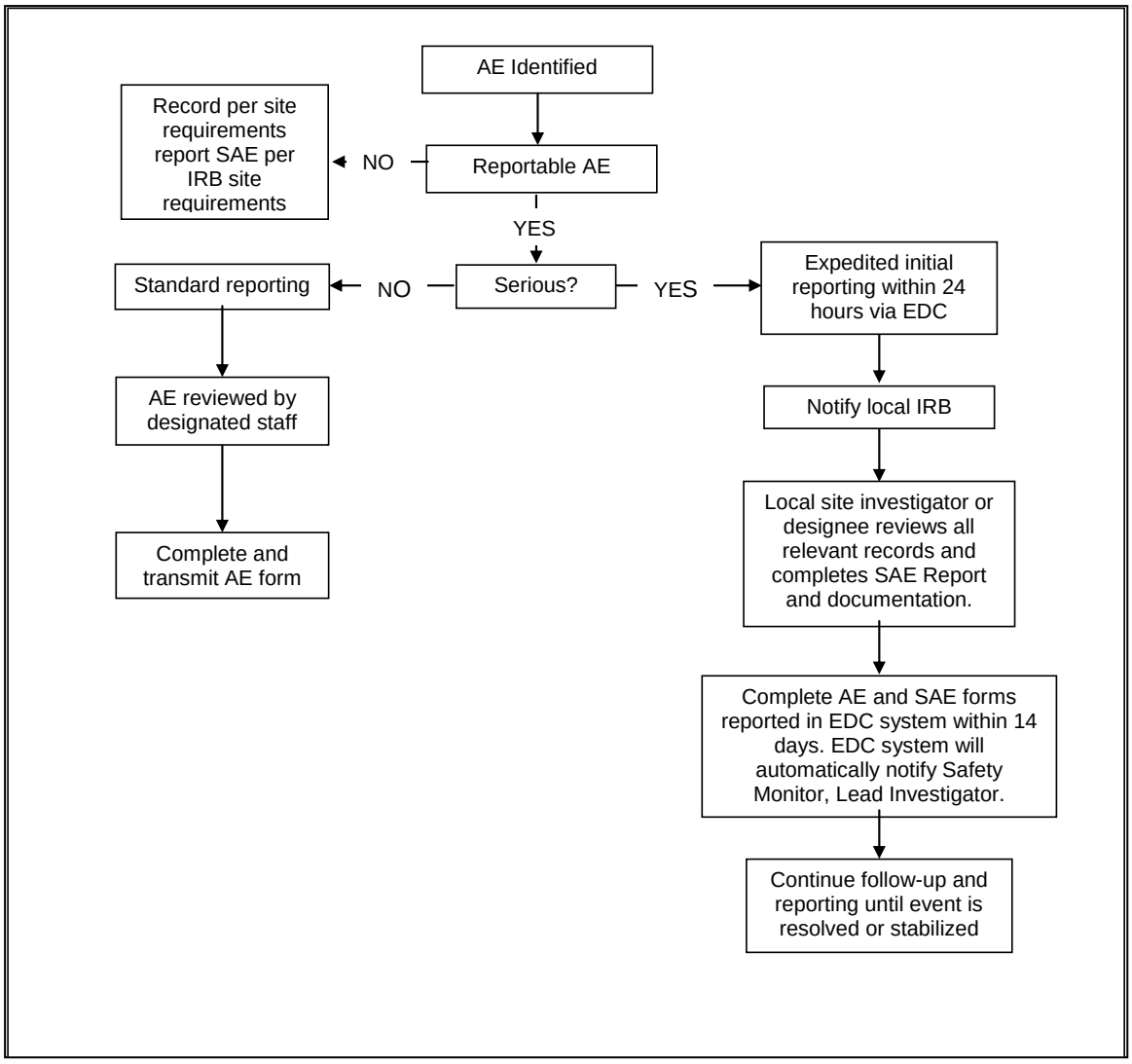
17.3 Reporting and Management Procedures of AE/SAEs

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). A participating site must alert the NIDA-assigned Safety Monitor and the Lead Investigator of reportable SAEs within 24 hours of learning of the event. The SAE form and summary and any other relevant documentation should also be submitted with the initial report if adequate information is available at the time of the initial report to evaluate the event and provide a complete report. Local sites are responsible for reporting SAEs to their IRB, per their IRB's guidelines.

Additional information may need to be gathered to evaluate the SAE and to complete the AE and SAE forms. This process may include obtaining hospital discharge reports, physician records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event. Within 14 days of learning of the event, an SAE form and related documents must be completed and entered into the data base. Documentation of the event that cannot be entered into the data base should be sent to the NIDA-assigned Safety Monitor. If the SAE is not resolved or stabilized at this time or if new information becomes available after the SAE form is submitted, follow-up SAE information must be submitted as soon as possible, but at least within 14 days after the site learns the information.

The study investigator at the site must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be removed from study intervention. The study investigator may consult with the Safety Monitor as needed. If necessary, an Investigator may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. Subsequent review by the Medical Monitor, DSMB, ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor and DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant should be asked to continue (at least limited) scheduled evaluations, complete an end-of-study evaluation and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or their condition becomes stable.

A NIDA-assigned Safety Monitor is responsible for reviewing all serious adverse event reports. The monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. Serious adverse events will be followed until resolved or considered stable, with reporting to the NIDA assigned Safety Monitor through the follow-up period. The site must actively seek information about the SAE as appropriate until the SAE is resolved or stabilized or until the participant is lost to follow-up and terminated from the study. The DSMB or the NIDA- assigned Safety Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, should be summarized by the Investigator in writing upon request for review by the NIDA-assigned Safety Monitor, DSMB, local ethics Committee/IRBs or regulatory authorities.


AE Identified
Reportable AE
NO
Record per site requirements report SAE per IRB site requirements
YES
Serious?
NO
Standard reporting
YES
Expedited initial reporting within 24 hours via EDC
AE reviewed by designated staff
Notify local IRB
Complete and transmit AE form
Local site investigator or designee reviews all relevant records and completes SAE Report and documentation.
Complete AE and SAE forms reported in EDC system within 14 days. EDC system will automatically notify Safety Monitor, Lead Investigator.
Continue follow-up and reporting until event is resolved or stabilized