

NIDA CTN Protocol 0054

**ACCELERATED
DEVELOPMENT OF
ADDITIVE
PHARMACOTHERAPY
TREATMENT
(*ADAPT*)**

for Methamphetamine Use Disorder

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention Deficit and Hyperactivity Disorder
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BRP	Extended-release Bupropion (as WellbutrinXL®)
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
CHRT	Concise Health Risk Tracking
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DL	Dose Logs
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyltranspeptidase
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IND	Investigational New Drug
LFT	Liver Function Test
LN	Lead Node
MA	Methamphetamine
mg	Milligrams
NDA	New Drug Application
NTX	Naltrexone
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
PI	Principal Investigator
PLB	Placebo
RAP-C	Research Advisory Panel of California
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UDS	Urine Drug Screen
TEA	Treatment Effects Assessment
TES	Treatment Effectiveness Score
VAS	Visual Analog Scale
XR-NTX	Extended-Release Naltrexone (as Vivitrol®)

2.0 ABSTRACT

2.1 Study Objective

The aim of this 2-stage, 3-site study is to investigate the effectiveness and safety of a combination of extended-release depot naltrexone plus extended-release bupropion as a potential pharmacotherapy for methamphetamine (MA) use disorder.

2.2 Study Design

Stage 1 will include 20 individuals with severe stimulant use disorder (methamphetamine type) enrolled across three study sites. Following a maximum 30-day screening period to establish eligibility, participants will receive a monthly injection of extended-release depot naltrexone (XR-NTX; as Vivitrol[®]) plus once-daily bupropion extended-release tablets (BRP; as Wellbutrin XL[®]) for 8 weeks. Take-home oral study medication (BRP) will be dispensed weekly for dosing on non-clinic days. Participants will be asked to attend clinic twice weekly for observed BRP dosing, collection of urine samples, assessments, and medical management. Following the 8-week active medication phase, participants will complete a follow-up phase, including a medication taper and post-medication phase follow-up visit during Week 9. If Stage 1 data document success (see criteria below) in at least 3 “responder” study participants, Stage 2 will follow utilizing the same protocol as in Stage 1, to enroll an additional group of 29 participants. Using the same criteria of “responder” success, if the combined stages document success in at least 9 of 49 study participants, the combination medication will be considered to have shown sufficient potential to advance to a large-scale placebo-controlled trial.

2.3 Study Participants

The total sample size will include 49 males and non-pregnant, non-lactating females, age 18 to age 65, who have met all eligibility criteria, including DSM-5 criteria for severe stimulant use disorder (methamphetamine type). Stage 1 will include 20 participants; Stage 2 will include 29 participants.

2.4 Intervention

The Stage 1 and 2 intervention consists of 8 weeks of pharmacotherapy, medical management, and medication adherence procedures. Extended-release depot naltrexone (XR-NTX) will be Vivitrol, by once-monthly injection. Extended-release bupropion (BRP) will be once-daily oral Wellbutrin XL. To increase dosing adherence, study components will include medical management, cellphone-based reminders, and cellphone-based dosing confirmation. Compensation will be provided for clinic attendance and dosing adherence.

2.5 Assessments

Screening/baseline assessments will include safety and medical measures including a medical and psychiatric history, physical examination, clinical lab tests (blood chemistry, hematology, and urinalysis), 12-lead electrocardiogram, vital signs, and pregnancy tests (for females). Screening/baseline assessments will also include psychological and drug use measures and

on-site urine drug screens (UDS). Assessments completed throughout the active medication phase include safety and medical measures, drug use and psychological measures, as well as dosing and adherence measures as outlined in the schedule of assessments. Bupropion adherence will be assessed by blood levels of bupropion and its metabolites, and via cellphone-based dosing confirmation procedures. Participants will complete post-medication phase follow-up assessments during Week 9.

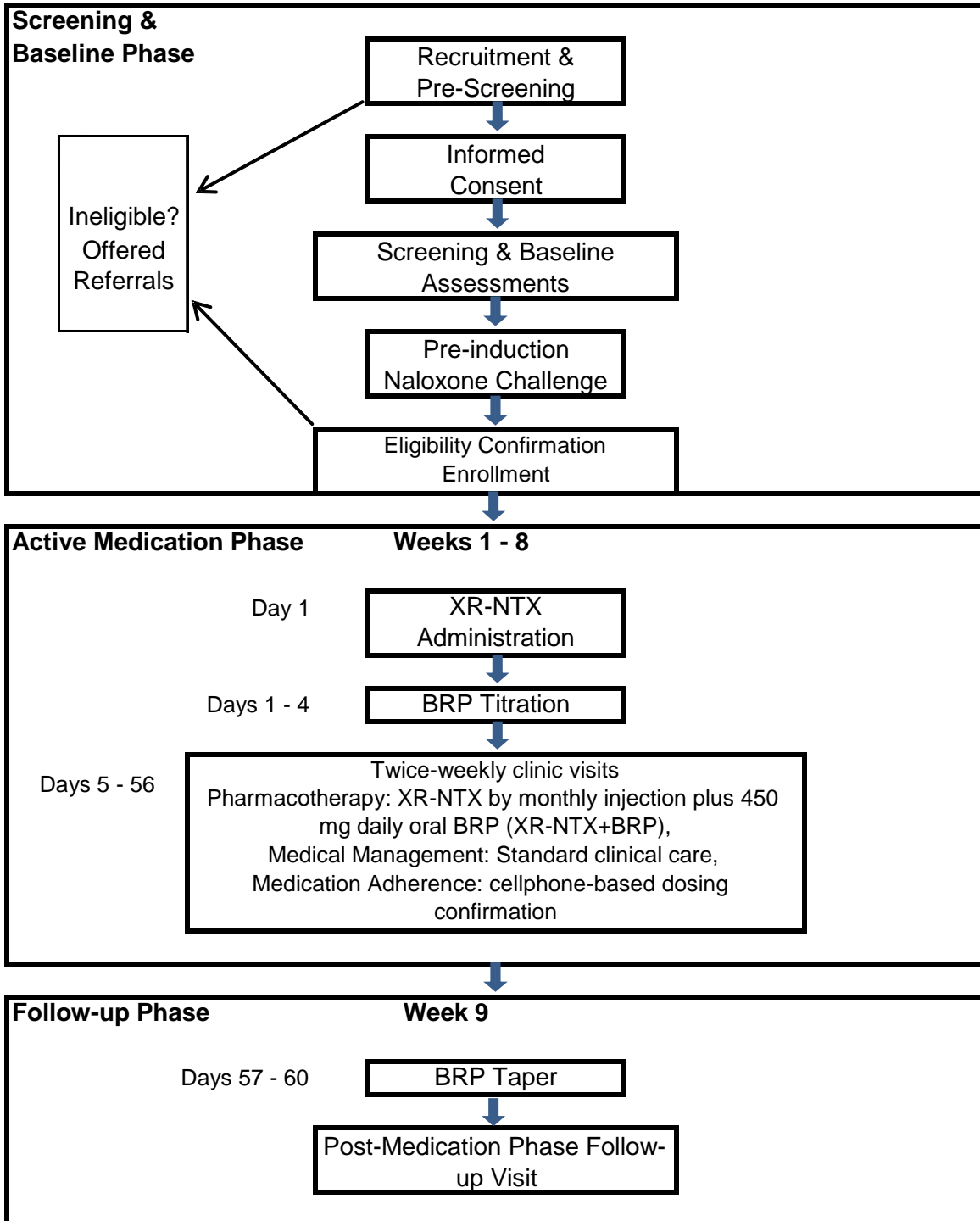
Safety of study participants and intervention tolerability will be assessed throughout the study by collection of AEs and concomitant medications. Participants who experience an AE deemed as compromising safety will be discontinued from further medication administration and provided referrals for medical care.

2.6 Analyses

The primary endpoint is an evaluation with a binary assessment of success in order to evaluate the potential therapeutic effect of the combination pharmacotherapy. Success is assessed by the number of “responders”: participants who provide at least 6 MA-negative urine tests during the second four-week period of the active medication phase, including the final test which must be obtained in the last week of the active medication phase.

Statistical analysis will use a one-sided 5% significance-level with P0 set at 0.1 and P1 set at 0.3 for measures of success in Stages 1 and 2, for an overall experimentwise 5% Type I error rate. The safety endpoint is measured by number and nature of study-related AEs. Descriptive analysis will examine participants’ baseline characteristics, success of efforts to enhance medication adherence, and adherence to other protocol parameters.

3.0 STAGE 1 STUDY SCHEMA*



Extended-release injectable naltrexone (Vivitrol) = XR-NTX
Extended-release bupropion (Wellbutrin XL) = BRP

* Stage 2 will follow same schema but with 29 participants

4.0 INTRODUCTION

4.1 Background and Rationale

Many years of concerted efforts have produced no effective medication to help initiate and maintain abstinence from methamphetamine (MA). Several promising candidates have shown preliminary clinical utility, including bupropion and naltrexone (Elkashef et al., 2008; Jayaram-Lindstrom et al., 2008). Development of a safe and effective pharmacotherapy is an important objective with considerable public health significance. This 2-stage trial is an innovative first step toward identifying truly promising candidate medications and medication combinations while efficiently culling those that fail in early-stage examination.

A recent advance in pharmacotherapy research has been the use of combinations of medications. Combinations of medication may be routine in clinical practice but are a recent phenomenon in medication development research. In medication development, single medications have traditionally been tested against placebo or other medications. Perhaps the best publicized combination medication study in psychopharmacology is a trial testing combination medications for depression (CO-MED; Zisook et al., 2011) made possible by the availability of a number of medications approved for depression. An ongoing trial addressing combination medications for the treatment of substance dependence is the Vivitrol+Suboxone combination trial for cocaine dependence—*Cocaine Use Reduction with Buprenorphine* (CURB, CTN-0048)—the first such attempt within the National Institute on Drug Abuse National Drug Abuse Treatment Clinical Trials Network (NIDA CTN).

Given the potential pool of available medication combinations, a strategy to quickly weed out the low-yield candidates is needed in order to devote resources to those with greater potential. This 2-stage protocol will enroll a small number of participants and identify “responders” who meet a statistically set cut-off for pre-determined conditions. Candidate agents failing to yield sufficient numbers of responders will be discarded and a protocol can move on to the next candidate test agent.

The current protocol will investigate the combination of extended-release bupropion and extended-release depot naltrexone for MA use disorder (severe per DSM-5 criteria). Interest in the combination of naltrexone with other drugs, especially with cognitive enhancers and anti-depressants (e.g., methylphenidate, bupropion, modafinil, mirtazepine), has increased: for example, “a formulation that combines naltrexone with methylphenidate could be a useful pharmaceutical approach to alleviate abuse potential of methylphenidate and other stimulants” (Zhu et al., 2011). The efficacy of naltrexone in reducing stimulant use has been empirically documented (Jayaram-Lindstrom, 2008). Still, the medication is not wholly effective, which is also true of another medication—bupropion—which has been extensively studied in trials for MA dependence. Bupropion has been found to be somewhat successful at reducing MA use in dependent patients but demonstrates an uneven response across patient types (e.g., many patients did not complete protocols, and participants assessed at baseline as high-frequency users did less well than low-frequency users).

The rationale for combining bupropion and naltrexone is predicated on their potentially complementary effects as shown in clinical research and as postulated in mechanistic arguments for naltrexone (e.g., Hanson, 2004), for bupropion, which may involve noradrenergic and/or dopaminergic effects (e.g., Ascher et al., 1995; Newton et al., 2006), and for the

combination, which could regulate the mesolimbic reward pathways (Ornellas & Chavez, 2011). Anecdotal reports derived from research involving opioid addicts who also use stimulants (e.g., Comer et al., 2006, etc.) also substantiate the utility of naltrexone for reducing MA use. The combination of naltrexone and bupropion has also been studied in recent research on the efficacy of the combination pharmacotherapy for controlling obesity (e.g., Greenway et al., 2010, Wadden et al., 2011). The pharmacology and safety of these study medications are discussed in later sections of the protocol (11.26, 11.27, and 11.28).

Combination pharmacotherapy, whereby medications exerting effects on different mechanisms of action may complement each other to help reduce stimulant use and to prevent relapse to stimulant use once abstinence has been attained, can be conceived in three ways: (1) one medication may act to enable the effects of other medication(s), as in CTN-0048, where the effect of Vivitrol allows buprenorphine to exert the hypothesized therapeutic effect under investigation; (2) one medication may act to enhance therapeutic effects of another, including possibly reducing side effects, as in combining different opioids in clinical pain management; and (3) the two medications may synergistically exert their combined effects as a novel compound and be studied as a single test agent.

This proposed protocol will treat the combination as a single test agent, potentially leading to future studies that make use of this platform to accelerate medication development research in and beyond the CTN. In this protocol, bupropion may serve to ameliorate some of the anhedonia and dysphoria that characterize early-phase abstinence from MA, and it also may counteract some of the side effects associated with naltrexone.

4.1.1 Treatment of Stimulant (Methamphetamine) Use Disorder with Bupropion

Bupropion is an attractive candidate medication for the treatment of MA use disorder for several reasons:

Bupropion is an antidepressant with stimulant properties and has been proven effective for the treatment of nicotine dependence (Richmond & Zwar, 2003).

Bupropion's pharmacologic activities are thought to operate partly through a dopaminergic mechanism which, when combined with its ability to alleviate the dysphoria seen in early abstinence, may reduce craving, thus helping to prevent relapse. The improvement seen in bupropion-treated patients with depression is a promising finding, as acute abstinence from MA in chronic users is associated with depression and impaired concentration (Newton et al., 2004).

Bupropion was found to be safe in clinical laboratory studies assessing its effects when administered concurrently with intravenous MA (Newton et al., 2006; 2005).

A Phase 2 efficacy study showed that bupropion significantly decreased MA use in MA-dependent participants who were using MA 18 days or less in the 30-day period prior to the start of screening (described below).

See Section 11.27.1 for additional details on research findings regarding the use of bupropion as a treatment for MA use disorder.

4.1.2 Treatment of Methamphetamine Use Disorder with Depot Naltrexone

The rationale for including extended-release depot naltrexone (XR-NTX) in this pharmacotherapy combination trial is based on preclinical and clinical pharmacology, as well as on results of clinical trials using oral naltrexone in the treatment of amphetamine-dependent individuals. Opiate antagonists, particularly naltrexone, have been shown to reduce

amphetamine-induced dopamine release and amphetamine-induced locomotor activity in rats (Hitzemann et al., 1982), attenuate amphetamine-induced locomotor sensitization in rats (Haggkvist et al., 2010), reduce cue-induced reinstatement for MA in rats (Anggadiredja et al., 2004), block amphetamine-induced reinstatement of amphetamine self-administration in rats (Haggkvist et al., 2009), reduce the subjective effects of amphetamine in amphetamine dependent patients (Jayaram-Lindstrom et al., 2008), and prevent relapse to amphetamine in a double blind, placebo controlled trial (Jayaram-Lindstrom et al., 2008). Seen from the perspective of the progression of work of preclinical effects of opiate antagonists, to a clinical pharmacology demonstration of attenuation of amphetamine by naltrexone, to an outpatient efficacy study, this trial seems like a logical extension using a dosage form that should enhance medication adherence.

See Section 11.27.2 for additional details on research findings regarding the use of naltrexone as a treatment for MA substance use disorder.

4.2 Significance of the Project to the Field

An effective medication—or combination of medications—to help achieve abstinence and to prevent relapse to methamphetamine use is an important objective with considerable public health significance. This study will test the combination of naltrexone and bupropion for its potential as a pharmacotherapy for MA use disorder. This study also provides an important foundation to evaluate the suitability of the platform as a basis for future research. This is an innovative move in a new direction for clinical trials within the CTN and, through the CTN's influence, the larger research community in our field.

4.3 Objectives

The objective of this 2-stage study is to investigate a combination pharmacotherapy, extended-release depot naltrexone (XR-NTX; as Vivitrol) and extended-release bupropion (BRP; as Wellbutrin XL) for MA use disorder.

4.3.1 Primary Objectives

The primary objective of this study is to determine the effectiveness and safety of the combination pharmacotherapy. Analyses will evaluate whether administration of XR-NTX+BRP will result in a set number of “responders” according to a statistically pre-defined and clinically meaningful clinical response criterion, defined as having six of eight MA-negative urine tests in the evaluation period (the last four weeks of the active medication phase), including the last test collected in the final study week of the active medication phase.

4.3.2 Secondary Objectives

Since medication adherence is paramount to a valid trial, the secondary objectives are to evaluate the acceptability of the combination medication, the usefulness of cellphone technology for documenting medication adherence, the utility of compensation and other outreach measures such as take-home dosing, to facilitate medication adherence, in addition to assessing any emerging adverse events.

5.0 STUDY DESIGN

5.1 Overview of Study Design

Stage 1 will include 20 participants enrolled and inducted on study medication across three study sites. Eligibility will be determined during a maximum 30-day screening period. To document an appropriate level of current methamphetamine use, prospective participants must submit at least three urine samples positive for methamphetamine of a possible four tests to occur within a 14-day period during which clinic visits occur with at least two days between visits. In addition, participants must self-report MA use on 20 or more days in the 30-day period prior to consent using the Timeline Follow-Back (TLFB) and meet diagnostic criteria for severe methamphetamine use disorder as per DSM-5. After screening is completed and eligibility is confirmed, including successful administration of a naloxone challenge test, participants will be enrolled in the active medication phase of the trial. Participants will receive a monthly injection of XR-NTX plus extended-release BRP for 8 weeks. Take-home oral study medication (BRP) will be dispensed weekly for dosing on non-clinic days. Participants will be asked to attend clinic twice weekly for observed BRP dosing, assessments, collection of urine samples, and medical management. On non-clinic days, participants will be provided with cellphone reminders and will participate in cellphone-based medication adherence activities (described in *Procedures*). Following the 8-week active medication phase, participants will complete a follow-up phase, including a medication taper and post-medication phase follow-up visit during Week 9. If Stage 1 data document success in at least 3 “responder” study participants, Stage 2 will follow and enroll an additional group of 29 participants utilizing the same protocol as in Stage 1. If the combined stages document success in at least 9 of 49 study participants, a large-scale, 8-week double-blind, placebo-controlled comparison of the medication combination to placebo may be conducted.

5.2 Duration of Study and Clinic Visit Schedule

The duration of this study will be approximately 13 weeks including up to 30 days for screening and the naloxone challenge, 8 weeks of active medication, and completion of the medication taper and post-medication phase follow-up assessment in Week 9. The screening phase may differ by participant in the length of time needed to complete eligibility assessments and confirm drug use status before medication induction. Confirmation of opioid-free status (urine drug screen and naloxone challenge) before XR-NTX induction will take approximately two hours. Twice-weekly clinic visits during the active medication phase will range from about 20–60 minutes in length depending on scheduled assessments. Twice-weekly medical management sessions will require about 15 minutes. The post-medication phase follow-up visit will take approximately 2 hours to complete.

An 8-week active medication period was selected to best reflect the typical medication duration for the target population in outpatient Community Treatment Programs (CTPs) and for pragmatic issues related to medication dosing. Participants will be asked to complete assessments as indicated on the schedule of assessments (see *Section 8.0*).

5.3 Study Population

A total of 20 MA-using males and females who meet eligibility criteria will participate in Stage 1; an additional 29 individuals will be enrolled in Stage 2.

5.3.1 Inclusion Criteria

Study participants *must*:

1. Be 18 to 65 years of age;
2. Be able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study;
3. Demonstrate understanding of study procedures by correctly answering all questions on the consent competency tool;
4. Be interested in reducing or stopping methamphetamine use;
5. Meet DSM-5 criteria for severe methamphetamine use disorder;
6. Self-report methamphetamine use on 20 or more days in the 30 day period prior to consent using the Timeline Follow-back (TLFB);
7. Submit at least three urine samples positive for methamphetamine out of a possible four tests to occur within a 14-day period during which clinic visits occur with at least two days between visits;
8. Meet subjective and objective measures of being opioid-free prior to enrollment and medication induction per study medical clinician's determination (including passing a naloxone challenge);
9. If female of childbearing potential, agree to use acceptable birth control methods during participation in the study;
10. Agree to use study cellphone to record videos of take-home dosing for transfer to study team.

5.3.2 Exclusion Criteria

Study participants *must not*:

1. Have an acute medical or psychiatric disorder that would, in the judgment of the study medical clinician, make participation difficult or unsafe;
2. Have Stage II hypertension as determined by study medical clinician (e.g., greater than or equal to 160/100 in 2 out of 3 readings during screening);
3. Have suicidal or homicidal ideation that requires immediate attention;
4. Have a known allergy or sensitivity to bupropion, naloxone, naltrexone, PLG (polyactide-co-glycolide), carboxymethylcellulose or any other component of the XR-NTX diluent;
5. Have a history of seizure, head trauma with neurological sequelae (i.e., loss of consciousness that required hospitalization), current anorexia nervosa or bulimia; in addition, any other conditions that increase seizure risk in the opinion of the study medical clinician will also be exclusionary;

6. Have evidence of second or third degree heart block, atrial fibrillation, atrial flutter, prolongation of the QTc; in addition, any other finding on the screening ECG that, in the opinion of the study medical clinician, would preclude safe participation in the study will also be exclusionary;
7. Have any liver function test (LFT) value > 5 times the upper limit of normal as per laboratory criteria;
8. Have platelet count <100k;
9. Have body habitus that precludes gluteal intramuscular injection of XR-NTX in accord with the administration equipment (needle) and procedures;
10. Have been in a prior study of pharmacological or behavioral treatment for methamphetamine use disorder within 6 months of study consent;
11. Have taken an investigational drug in another study within 30 days of study consent;
12. Be currently enrolled in behavioral or pharmacological addiction treatment services at the CTP;
13. Be receiving ongoing treatment with tricyclic antidepressants, duloxetine, venlafaxine, xanthines (i.e., theophylline and aminophylline), systemic corticosteroids, nelfinavir, efavirenz, chlorpromazine, MAOIs, central nervous system stimulants (i.e., Adderall, Ritalin, etc.), or any medication that, in the judgment of the study medical clinician, could interact adversely with study drugs;
14. Have been prescribed and taken naltrexone or bupropion within 30 days of consent;
15. Have pending legal action or other situation (e.g., unstable living arrangements) that could prevent participation in the study or in study activities;
16. Have a surgery planned or scheduled during the study period;
17. Require treatment with opioid-containing medications (e.g., opioid analgesics) during the study period;
18. Have a current pattern of alcohol, benzodiazepine, or other sedative hypnotic use which would preclude safe participation in the study as determined by the study medical clinician;
19. Be currently pregnant or breastfeeding.

5.4 Participant Recruitment

Study participants will be recruited using a variety of methods including word-of-mouth, referral, advertising, and study announcement flyers posted in local treatment programs.

5.5 Number of CTP Sites

The trial will involve three community treatment programs (CTP).

5.6 CTP Characteristics

Participating CTPs must:

1. Have a physician who can commit the time necessary to take a leadership role and oversee medical aspects of the study, perform medical assessments, confirm participant eligibility, prescribe study medications, administer study medications, review adverse events, and respond to adverse reactions that may occur during the course of the study.
2. Have at least one other medical clinician (i.e., physician, physician's assistant, or nurse practitioner) who can, in accordance with the regulations of the state where the site is located, make independent medical decisions and commit the time necessary to perform medical assessments, determine participant eligibility, prescribe study medications, administer study medications, review adverse events, and respond to adverse reactions that may occur during the course of the study.
3. Have a standard operating procedure in place for handling medical and psychiatric emergencies.
4. Have a physician available to provide after-hours clinical back-up for study-related emergencies.
5. Have access to a phlebotomist or other appropriately qualified medical personnel to complete blood draws.
6. Have access to, or the ability to contract with, a pharmacy/pharmacist (or other appropriate licensed entity) to store/dispense study medications as directed by the protocol, in accord with local regulations and NIDA stipulations.
7. Have adequate facility space available that will enable the performance of study procedures.

5.7 Rationale for CTP Selection

The three sites selected for participation in this trial were selected, in part, based on the node's interest in participating in the trial, and the presence of an existing team of experienced personnel knowledgeable in clinical trial operations and trained in core CTN assessments at the site. Information on site readiness and capacity gathered via a survey sent to Node Principal Investigators confirmed the following.

- An ability to recruit and enroll a minimum of 2.5 methamphetamine dependent individuals (not currently in treatment) each month over a rapid recruitment period.
- Experienced regulatory personnel capable of timely preparation of necessary regulatory documents and the ability to facilitate an expeditious IRB submission, approval, and continuing review process.
- Medical staff who could commit the time necessary to oversee medical aspects of the study, perform medical assessments, confirm participant eligibility, prescribe and administer study medications, and respond to possible adverse reactions that may occur during the course of the study.
- Familiarity with Electronic Data Capture systems and the capacity and discipline to conform to protocol-required direct data entry procedures.

- Adequate and available space that is appropriately fitted to enable the performance of study procedures.

6.0 OUTCOME MEASURES

6.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is MA-negative urine drug screen (UDS) test results over the course of twice-weekly visits in the final four weeks of the active medication phase. Participants who provide at least 6 of 8 MA-negative UDS tests during the evaluation period, including a MA-negative UDS test at the last clinic visit in the last week of the active medication phase, will be defined as “responders.” To determine the efficacy of XR-NTX+BRP for reducing MA use, the primary endpoint will be the number of “responders” at the completion of the trial. Three or more responders at the end of Stage 1 and 9 or more responders at the end of Stage 2 will indicate that the medication combination has shown sufficient potential efficacy to warrant moving forward to a large-scale Phase II-III, placebo-controlled trial.

6.2 Primary Safety Outcome Measure

The safety and tolerability of the combination medication condition will be determined using participants’ reports of adverse events and serious adverse events collected at clinic visits or via other contact.

6.3 Secondary Outcome Measures

- Participant-reported acceptance of protocol medications and procedures will be measured by satisfaction scales.
- Craving and psychological measures will be collected weekly.
- Data on other measures of interest will also be collected, including the success of cellphone based procedures and other measures to enhance medication adherence and adherence to other study procedures.

7.0 STUDY PROCEDURES

7.1 Screening and Baseline Phase

Assessments administered during screening will determine whether participants meet eligibility criteria and will provide baseline measures of drug use and other important life domains. Participants who do not successfully complete all screening items within 30 days of consent, including the naloxone challenge, will be considered screen fails.

7.1.1 Pre-screening Assessment

Individuals responding to recruitment materials or otherwise referred to the study will be pre-screened on the phone or in person to ascertain preliminary eligibility status. A series of questions (e.g., presence of MA use history, interest in participating in research to investigate medications that have potential to reduce MA use, ability and willingness to participate for the duration of the trial, etc.) will determine preliminary eligibility. Full screening appointments will be scheduled for those who meet preliminary eligibility criteria.

7.1.2 Informed Consent

At the start of the screening appointment before any assessments are administered, qualified study personnel will conduct the consent interview with prospective participants. The consent interview will include a description of the study, including study procedures and study medications. Participants will be given a copy of the IRB-approved consent form to review either on site or at home in accordance with requirements of the local IRB. Participants who remain interested after review of the consent form will be given a short quiz to ascertain their understanding of the project, its purpose, procedures involved, and the voluntary nature of participation. Those who do not successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate and will be assisted in finding other treatment resources if desired. Those who demonstrate understanding of the study and who voluntarily agree to participate will be asked to sign the informed consent form and proceed with screening assessments.

7.1.3 Screening Assessments

Upon signing the informed consent, participants enter a maximum 30-day screening phase to complete assessments to determine eligibility and to collect baseline data. Eligible participants must meet DSM-5 criteria for severe stimulant use disorder (methamphetamine type).

During the screening phase, prospective participants must submit at least three urine samples positive for methamphetamine out of a possible four tests to occur within a 14-day period during which clinic visits occur with at least two days between visits. In addition, participants must self-report MA use on 20 or more days in the 30-day period prior to consent using the Timeline Follow-Back. These criteria will be used to confirm current MA use and further substantiate a diagnosis of severe methamphetamine use disorder.

Once the participant completes all screening and baseline assessments, submits three MA-positive UDS tests, and is found otherwise eligible for continued participation, he/she may begin the pre-induction procedure (see below). Participants who do not complete all screening assessments within the 30-day screening period or who are otherwise found to be ineligible for participation in the study will be considered screen fails. Participants who fail screen will not be

allowed to return at a later date to repeat the screening process. Section 8.0 describes all study assessments.

7.1.4 Pre-Induction Strategy

The screening/baseline phase includes a pre-induction procedure to be conducted after all other eligibility criteria have been met. The pre-induction strategy is designed to ensure participants meet subjective and objective measures of being opioid-free, per study medical clinician's determination, prior to enrollment and medication induction. The bullets below outline steps for determining final eligibility of all study participants.

- Participants must self-report no clinically significant opioid use (i.e., at any level that could constitute a potential risk of precipitating opioid withdrawal upon naloxone administration) in the seven days prior to the naloxone challenge, as measured using the Timeline Follow-Back and by the Prior and Concomitant Medication assessment.
- To confirm opioid abstinence, a UDS administered on the day of the naloxone challenge must be negative for opioids prior to administration of the challenge. Individuals who are opioid-negative will continue in the pre-induction process. Individuals may provide an additional urine drug screen on a subsequent day if the study medical clinician determines that a second screen is appropriate.
- The naloxone challenge will be administered prior to study medication induction. A minimum 0.8mg bolus must be given before determining the outcome of the challenge. The study medical clinician will determine whether the participant is eligible to continue on to XR-NTX induction based on clinical judgment. Evidence of withdrawal signs or symptoms following naloxone administration will result in postponement of XR-NTX administration until a negative challenge result is achieved.

Participants who experience withdrawal symptoms following the naloxone challenge may be treated with ancillary medications, observed until symptoms resolve, and given the opportunity to return another day and be re-challenged if clinically indicated. Participants who are not interested in continuing to participate, or who fail a repeat naloxone challenge, will not be eligible to participate in the study but will be given referrals to local treatment programs as appropriate.

7.1.5 Final Determination of Eligibility and Enrollment

After completing all screening assessments including the naloxone challenge, the study physician must review and approve safety and eligibility assessments in order to confirm participant eligibility prior to enrollment. Enrollment will occur on the same day following the successful naloxone challenge after study eligibility has been confirmed and documented. The enrollment procedure will be conducted in a centralized process through the CTN Data and Statistics Center (DSC).

7.2 Active Medication Phase

7.2.1 Intervention

7.2.1.1 Pharmacotherapy

Extended-release Depot Naltrexone (XR-NTX). Participants will receive the first XR-NTX injection on the day of enrollment, following a successful naloxone challenge and confirmation of study eligibility. The second injection of XR-NTX will be administered at the beginning of Week 5. Prior to the second XR-NTX administration, a naloxone challenge may be administered again at the discretion of the study medical clinician to ensure continued suitability for XR-NTX. The XR-NTX injection shall be administered following guidelines in the package insert.

Well-developed precautionary procedures will be followed to avoid adverse events associated with medication administration. For example, body habitus will be assessed during the physical exam at screening to assure that intramuscular administration is feasible as an inadvertent subcutaneous injection of XR-NTX may increase the likelihood of injection site reactions. Individuals whose body habitus precludes a gluteal intramuscular injection of naltrexone using the needles provided will be excluded from the study.

Extended-Release Bupropion (BRP). The first dose of BRP will be given on the day of enrollment (Day 1) immediately following XR-NTX administration. Take-home oral study medication (BRP) will be dispensed weekly for dosing on non-clinic days. Participants will be asked to bring their BRP medication bottle to the clinic for each visit so that self-administration of the BRP dose for each in-clinic visit day can be observed by medical staff. A daily dose of 150 mg will be dispensed for Days 1 and 2, 300 mg daily for Days 3 and 4, and 450 mg daily for Days 5 through 56. If the participant reports intolerable symptoms or side effects at the full 450 mg BRP dose, and it is deemed appropriate by the study medical clinician, a dose reduction may occur. The dose may be reduced to 300 mg daily. If intolerable adverse effects continue, the participant may be withdrawn from further medication administration. If intolerable adverse effects resolve after an initial dose reduction, and it is deemed appropriate by the study medical clinician, titration to the full 450 mg target BRP dose may be attempted again up to Day 21.

7.2.1.2 Medical Management

At each clinic visit, participants will meet with a study medical clinician to discuss adverse events, consider potential medication side effects, and discuss other pertinent issues in keeping with sound medical practice. Ancillary medications may be provided for study medication-related adverse events as clinically indicated. A range of prescription and over-the counter ancillary medications may be used for anxiety, nausea, vomiting, diarrhea, muscle pain, and insomnia. At all medical management visits, the medical clinician will remind participants about the importance of adhering to the study procedures, including attending scheduled clinic visits and complying with cellphone-based dosing confirmation procedures.

7.2.1.3 Medication Adherence Procedures

To improve adherence to the bupropion dosing regimen and other protocol activities (e.g., clinic attendance), the protocol includes a cellphone component designed to increase and document daily dosing adherence.

Technology Training. After eligibility has been established and the participant has been enrolled in the active medication phase of the study, staff will provide instruction on the use of the study-provided cellphone to enhance and document adherence with medication taking.

Cellphone Equipment. Participants will be provided with a study cellphone (and battery charger). Phones will be camera-equipped and capable of e-mail, text messaging, voicemail, still photo and video recording. Airtime/service plans will be included, to allow participants to make personal calls and send text messages without restriction. The cellphone equipment will be retained by participants through the end of their participation in the study. If the participant does not require a replacement cellphone during the course of the study, the participant will have the option to keep the study cellphone. Airtime/service plans will not be provided beyond the end of participation in the study. Replacement cellphones and cellphones participants chose not to keep should be returned at the end of study participation.

Cellphone-based Procedures. Prior to enrollment, study personnel will request a signed agreement from participants regarding the use of the cellphone for the purposes of the study. Participants will be informed of the medication adherence procedures, including the requirement to record videos of oral study medication ingestion at home. If a participant fails to bring his/her oral study medication to the clinic so that self-administration of the dose can be observed, the participant will be asked to record a video of him/herself taking the dose for that day at home (if the dose has not already been taken). If the participant records the video, he/she will be compensated as if the medication bottle was returned to the clinic that day for in-clinic observed dosing. Because the purpose of providing study cell-phones is to document medication dosing on non-clinic days, participants who withdraw from medication will not be provided with replacement phones. Participants will be informed of and trained on video recording and transfer procedures (including practice sessions in clinic; details in MobiControl Video Instructions SOP.)

Set-up and Maintenance of Cellphone Equipment. IT staff will prepare the phones, pre-program the cellphone number, and install required applications including the Device Management System (i.e., MobiControl) used to securely store and transmit the recorded dosing videos. IT staff will work with clinical and research staff to ensure proper use of phones and to resolve problems and replace equipment as needed in a timely manner.

Lost/Stolen/Inoperable Cellphones. Participants will be notified that failure to maintain the phone in their possession will result in a “lost or stolen phone” report to the service provider, disabling the SIM card, deleting the contents, and nullifying the service on the phone, thus rendering the cellphone useless and of limited value. Tracking programs installed on study cellphones will only be accessed upon report of a lost/stolen phone. Study staff will not use the cellphone tracking application to track or locate participants. A one-time replacement of a lost, stolen, or inoperable study-provided phone may be permitted. A second loss/theft of a study phone will not be replaced.

Protection of Participant Privacy Regarding Cellphone. At no time will the study personnel access the cellphone-based memory of usage in terms of time, numbers called, text messages received or sent, or web browsing history, unless requested by the participant to help troubleshoot a problem. Additionally, the tracking program will be accessed only in the case of a lost/stolen phone. Access to the phones is restricted to the study personnel who are directly involved in the trial. Participants will be advised on how to secure their phones with passwords and how the mobile device management application (i.e., MobiControl) will be used to transmit

dosing video to the study team as an encrypted file. Participants will be advised to delete video recordings on the cellphone upon staff confirmation of successful transmission.

Staff-to-Participant Cellphone Contact. Staff will make calls and/or send texts or e-mails as regular reminders for clinic visits or dosing requirements. If a participant has not recorded the dosing video by an agreed upon time on a take-home dosing day, study staff will contact the participant to ask the participant to take his/her study drug dose and document it via cellphone-recorded video as soon as possible.

7.2.2 Management of Study Medications

This is an open-label, non-blinded trial, and Stage 1 and Stage 2 participants will receive the same medications.

As set forth in the protocol agreement signed by each site principal investigator (see Section 14, *Signatures*), study CTPs, are required to observe local, state, and federal regulations regarding receipt, custody, dispensing, disposition, and associated documentation of all medications used in this study. This includes study medications (extended release bupropion and extended-release depot naltrexone) provided by the NIDA contractor and naloxone purchased and maintained by each CTP.

Appropriately qualified and trained medical personnel will maintain an accurate and real-time accounting of all study medication, which will be available for verification by study monitors. Drug-accountability records including perpetual inventory, will include the amount of study medication ordered, received, transferred between areas of the study site (from pharmacy to clinic, for example), and those dispensed to and returned by an individual participant. Documentation will also record unused medications returned to the NIDA contractor for destruction. As with all study documentation, drug accountability records, must be maintained in accordance with Good Documentation Practices and must be attributable, legible, contemporaneous, original and accurate.

7.2.2.1 Study Medication Storage

All medication used in this study will be stored in compliance with federal, state, and local laws and institutional policy. Study medications will be stored in a locked, secure, limited-access location under the conditions specified by the package insert; XR-NTX will be stored in a secure, limited-access refrigerator.

7.2.2.2 Used/Unused Medication

Unused study medication will be returned and logged into a perpetual inventory of returned medication. Returned medications will be accurately labeled, securely stored, and kept separately until returned to NIDA for destruction. Damaged, returned, expired, or unused study medication will be accounted for by the NIDA contract monitor before being returned for destruction. Expired naloxone and other ancillary medications obtained for this study will be destroyed on site or sent for destruction per local institutional policies.

7.2.2.3 Lost Medication

There will be no replacement of any dispensed study medications.

7.2.2.4 Prescribing and Dispensing Study Medications

All study medications shall be prescribed and dispensed by delegated medical staff licensed and appropriately trained to prescribe and dispense study medications. XR-NTX injections will be administered during Week 1, and again at the first visit of Week 5. Oral BRP will be provided to the participant weekly in labeled medication bottles that will include both in-clinic, observed doses and self-administered doses for non-clinic days.

7.2.2.5 Drug Packaging

XR-NTX will be supplied in single use packages marked with medication kit numbers. Each package will contain one 380 mg vial of Vivitrol[®] microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of Vivitrol[®], one 5 mL prepackaged syringe, one 1-inch 20 gauge needle, two 1.5-inch 20 gauge needles, and two 2-inch 20 gauge needles with needle protection devices. Lot number and medication expiration date will be included on the package labels supplied by the manufacturer.

The BRP tablets will be dispensed in weekly medication bottles labeled to include lot numbers, study week number, protocol number, and study drug information. The label will also include: "Caution: New Drug- Limited by Federal Law to Investigational Use. Store at Controlled Room Temperature (20-25°C or 68-77°F)" as well as the manufacturer and distributor information.

7.2.3 Participant Withdrawal

Participants will be withdrawn from further medication administration if it is clinically determined that continuation may be unsafe. For example, participants who develop uncontrolled hypertension (160/100 or higher on three consecutive visits) will be withdrawn from further medication. Women who become pregnant during the medication period will be withdrawn from study medication. Participants reporting use of medications that may interact with naltrexone or bupropion will be withdrawn based on clinical judgment. Participants who experience intolerable side effects or other physical or psychiatric conditions regardless of relationship to the study medication may also be withdrawn from further study medication administration.

The medical clinician may determine that a participant's clinical condition has deteriorated during the course of the study. Examples of clinical deterioration that might trigger a decision to withdraw the participant from medication include the following:

- New onset of psychiatric or medical conditions that would require intervention and preclude continued participation in the study (e.g., emergence of psychosis, suicide risk, severe cognitive impairment, or dangerous criminal behaviors);
- Worsening of pre-existing psychiatric or medical condition that would preclude continued safe participation in the study;
- Worsening of substance use disorder or overdose such a higher level of care is indicated.

The study medical clinician, in collaboration with the study physician and site principal investigator, may consult with the lead investigator(s) and study medical monitor in making this decision. In the event a participant is withdrawn from further medication administration, referrals to treatment programs or recommendations for medical care should be provided. At any time, participants may decide that they no longer wish to continue to receive medication or to participate in the study. Those who opt out of study medication will be encouraged to continue to make clinic visits and complete assessments. Unless consent is withdrawn, effort will be made to continue twice-weekly visits throughout the duration of the planned treatment phase

(weeks 1 – 8) with all participants who prematurely discontinue medication administration during the active medication phase. In the event a participant becomes pregnant during the medication period, a taper is not indicated. The participant will be discontinued from further study medication administration, referred for medical care, and the pregnancy followed until an outcome is known. In most cases, a taper is not indicated if the study medical clinician determines medication discontinuation is warranted for medical or psychiatric reasons. If a taper is believed to be necessary based on clinical judgment, the study medical clinician, in collaboration with the study physician and site principal investigator, should consult with the lead investigator(s) and study medical monitor.

7.3 Follow-up Phase

7.3.1 Bupropion (BRP) Taper

A taper will occur during the first four days of Week 9 (Days 57 – 60) for participants continuing on bupropion through the end of the active medication phase. The daily dose will be reduced to 300 mg for Day 57 and Day 58, and to 150 mg for Days 59 and 60. For any participant who is already taking a reduced dose, the daily dose will be reduced to 150 mg for Day 57 and Day 58. No additional doses will be provided for Days 59 and 60.

7.3.2 Post-Medication Phase Follow-up Assessment

All enrolled participants will be asked to complete post-medication phase assessments during Week 9 according to the schedule of assessments (see Table 2, section 8.0). Tracking and locating strategies will be used to ensure the highest possible follow-up rates. A locator form with detailed contact information will be completed at screening and updated at week 5, or when the participant reports a change in locator information.

7.4 Participant Reimbursement

Study participants will be provided with study medication and medical management at no cost. In addition, participants will receive gift cards or cash (based on local regulatory requirements) as compensation for time, travel, parking, and other costs borne by the participant. A total of \$60 will be provided for completion of screening/baseline assessments (divided among multiple screening visits if required). A total of \$10 will be provided for each additional clinic visit to provide a urine sample during the screening/eligibility phase. During the active medication phase, a total of \$20 will be provided in compensation per visit for 15 visits, with \$15 provided for completion of assessments including a urine sample (\$10 will be provided for assessment without a urine sample), and \$5 for bringing in the study medication bottle (no bottle will be returned on the first visit) for in-clinic observed dosing. In summation, participants will receive \$60 for screening, \$10 for each eligibility clinic visit (5 possible), \$30 for each Vivitrol injection visit (\$30 x 2 injections = \$60), \$20 for completion - 15 clinic visits over the 8-week active medication phase (15 visits x \$20 per visit = \$300) and \$15 for the first clinic visit, \$10 for each of the video-confirmed self-administration dosing events on non-clinic days (5 x 8 = 40 x \$10 = \$400); \$10 for each of the video-confirmed self-administration dosing events on non-clinic days during the follow-up phase taper (4 x \$10 = \$40), \$55 for the post-medication phase follow-up plus \$30 for return of cellphone. The total compensation possible is \$1,010 as outlined in Table 1 below.

Table 1. Compensation Schedule

Visit/Assessment	Amount	# of Payments	Total
Screening Assessments	\$60	1	\$ 60
Eligibility Phase Clinic Visits (5 possible)	\$10	5	\$ 50
Vivitrol Injection Visit	\$30	2	\$ 60
Clinic Visits (8 week Active Medication Phase)	\$15	16	\$ 240
Medication Bottle Return	\$5	15	\$ 75
Cellphone dosing video	\$10	44	\$440
Post Medication Phase Follow up	\$55	1	\$ 55
Cellphone Return	\$30	1	\$ 30
Maximum Compensation Possible			\$ 1,010.00

8.0 STUDY ASSESSMENTS

Study measures were chosen to minimize the research burden on participants yet collect adequate data to support analyses and ensure safety. Importantly, many of the study measures were selected to record vital health information and are similar to other recent and ongoing studies of bupropion and extended-release naltrexone. Additional measures were selected to obtain information usually included in medication studies, and include assessments of drug abuse and dependence diagnoses, psychological status, and measures of craving. Safety is assessed at each visit. Additional forms are used to collect and document information such as dosing and protocol satisfaction. The NIDA endorsed Substance Abuse and Addiction (SAA) common data elements from Core Tier 1 of the PhenX Toolkit (www.phenxtoolkit.org), which include demographic and other baseline information, will be captured directly or will be populated from the answers to questions from other assessments. A table that describes the way in which each PhenX question is mapped to the corresponding trial assessment item is included as part of the trial documentation. Table 2 provides the schedule of study assessments. On average, screening and eligibility assessments will be completed in 4-6 hours, including confirmation of opioid-negative status required before XR-NTX induction. Twice-weekly assessments during the active medication phase will be completed in approximately 20 to 60 minutes. The post-medication phase follow-up visit is expected to take approximately 2 hours.

Table 2. Schedule of Assessments

Study Phase	Screening and Baseline Phase ^E		Active Medication Phase																Follow-up Phase
	0		1		2		3		4		5		6		7		8		9
Study Week	0		101	102	201	202	301	302	401	402	501	502	601	602	701	702	801	802	901/PMP-FU
Study Visit	SV01- Final SV	Final SV	101	102	201	202	301	302	401	402	501	502	601	602	701	702	801	802	901/PMP-FU
Informed Consent	X																		
General Measures																			
Inclusion/Exclusion	X	X																	
Locator Form	X										X								
Demographics Form	X																		
Protocol Satisfaction Survey																			X
End of Medication																			X
Study Termination																			X
Safety and Medical Measures																			
Medical and Psychiatric History	X																		
Self-Report of HIV Testing	X																		
Physical Examination	X																		X
Injection Site Examination				X								X							
Electrocardiogram	X																		
Clinical Laboratory Tests	X																		X
Bupropion Blood Levels											X						X		
Pregnancy and Birth Control Assessment ^A	X	X	X								X						X		
Vital Signs ^B	X	X	X		X		X		X		X		X		X		X		X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events and Serious Adverse Events ^C	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Use and Psychological Measures																			
Timeline Follow-back	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Analog Craving Scale	X	X	X		X		X		X		X		X		X		X		X
Concise Health Risk Tracking	X		X				X				X				X				X
DSM-5 Checklist	X																		
Treatment Effect Assessment	X																		X
Alcohol and Substance Use History	X																		
Tobacco Use History	X																		X
Quality of Life	X																		X
Medication Procedures and Measures																			
Naloxone Challenge	X	X																	
XR-NTX Administration			X								X								
BRP Observed Dosing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose Logs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cellphone confirmation of dosing ^D																			
Issue Study Cellphone			X																

^A Collected according schedule of assessments, including PRIOR TO the naloxone challenge and XR-NTX administration.

^B Collected according to schedule of assessments, including BEFORE and AFTER administration of naloxone, XR-NTX, and first dose of BRP.

^C Collected at each visit after consent (i.e. SV02 through the post-medication phase follow-up visit)

^D Collected on non-clinic visit days and days the participant fails to return medication bottle for in-clinic observed dosing

^E The "SV01-Final SV" column lists all assessments collected during the SCR and BL period. Some SCR and BL assessments are collected once, others are collected multiple times during this period. The "Final SV" column lists the assessments that must be completed on the final SV, which becomes the date of enrollment.

8.1 General Measures

8.1.1 Prescreen

Individuals responding to recruitment materials or otherwise referred to the study will be pre-screened on the phone or in person to ascertain preliminary eligibility status. Prior to administering the IRB-approved pre-screen interview, staff will provide a brief overview of the study and will obtain and document verbal consent.

8.1.2 Inclusion/Exclusion

Individual inclusion and exclusion criteria are listed to enable documentation of eligibility. Only participants who continue to meet study eligibility criteria will be allowed to continue in the screening phase, including pre-induction procedures, and active medication phase.

8.1.3 Locator Form

A locator form will be used to obtain information to assist in tracking participants during treatment and at follow-up. This form will collect participants' current address, email address, and phone numbers, as well as names, addresses and phone numbers of family/friends who may know how to reach the participant if direct contact efforts are unsuccessful. This information will be collected at screening and updated at week 5, or when the participant reports a change in locator information. No information from this form will be used in data analyses.

8.1.4 Demographics Form

The demographics form will collect information about demographic characteristics of the participant at screening, including sex, date of birth, ethnicity/race, education, employment pattern, and marital status.

8.1.5 Protocol Satisfaction Survey

Satisfaction with medication components, cellphone, and other study procedures will be recorded on the Protocol Satisfaction Survey completed at the post-medication phase follow-up assessment in Week 9. A survey will be completed by both the participant and a study team member. These forms will be used in data analyses to evaluate secondary objectives including the acceptability of the combination medication and the usefulness of cellphone technology for documenting medication adherence.

8.1.6 End of Medication

This form documents the participant's status with regard to the study medication. It will be completed at the time a decision is made to discontinue a participant from further medication administration or at the post-medication phase follow-up assessment in Week 9.

8.1.7 Study Termination

The participant's status with regard to study visits will be recorded at the end of the study, providing information on when and why study visits were stopped, and whether the participant completed the final protocol visit at week 9.

8.2 Safety and Medical Measures

8.2.1 Medical and Psychiatric History

The participants' medical and psychiatric history will document past and present health conditions at screening to help determine eligibility and to provide baseline information.

8.2.2 Self-Report of HIV Testing

HIV testing status will be assessed using PhenX Core Tier 1 items. Participants will be asked whether the participant has ever had an HIV test, when the most recent test occurred, the test result, and the most important reason the participant was not tested, if the participant was not tested in the past 12 months.

8.2.3 Physical Examination

A physical examination will be completed at screening to ensure that there are no exclusionary medical conditions and to gather baseline information. At screening, the physical will include an examination of the participant's body habitus and the planned injection site(s) to assess appropriateness for XR-NTX gluteal intramuscular injections. The physical examination will be repeated at the post-medication phase follow-up assessment in Week 9.

8.2.4 Injection Site Examination

Appropriate medical personnel will examine the injection site on the next visit following each XR-NTX injection. These examinations usually occur at visits 102 and 502 but should occur at the next attended visit if visit 102 or 502 is missed. Additional monitoring may also be required. Participants will be asked to immediately report any injection site reactions to allow evaluation, monitoring, and possible referral, as needed. Injection site reactions should be documented on the Injection Site Abnormality Log

8.2.5 Electrocardiogram (ECG)

A 12-lead ECG will be administered at screening to assist in determination of participant eligibility.

8.2.6 Clinical Laboratory Tests

A comprehensive blood chemistry including liver function tests (LFTs: including AST, ALT, ALP, and bilirubin), hematology panel, and a standard urinalysis will be performed to help determine eligibility at screening. These tests will be repeated at the post-medication phase follow-up visit. An accredited central laboratory (College of American Pathologists or equivalent), that meets CLIA guidelines will perform testing, provide normal values, and proof of lab certifications.

8.2.7 Bupropion Blood Levels

Blood will be collected to test for bupropion levels, once prior to XR-NTX and BRP administration at visit 501 and again prior to BRP administration at visit 801.

8.2.8 Pregnancy and Birth Control Assessment

Pregnancy test administration for females, test results, and self-reports of birth control method(s) will be documented during screening. A pregnancy test will be performed just prior to the naloxone challenge, XR-NTX administration(s), and during the first visit of Week 8.

8.2.9 Vital Signs

Vital signs (e.g., body temperature, blood pressure, pulse, respiration rate) will be collected at screening and once weekly thereafter, before and after the naloxone challenge, before and after XR-NTX administration, and before and after the first dose of BRP. Vital signs can be repeated to confirm the reading or on more frequent intervals, as clinically indicated.

8.2.10 Prior and Concomitant Medications

This form will collect information about prescription and over-the-counter medications used by participants. At screening, the form will be used to record medications taken in the prior 30-day period. At other clinic visits, the form will document medications taken since the previous data collection visit. Exclusionary medications include tricyclic antidepressants, duloxetine, venlafaxine, MAOIs, chlorpromazine, stimulants, xanthines, and systemic steroids (which may lower the seizure threshold), and nelfinavir and efavirenz (which may alter bupropion levels). The study medical clinician may also exclude any participant who is taking medications that could interact adversely with study medications. Participants will be instructed to contact the study medical clinician before taking any non-study medications, including prescription medications, over-the-counter preparations, and herbal supplements, during the course of the study.

8.2.11 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Medical or psychiatric adverse events (AEs) will be collected by inquiring of participants: "How have you been feeling since your last visit?" AEs will be recorded at each visit after consent according to the adverse event reporting definitions and procedures. If an AE or abnormality suggests medical or psychological deterioration, it will be brought to the attention of the study medical clinician for further evaluation. All AEs and SAEs will be medically managed, reported, and followed in accordance with applicable regulatory requirements. Seizures will be reported to the DSMB.

8.3 Drug Use Measures and Psychological Measures

8.3.1 Timeline Follow-back (TLFB)

The Timeline Follow-back procedure (Sobell & Sobell, 1992; Fals-Stewart, 2000) will be used to elicit the participant's self-reported use of alcohol and illicit substances. At screening, substance use reported by the participant in the 30-day period prior to consent will be assessed. The TLFB will be administered at each study visit throughout the screening phase, the active medication phase and at the post-medication phase follow-up to document the participant's self-reported use of substances for each day since the previous TLFB assessment. Adherence to this procedure will ensure self-reported substance use for the entire study period is documented without gaps.

8.3.2 Urine Drug Screen (UDS)

Urine samples will be collected at every clinic visit. For screening phase visits, urine drug screen testing will be performed on-site using a FDA-approved one-step temperature-controlled urine drug test card following all of the manufacturer's recommended procedures. The UDS will test for the presence of opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamine, marijuana, methadone, and Ecstasy (MDMA). For specimens collected during the active medication phase and at the post-medication phase follow-up visit, a central laboratory will be used to perform urine drug screen testing. A validity check will be performed

on all urine samples collected using a commercially available adulterant test strip that indicates normal ranges for creatinine, pH (at minimum), nitrate, glutaraldehyde, specific gravity, bleach and pyridinium chloromate. Study teams at each site may opt to observe the urine collection process either at each collection, or as deemed necessary (e.g., if specimen tampering is suspected) according to clinic standard operating procedures.

8.3.3 Visual Analog Craving Scale (VAS)

Participants' craving for methamphetamine will be documented on a visual analog scale (VAS) that ranges from 0 (no craving) to 100 (most intense craving possible). This scale will be completed at each screening visit and once weekly throughout the active medication phase, and at the post-medication phase follow-up visit.

8.3.4 Concise Health Risk Tracking (CHRT); Participant Rated Module

The CHRT will assess aspects of suicidal ideation and behavior, including ideation frequency, duration and severity; identifiable deterrents to an attempt; reasons for living/dying; degree of specificity/planning; method availability/opportunity; expectancy of actual attempt; and actual preparation, using 16 questions scored on a 5-item Likert scale. The CHRT will be used at screening, twice-monthly during the active medication phase (visits 101, 301, 501, and 701), and at the post-medication phase follow-up assessment. Participants who report a significant suicidal/homicidal risk will be assessed by a qualified clinician before leaving the clinic.

8.3.5 DSM-5 Checklist

The DSM-5 Checklist has been designed as a semi-structured interviewer administered instrument that provides current diagnoses for substance use disorders based on DSM-5 diagnostic criteria. The DSM-5 Checklist will be completed at screening.

8.3.6 Treatment Effect Assessment

The TEA (Ling, 2009) is a 4-item self-administered assessment that uses a Likert scale (1-10) to document changes in four life domains: substance use, personal responsibilities, health, and citizenship. Analyses are underway addressing psychometric properties of this measure. The TEA will be collected at screening and at the post-medication phase follow-up assessment.

8.3.7 Alcohol and Substance Use History

The Alcohol and Substance Use History (ASU) will be completed at screening to incorporate PhenX Core Tier 1 items. The participant will be asked whether he/she has ever used alcohol and various substances as well as his/her age when the substance was first used.

8.3.8 Tobacco Use History

The Tobacco Use History (TUH) will be administered at screening and at the post-medication phase follow-up assessment to incorporate PhenX Core Tier 1 items. Tobacco use items assessed include lifetime, 30-day quantity and frequency, and age of first tobacco use.

8.3.9 Quality of Life

Quality of Life will be assessed using items from PhenX Core Tier 1. Participants will be asked to provide ratings of general health, physical health, and mental health during the past 30 days at screening and at the post-medication phase follow-up assessment.

8.4 Medication Procedures and Measures

8.4.1 Naloxone Challenge

The naloxone challenge will be administered before study medication induction according to the pre-induction strategy described in section 7.1.4. Potential participants must pass the naloxone challenge in order to be eligible for study enrollment.

8.4.2 XR-NTX Administration

XR-NTX is administered following enrollment on study Day 1. The second XR-NTX administration takes place at the first visit in Week 5.

8.4.3 BRP Observed Dosing

Oral study medication (BRP) will be dispensed for take-home weekly. Participants will be asked to bring his/her BRP medication to the clinic for each visit so that self-administration of BRP dose for each in-clinic visit day can be observed by medical staff. If a participant fails to bring his/her oral study medication to the clinic so that self-administration of the dose for the in-clinic visit day can be observed, the participant will be asked to provide a video recording of themselves taking the dose for that day at home. If the participant records the video, h/she will be compensated as if the medication bottle was returned to the clinic that day.

8.4.4 Dose Logs (DL)

Dose Logs document medication administered in-clinic, dispensed for take-home dosing, and the participant's self-reported dose taken, including documentation of BRP doses observed via video recordings transferred to the study team as an encrypted file through the secure Mobile Device Management System (i.e., MobiControl). Medications to be recorded on dose logs include naloxone, XR-NTX, and BRP. These logs will be completed at each visit for each dose dispensed and/or administered throughout the study.

8.4.5 Cellphone Confirmation of Dosing

A log will be maintained to document video recordings received showing participants' self-administration of BRP on non-clinic visit days and days the participant fails to return medication bottle for in-clinic observed dosing.

9.0 TRAINING

The study staff will be trained as specified in the study Training Plan. Required training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP), as well as protocol-specific training as needed (e.g., assessments, study interventions, safety procedures, data management and collection). Support mechanisms are identified (e.g., who to contact for aid, questions, resources). All study staff will also be required to complete any training requirements per their study site and local IRB requirements. Further details are presented in the study Operations Manual.

10.0 STATISTICAL ANALYSES

10.1 General Design

10.1.1 Study Hypothesis

The primary hypothesis is that the combination of extended-release bupropion and extended-release depot naltrexone will be associated with a pattern of MA non-use as measured by the number of responders in Stages 1 and 2.

10.1.2 Primary Endpoints

The primary efficacy endpoint is the number of responders. Responders are defined as participants who provide at least 6 MA-negative UDS tests during the last four-weeks of the active medication phase (weeks 5 – 8), including a MA-negative UDS test at the last clinic visit in week 8. Three or more responders in Stage 1 will result in conduct of Stage 2. Nine or more responders at the end of Stage 2 (combining responders in both Stage 1 and Stage 2) will indicate that the medication combination has shown sufficient potential efficacy to warrant moving forward to a large-scale phase II-III, placebo-controlled trial. Exact binomial calculations were used to determine the critical values for the assessment of the primary endpoint.

The primary safety endpoint is participants' reports of treatment emergent adverse events including serious adverse events collected at scheduled clinic visits or via other contact.

10.1.3 Secondary Endpoints

Secondary endpoints include methamphetamine and other drug use in the pre-evaluation period (Days 1-28), in the evaluation period (Days 29-56), over the entire medication period, and at the follow-up assessment for responders, non-responders, and other sub-groups. Secondary endpoints also include craving, quality of life and ratings of participant and staff satisfaction with study procedures, including use of cellphones, compensation, and study medication.

10.1.4 Rationale for Sample Size

This trial is designed to select between 2 hypotheses. In the Elkashef et al. (2008) report on methamphetamine-dependent patients, among 72 placebo recipients in the 12-week trial, only 4 (5.6%) were observed to be methamphetamine-use free over the last 4 study weeks. Under the null hypothesis, the response rate (P_0) is hypothesized to be 10% or less. If the proposed combination regimen is associated with a true response rate (P_1) of 30% or more, then it would be worthy of advancing to further definitive evaluations. A two-stage optimal design is chosen that can successfully select between these 2 hypotheses with Type 1 and Type 2 error rates of 5% (Simon, 1989).

Two-Stage Optimal Design to test P_0 vs. P_1 , with Type1=Type2=5% error rates

P_0	P_1	Stage 1 Sample Size	# Responses to advance to Stage 2	Total Sample Size	Total # of Responses to select P_1	Expected Sample Size under the null
0.1	0.3	20	3 or more	49	9 or more	29.4

Under the design plan, 20 individuals will be evaluated for response in Stage 1. If 3 or more responders are recorded in the first stage, then a second stage of 29 individuals will be

conducted. If 9 or more total responders are observed after the second stage is completed, then this medication combination would be considered as a candidate for a full-scale study. The optimal design strategy selects the design with smallest expected sample size under the null that satisfies the associated error requirements. If the null hypothesis is true, then 67.7% of the trials of this type would terminate after the first stage with an expected sample size of 29.4.

10.1.5 Projected Number of Sites

A total of 3 sites will participate in the trial.

10.1.6 Projected Number of Participants per Site

It is anticipated that 3 sites will each enroll 6-9 participants in the active medication phase over the Stage 1 recruitment period and enroll 9-12 participants in the active medication phase over the Stage 2 recruitment period.

10.2 Statistical Methods for Primary and Secondary Outcomes

The unbiased point estimate, confidence interval, and trial p-value will be calculated to determine response rate (responders) in the intent-to-treat population using methods discussed by Koyama and Chen (2008). Safety analyses are outlined below.

Drug use and severity, and type of drug-related problems will be analyzed by methods including but not limited to the TES, days of self-reported drug use, number of consecutive negative UDS, and UDS as a binary outcome (positive or negative) across time. The Treatment Effectiveness Score (TES) (Ling et al., 1997) is the percentage of the scheduled urine drug screens that were negative for each drug. Mixed-model analysis of repeated measures will be used to explore the presence of time-related medication effects, including severity of cravings in responders and non-responders. In the models, we will control for baseline MA use, other key demographic and participant variables. Additional analyses will include assessment of drug use in the pre-evaluation period (Days 1-28), over the entire medication period, and at the follow-up assessment. Changes occurring over the medication period in severity and type of drug-related problems and in quality of life will be analyzed with parametric and nonparametric measures. Participant and staff satisfaction ratings will be summarized.

10.3 Significance Testing

The design uses a 5% error rate to control the frequency of Type 1 errors.

10.4 Interim Analyses

The study has 2 stages and an interim evaluation as to whether to proceed to the second stage as described in this paragraph. While theoretically possible, termination after the initial stage because of success is not planned in order to permit improved precision for primary and secondary endpoints. As soon as 20 participants from Stage 1 have reached outcome and their urine drug screen results have been obtained, a Data and Statistics Center (DSC) statistician will calculate the number of responders. The DSC statistician will then notify the NIDA CCTN, the Lead Node, DSC, and CCC as to whether the Stage 1 success criterion has been met, and the NIDA CCTN and/or DSC will notify the DSMB. The decision to conduct Stage 2 will be predicated entirely on the number of responders in Stage 1. Since the number of responders is the primary endpoint of the trial, the exact number of responders from Stage 1 will not be shared

by the DSC statistician with anyone until the final database lock. While waiting for the outcome of the 20th participant, which could take 10 weeks, sites will proceed to enroll participants into Stage 2. During this period, up to 6 participants may be enrolled across study sites starting on the day the 20th participant was enrolled. If there are fewer than 3 responders in Stage 1, the study will be terminated. Any participants enrolled in Stage 2 will be informed, at their first clinic visit following DSC notification, that the study has been discontinued by the sponsor and that their participation in the study will be discontinued according to an individualized plan that includes a proper safety evaluation.

10.5 Missing Data and Adherence Assessments

The primary assessment of response will be performed on all individuals who are enrolled in the study (i.e., are inducted onto study medication). Secondary analyses will be performed by examining responses in subgroups with varying characteristics. Response rates and associated confidence intervals will be assessed for the participants who initiate the evaluation period, commencing on Day 29 *and* who receive the second XR-NTX injection. Adherence with bupropion dosing will be measured by cellphone-based take-home dosing videos and in-clinic observation. A dosing adherent per-protocol analysis will be performed by evaluating response rates in the medication-adherent group, namely, all individuals receiving both naltrexone injections and with $\geq 80\%$ adherence with prescribed daily doses of bupropion confirmed by video or observation in clinic. Subsequent adherence-based analyses will be supplemented by blood level assessments.

10.6 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for participants enrolled in the active medication phase of the trial. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

10.7 Safety Analysis

AEs, including SAEs, will be summarized by body system and preferred term using MedDRA codes (per The Medical Dictionary for Regulatory Activities). AEs will be presented as: (1) the number and proportion of participants experiencing at least one incidence of each event overall; and (2) the total number of each event overall in tabular form. Listings of SAEs will be sorted by body system, and preferred term. Detail in these listings will include severity, relationship to study drug(s), and action taken, as available.

11.0 REGULATORY COMPLIANCE AND SAFETY MONITORING

11.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, consistent with the International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. An Operations Manual will be provided as a reference guide and study quality management tool.

11.2 Institutional Review Board Approval

Prior to initiating the study, site investigators will obtain written local IRB approval to conduct the study at their respective site. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials given to the participant. Annual reports and progress reports will be submitted to the IRBs annually or at a frequency requested by each IRB so that continuous study approval is maintained without lapse. The lead investigator is responsible for maintaining in his research files copies of all performance site(s) current IRB/IEC approval notice(s), IRB-approved consent document(s), including approval for all protocol modifications. These materials must be received by the lead investigator prior to the initiation of research activities at a given site, and must be available at any time for audit.

11.3 Research Advisory Panel of California (California sites only)

Prior to initiating the study, the sponsor or designee will obtain written approval from the Research Advisory Panel of California (RAP-C). Any planned research project to be conducted in California requiring the use of a Schedule I or Schedule II Controlled Substance as its main study drug as well as research for the treatment of controlled substance addiction or abuse utilizing any drug, scheduled or not (SAT) must be submitted to RAP-C for review and approval prior to study start-up. Study approval is based on review of the study protocol, consent form, and other pertinent study documents. Yearly reports will be provided to the RAP-C by the sponsor or designee in order to obtain continuing study approval.

11.4 Informed Consent

All potential candidates for the study will be given a current local IRB-approved copy of the Informed Consent Form to read in English. In accordance with local IRB policies, appropriately qualified and trained study personnel will explain all aspects of the study in lay language and answer all of the study candidate's questions. Participants who remain interested after receiving an explanation of the study will be given a short quiz to test his/her understanding of the project, the purpose and procedures involved, and the voluntary nature of his/her participation. Those who cannot successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree

to participate will be asked to sign the informed consent form. Participants will not be administered any assessments or study procedures prior to signing informed consent.

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent form must be updated or revised whenever important new information is available, or whenever the protocol is amended in a way that may affect a study participant's participation in the trial. Each study site must have the study informed consent approved by their local IRB(s). The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their local IRB and institutional policies and that is accessible for quality assurance review and regulatory compliance. Every study participant will be provided with a copy of the signed and dated consent form to use as continual reference for items such as procedure risks and/or side effects, questions and for emergency contact information. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

11.5 Drug Accountability

Upon receipt, the investigator, pharmacist, or authorized designee at each site is responsible for maintaining written inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent shall be accounted for.

11.6 Quality Assurance and Safety Monitoring

Protection of the rights and welfare of study participants will be a vigilant process conducted by the research teams at all sites and at the Lead Node and by the sponsors of the research. In addition to the data and safety monitoring procedures described in this protocol, additional safety monitoring through the Data and Safety Monitoring Board will be conducted regularly throughout the duration of the study.

11.7 Data and Safety Monitoring Board (DSMB)

This study will utilize the CTN DSMB to oversee ongoing trial progress. The purpose of this board is to determine whether risks emerge during the conduct of the trial that make continuation unethical. This process is intended to assure the IRBs, the sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in CTN research trials. Safety monitoring begins with the initial review of the protocol during the study development process. Reports of participant seizures will be provided to the DSMB as they occur. The DSMB will meet as necessary over the study duration.

11.8 Medical Monitor

Under the supervision of the NIDA-assigned Medical Monitor, the study Safety Monitor will be responsible for overseeing safety and for evaluating all Adverse Events (AEs). He/She will review all Serious Adverse Events (SAEs) within five days of their reporting in the EDC and all other Adverse Events on a regular basis. The Medical Monitor will review events regularly and will be available at all times for consultation. It is the responsibility of the site principal

investigator to provide this information to the safety monitor. It is also the site principal investigators' responsibility to inform the IRBs per local IRB guidelines.

In addition, the Medical Monitor will independently review the safety data, present it to the DSMB for periodic review, and provide site principal investigators a "Safety Letter" when necessary. The medical monitor will determine which safety events require expedited reporting to NIDA, the DSMB, study drug manufacturers, and regulatory authorities. This will include all suspected adverse reactions that are serious and unexpected. Furthermore, in the event of participant seizures, reports will be submitted to the DSMB using the AE form with additional information about the event as deemed appropriate.

11.9 Quality Assurance Monitor

Monitoring of the study sites will be conducted on a regular basis using a combination of NIDA-contracted monitors, local node quality assurance monitors, and lead node staff. The purpose of these visits is to encourage and assess compliance with the study protocol, Good Clinical Practice guidelines, and to ensure the integrity of the trial progress.

NIDA contract monitors will assure that submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent, eligibility for participation, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and principal investigator supervision and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA.

Qualified Node personnel (Node 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 ensure site staff is trained and able to conduct the protocol appropriately and that study procedures are properly followed. 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 monitoring, local node, lead node, and data monitoring are found in the study QA monitoring plan.

11.10 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 department that issues the CoC will be advised of changes in the CoC application information, as required. Participating CTP sites will be notified if CoC revision is necessary. Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations.

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

11.11 Health Insurance Portability Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

11.12 Investigator Assurances

Each community treatment program site (CTP) must file (or have previously filed) a Federal Wide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to adhere to appropriate policies and procedures for the protection of human research subjects. FWA must be current at trial initiation and must be maintained throughout the duration of the study with documentation sent to NIDA or its designee as requested. 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 and sub-investigators at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

11.13 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. It is the responsibility of the investigator to maintain appropriate disclosure to their individual institution according to their requirements.

11.14 Inclusion of Women and Minorities

Although few in number, the study sites should attract a diverse study population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and or treatment programs that serve a large number of women and/or minorities, advertising in newspapers or radio stations with a high female/minority readership/listening audience, etc.

11.15 Description of Plans to Conduct Valid Analyses of Study Results by Gender and Race/Ethnicity

The association between specific demographic characteristics and outcome will be studied. The demographic characteristics of potential importance include: age, gender, race, and ethnicity.

11.16 IND Requirements

This study meets the requirements for an exemption from IND requirements, according to 21 CFR 312.2. Therefore an IND application will not be submitted for this pilot study. This clinical investigation is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling or the advertising of these approved and marketed drugs. This clinical investigation does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of these products. This small pilot study will be conducted in compliance with FDA requirements for IRB review, informed consent, and requirements concerning the promotion and sale of drugs. If the pilot data looks promising, according to the statistical analysis plan described in the protocol, large-scale phase II-III, placebo-controlled trial may be considered and an IND sought.

11.17 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 regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

11.18 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with local IRB, State and Federal requirements, whichever is longest. The sponsor and lead investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

11.19 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the Pacific Region Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the sites' Institutional Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

11.20 Reporting to Sponsor

The site principal investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event reporting and Serious Adverse Event reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

11.21 Study Documentation

Study documentation includes, but is not limited to, all case report forms, electronic files, 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 current and previous consent forms and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. The original recording of an observation should be retained as the source document.

11.22 Protocol Deviations and Reporting and Management

Any divergence from procedures and requirements outlined in the protocol will be classified as protocol deviations. A protocol deviation is an action (or inaction) that alone may or may not affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. In some cases, a protocol deviation may compromise participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and is cause for corrective action to resolve the departure and to prevent re-occurrence. Protocol deviations 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 deviation from the protocol will be designated as minor or major will be made by the protocol's Lead Investigator(s) in conjunction with the Clinical Coordinating Center (CCC). The consequences will be specified and participating sites will be informed.

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

11.23 Safety Monitoring

11.23.1 Adverse Events (AEs)

All adverse events (medical and/or psychiatric) occurring during the course of the study will be assessed, documented, and reported. AEs occurring during the course of the clinical trial will be collected, documented, and reported by the principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix A. Appropriately qualified and trained medical personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs (i.e., the first visit following informed consent and at every visit thereafter). Study staff will follow-up on the status of any AEs that remain at the post-medication phase follow-up visit assessment for up to 30 days post last study visit.

An 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 investigational product-related or clinically significant. For this study, AEs will include events reported by the participant, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A

new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE log and CRF. The AE log and CRF are also used to record follow-up information for unresolved events reported on previous visits.

Each week, appropriately qualified and trained medical personnel must review the AE log and CRF completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution.

A study Medical Clinician (MD, DO, PA, or NP) will review or provide consultation for each adverse event. These reviews will include an assessment of the severity and causality to the study drug or study procedures. The study medical clinician, in collaboration with the study physician and site principal investigator, will also make decisions to exclude, refer, or withdraw participants as required. The study staff will be trained to monitor for and report adverse events and serious events.

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

11.23.2 Definitions of Adverse Events and Serious Adverse Events

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

11.23.3 Reportable Adverse Events and Serious Adverse Events

Reporting of AEs and SAEs is described in Appendix A. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA in order that the NIDA can review and submit to the DSMB as needed.

Adverse Events

For the purpose of this study, all AEs will require reporting in the data system.

Serious Adverse Events

All SAEs will be documented in the source documentation and reported through the data system. The local site is responsible for reporting all of their local SAEs to their local IRBs per local IRB guidelines.

11.24 Known Potential Toxicities of Study Drug: Bupropion

Much of the material in these sections is derived from the manufacturer's package insert.

11.24.1 Potential Toxicities of Bupropion

The most serious reported side effect related to use of bupropion is seizures, and thus use of bupropion is contraindicated in those: 1) With a seizure disorder; 2) Who are concurrently using a bupropion containing medication; 3) Who have a current diagnosis of bulimia or anorexia

nervosa; 4) Who are abruptly discontinuing alcohol or sedatives (including benzodiazepines); 5) Who are concurrently taking a monoamine oxidase (MAO) inhibitor; 6) Who have had an allergic response to bupropion. Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold. Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin. Concomitant medications such as antipsychotics, antidepressants, theophylline, and systemic steroids are known to lower seizure threshold. The risk of seizure may be minimized if the total daily dose of bupropion XL dose does not exceed 450mg.

The most commonly observed adverse events associated with the use of bupropion include dry mouth, insomnia, agitation, headache, nausea/vomiting, constipation, and shakiness. Other possible adverse events include allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath). Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. In depression trials, participants reported neuropsychiatric signs and symptoms such as delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Antidepressants can also precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible individuals. In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion SR alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension.

Bupropion, like other antidepressants, carries a "black box" warning regarding emergence of suicidality in children and adolescents. Furthermore, antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, although bupropion's part in such psychiatric disturbance has been examined and found unrelated (Zisook et al., 2011). Potential side effects of bupropion include agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor. Adverse events were sufficiently troublesome to cause discontinuation of treatment with bupropion in approximately 10% of the 2,400 patients and volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose. Bupropion should be used with caution in patients taking drugs that reduce the seizure threshold: neuroleptic and antidepressant medications. Patients who are withdrawing from benzodiazepines or alcohol are at increased risk for seizures.

Possible drug interactions may occur between bupropion SR and drugs that are substrates or inhibitors of the CYP 2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, *in vitro* studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, ritonavir, and efavirenz inhibit the hydroxylation of bupropion. Because

bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin), while other drugs may inhibit the metabolism of bupropion (e.g., cimetidine).

11.24.2 Pharmacology of Bupropion

Pharmacokinetics. Tablets of bupropion hydrochloride are available in immediate-release, sustained-release (SR), and extended-release (XL) formulations. The bupropionXL, 150 mg and 300 mg, daily formulations may be used for this study. BupropionXL has been shown to be bioequivalent to 100 mg three times daily of the immediate release formulation for rate and extent of absorption and parent drug and metabolites in clinical trials for depression. Better adherence is expected with once daily dosing as opposed to twice or thrice daily dosing, making bupropionXL the preferred choice for inclusion in the current study.

The half-life of bupropion is approximately 21 hours after chronic dosing. Peak plasma concentrations of bupropion are achieved within 3 hours following oral administration. The mean peak concentration (C_{max}) values were 91 and 143 ng/mL from 2 single-dose (150-mg) studies. At steady state, the mean C_{max} following a 150-mg dose every 12 hours is 136 ng/mL. In a single-dose study, food increased the C_{max} of bupropion by 11% and the extent of absorption as defined by area under the plasma concentration-time curve (AUC) by 17%. The mean time to peak concentration (T_{max}) was prolonged by 1 hour. This effect was of no clinical significance.

Steady state plasma concentrations of bupropion are reached within 8 days. Four basic metabolites have been identified. These metabolites are pharmacologically active, but their potency and toxicity relative to bupropion have not been totally characterized. They may be of clinical importance because the plasma concentration of metabolites is higher than those of bupropion.

Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. Bupropion follows biphasic pharmacokinetics best described by a 2-compartment model. The terminal phase has a mean half-life (\pm % CV) of about 21 hours (\pm 20%), while the distribution phase has a mean 57 half-life of 3 to 4 hours.

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 μ g/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion. The volume of distribution (V_{ss}/F) estimated from a single 150-mg dose given to 17 subjects is 1,950 L (20% CV).

Metabolism. Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less

potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high as or higher than those of bupropion.

Bupropion/Drug interactions. Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the CYP2B6 isoenzyme. Although bupropion is not metabolized by CYP2D6, there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme. Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of bupropion SR. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (± 5) hours, and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite; however, their elimination half-lives are longer, 33 (± 10) and 37 (± 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

11.25 Known Potential Toxicities of Study Drug: Naltrexone

Much of the material in these sections is derived from the manufacturer's package insert.

11.25.1 Potential Toxicities of Naltrexone (as XR-NTX)

Serious adverse reactions that may be associated with extended-release naltrexone by injection (XR-NTX; Vivitrol®) include: severe injection site reactions, eosinophilic pneumonia, allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose, depression and suicidality. Other adverse events seen in association with XR-NTX include hepatic enzyme abnormalities, nausea, and insomnia. Vivitrol® injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; in some cases, injection site reactions may be very severe. In clinical trials, one participant developed an area of induration that continued to enlarge after 4 weeks, with subsequent development of necrotic tissue that required surgical excision. In the post-marketing period, additional cases of injection site reaction with features including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis, have been reported. Some cases required surgical intervention, including debridement of necrotic tissue, and some resulted in significant scarring.

In clinical trials of extended-release naltrexone by injection XR-NTX (Vivitrol), there was one diagnosed case and one suspected case of eosinophilic pneumonia. Should a person receiving XR-NTX develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered.

The most serious potential adverse effect of naltrexone is hepatocellular injury, which has almost always been associated with oral doses of 1400 to 2100mg per week. These doses result in much greater exposure to naltrexone than the 380mg/monthly dose of XR-NTX. Transient, asymptomatic hepatic transaminase elevations have been observed in clinical trials of XR-NTX and during the postmarketing period. At oral doses below 600mg/week, only relatively minor changes in liver tests have been reported and these have not been clearly attributed to naltrexone.

XR-NTX may precipitate opioid withdrawal in opioid dependent individuals who have not been opioid-free for at least 7-10 days prior to administration. Opioid withdrawal symptoms that occur

upon discontinuation of opioids (e.g., nausea, vomiting, diarrhea, muscle ache, and sweating) are uncomfortable, but they do not generally necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent individual, the resulting withdrawal syndrome can be severe enough to require hospitalization. In addition, abrupt precipitation of opioid withdrawal may lead to severe systemic sequelae, including acute liver injury.

Any attempt to overcome the blockade produced by XR-NTX by administering large amounts of opioids is very dangerous and may result in fatal overdose. Although XR-NTX blocks the effects of exogenous opioids for 28 days after administration, cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval or when missing a dose. Patients who have been treated with XR-NTX may be more sensitive to opioids, even at lower doses. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.).

Patients taking XR-NTX may not benefit from opioid-containing medicines. Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics.

The commercial formulation of XR-NTX (Vivitrol) has been classified Pregnancy Category C. Female participants of childbearing potential will be required to practice acceptable birth control. Female participants will also be required to have a negative pregnancy test prior to the challenge and prior to the first and second administration of XR-NTX.

11.25.2 Pharmacology of Naltrexone and Depot Naltrexone

Naltrexone is an opioid antagonist with a high affinity for the mu opioid receptor and few other effects. It is approved for use in treating opioid dependence and alcohol dependence in the U.S. An oral dose of 50mg/day provides substantial opioid blockade for 24 hours and its duration of effect can be extended to 48-72 hours by increasing the oral dose to 100-150 mg/day within two to three days. Naltrexone is effective in preventing relapse to opioid use provided the patient takes it as prescribed. Studies of oral naltrexone in the U.S. have documented high medication non-adherence and dropout rates with the exception of those done in criminal justice or other settings where severe adverse consequences will quickly result in the event of relapse (Volpicelli et al., 1997; O'Brien, 2001; Rothenberg et al., 2002). These data, from many studies in the U.S. and other western countries, have led to intensive efforts to develop long-acting naltrexone preparations that can be administered as an injection or placed as an implant once per month or less frequently (Lobmaier et al., 2008).

There is a large amount of experimental data concerning naltrexone for alcohol dependence. For example, in animal models blocking opioid receptors prevented alcohol drinking in alcohol-preferring monkeys and rats. Microdialysis studies demonstrated that ethanol caused dopamine to increase in the nucleus accumbens and that this effect is blocked by naltrexone. These animal findings were applied to humans and 29 double-blind trials for treating alcoholism have been conducted, with most showing a significant advantage of naltrexone over placebo for preventing relapse (O'Brien, 2008).

Overall, these study results suggest that naltrexone interferes with the beta-endorphin/dopamine reward system by attenuating the impact of alcohol-induced beta-endorphin release on dopamine release, thereby reducing the reinforcing properties of alcohol. Consistent with this finding has been the clinical observation that some alcoholics taking naltrexone did not relapse even if they drank, suggesting that naltrexone attenuated the usual

relationship between drinking and relapse in persons trying to recover from alcohol dependence. Since adherence has been a problem in naltrexone studies using the 50mg tablet, an extended-release naltrexone formulation (e.g., Vivitrol[®]) may be a better formulation to use in relapse prevention because it does not depend on daily decisions to take a pill.

Extended-release Injectable Naltrexone: Vivitrol. Vivitrol is a combination of naltrexone-containing microspheres that are suspended in a diluent and delivered by monthly injection into the muscles of the buttock. The microspheres consist of a biodegradable sterile polylactide-co-glycolide (PLG), off-white to light-tan powder and come in a vial containing 380mg naltrexone. The microspheres are suspended by adding a clear, colorless diluent that comes with the product and shaking the mixture vigorously for about a minute shortly before it is injected. Plasma concentrations of naltrexone and 6-beta naltrexol (its main metabolite) after a single Vivitrol injection are detectable for at least 30 days and must be re-administered to maintain its effect. Naltrexone will precipitate withdrawal if given to a person who is physiologically dependent on opioids.

Vivitrol Pharmacokinetics and Pharmacodynamics. After intramuscular injection there is a transient peak of naltrexone in about two hours, followed by a second peak 2-3 days later that reaches a level of around 25 ng/ml. This second peak is followed by a decline to about 12 ng/ml by Day 7, and then a more gradual reduction that reaches 1-2 ng/ml in 30 days. The once/month injection reduces the first pass metabolism to 6-beta-naltrexol that occurs after the oral formulation, which allows for less total drug to be administered than the oral formulation, though total naltrexone exposure is 3-4 times higher over the 28 days following a Vivitrol injection than with a 28-day course of the usual 50mg/day oral dose (PDR; 2009, pp 988-992). The liver metabolizes naltrexone to 6-beta-naltrexol, its primary metabolite. The P450 system is not involved, thus reducing the chances for interactions with many other drugs including those used to treat hepatitis C and HIV. Naltrexone and its metabolites form glucuronide conjugates and are excreted in the urine. The elimination half-life of naltrexone and 6-beta-naltrexol is 5-10 days and dependent on the erosion of the PLG polymer.

Vivitrol Safety. Naltrexone carries a risk of hepatocellular injury when given in excessive doses. Vivitrol does not appear to have hepatotoxic effects at recommended doses, but it should be used cautiously in patients with active liver disease and is contraindicated in patients with acute hepatitis or liver failure. Vivitrol injection site reactions may occur, characterized by pain, tenderness, induration, swelling, erythema, bruising, or pruritus, and in some cases, reactions may be severe. Other potential adverse effects associated with Vivitrol include nausea or vomiting, depression, and suicidal ideation.

Precipitated withdrawal. To prevent occurrence of withdrawal symptoms in patients dependent on opioids (an unlikely event in this trial, which excludes such individuals and screens for opioid drugs via interview and urine test), patients should be opioid-free before starting Vivitrol. Patients should be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of Vivitrol, typically by urine test and naloxone challenge.

Post-treatment overdose. Vivitrol blocks the effects of exogenous opioids for 28 days after administration. After treatment with Vivitrol, patients are likely to have reduced tolerance to opioids. Opioid use at the end of a dosing interval or after missing a dose could result in potentially life-threatening opioid intoxication (involving respiratory compromise or arrest, circulatory collapse, etc.). Attempting to overcome the blockade by administering large amounts of exogenous opioids is also associated with potential risk of overdose.

11.26 Potential Side Effects of the Combination of Naltrexone and Bupropion

The combination of naltrexone and bupropion has been studied in clinical trials for other indications (e.g., obesity). The most common adverse events (AEs) related to the combination medication examined in two studies were gastrointestinal, including nausea (reported by 27% and 34% of participants), and headache (reported by 14% and 24% of participants) respective to the two studies (Greenway et al., 2010; Wadden et al., 2011). Compared to study participants receiving placebo in both studies, those who received the active combination reported higher rates of constipation (15% and 24%), dizziness (7% and 14%), and dry mouth (8%) than participants receiving placebo.

11.27 Additional Information on Study Medications for MA Dependence

11.27.1 Bupropion Treatment for MA Dependence

Bupropion is an antidepressant of aminoketone class that is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitors (SSRIs), or other known antidepressant agents. The mechanism of its antidepressant action may be related to its noradrenergic and dopaminergic activity. Bupropion has a favorable side effect profile: it causes fewer anticholinergic, cardiovascular, sedative or adverse sexual effects than tricyclics and does not cause weight gain (Bryant, Guernsey, & Ingram, 1983).

Because bupropion is a relatively weak inhibitor of the neuronal reuptake of dopamine, it has a low abuse liability (Nomikis et al., 1989). Its potency to block dopamine reuptake in animals manifests at doses higher than those necessary for its antidepressant effect. It is possible, however, that the mild dopaminergic activity that bupropion does possess is sufficient to exert anti-craving effect and to treat the signs of withdrawal.

Bupropion has been investigated for treatment of cocaine abuse. In a pilot study, Margolin et al. (1991) found that 300 mg/day bupropion substantially reduced cocaine use in four of the five cocaine-dependent methadone-maintenance patients, was well tolerated, and reduced self-reported craving for cocaine. A multicenter placebo-controlled double-blind clinical trial of bupropion for cocaine dependence in methadone-maintenance patients indicated efficacy of bupropion for the subgroup of patients with depression at study entry (Margolin et al., 1995).

The results of animal studies designed to test the effectiveness of bupropion to block effects of MA support clinical use for the treatment of MA dependence (Kim et al., 2000). Bupropion provides complete protection against MA-induced decrease in dopamine uptake in the striatum in an in vitro model of MA-induced dopamine nerve terminal toxicity. It is logical to postulate that the combination of bupropion's dopaminergic activity and antidepressant properties may enhance its efficacy in the treatment and relief of the signs and symptoms of MA withdrawal and for prevention of the relapse.

Clinical research with bupropion for MA dependence has provided good substantiation for its inclusion in this trial as a medication in combination with naltrexone; additional material on human trials experience with both medications appears below:

Phase 1 and Phase 2 clinical trials assessing the safety and efficacy of bupropion for MA dependence have been conducted with positive outcomes. In a Phase 1 double-blind inpatient clinical laboratory study, 26 subjects with a DSM-IV diagnosis of MA dependence or abuse were randomized to receive either twice daily bupropion SR (150 mg BID) or placebo control and

infusions of saline or 15 mg and 30 mg of MA. Of the 26 subjects who were enrolled, 20 completed the entire study with 10 subjects in each of the bupropion and placebo control groups. Bupropion treatment was associated with reduced ratings of “any drug effect” ($p=0.02$), and “high” ($p=0.02$) as assessed with visual analog scales following MA administration. Bupropion also significantly reduced cue-induced craving [General Craving Scale total score ($p = 0.002$); Behavioral Intention subscale ($p = 0.001$)] (Newton et al., 2006). Bupropion treatment was well tolerated, with the bupropion- and placebo-treated groups reporting similar rates of adverse events. MA administration was associated with expected stimulant cardiovascular effects, and these were not accentuated by bupropion treatment. Instead, there was a trend for bupropion to reduce MA-associated blood pressure increases and a statistically significant reduction in MA-associated heart rate increases. Pharmacokinetic analysis revealed that bupropion treatment reduced the plasma clearance of MA and reduced the appearance of amphetamine in the plasma. MA administration did not alter the peak and trough plasma concentrations of bupropion or its metabolites.

NIDA conducted a Phase 2 study evaluating bupropion for MA dependence. Participants were selected from a group of MA users that was not restricted to low use prior to the start of the study (i.e., low use being defined in the current study population as ≤ 18 days of MA use in the 30 day period before the start of screening). This study was a double-blind, placebo-controlled, randomized, two arm parallel-group design comparing 150 mg of bupropion to placebo administered twice daily to MA dependent outpatients. Of the 151 participants in the ITT sample, 121 were considered evaluable. Conclusions regarding the efficacy of bupropion include:

- Results of analysis of the primary outcome measure (weekly proportion of participants with all urine specimens free of MA) showed statistically significant effects favoring bupropion over placebo for the entire population (GEE, $p = 0.09$).
- Bupropion showed a statistically significant effect for MA-free week in participants who used MA ≤ 18 -days in the 30 days prior to the start of screening (GEE, $p < 0.04$).
- A higher percentage of participants in the bupropion group than the placebo group reduced their proportion of MA use days to 50% or less of their baseline rate based on self report only (Chi-square test, $p = 0.02$).
- Bupropion showed a statistically significant effect for MA-free weeks in males (GEE, $p = 0.04$).
- Bupropion showed a trend toward significance favoring bupropion for MA-free weeks in non-depressed participants (GEE, $p = 0.08$).
- Bupropion showed a statistically significant effect for MA-free weeks in participants without attention-deficit disorder (GEE, $p = 0.02$).

In this study, participants were randomized to receive thrice-weekly CBT and either 150 mg twice daily bupropion SR or placebo. One randomization variable was the frequency of MA use, by self-report, in the 30 days prior to the start of screening based on two rates of use: 1) low-rate users had 18 or fewer days of MA use; 2) high-rate users had 19 or more days of MA use. Of the ITT sample, 47% were low rate users and 53% were high-rate users. A GEE analysis performed on the primary outcome measure for each of these two study subpopulations as well as for the entire ITT sample showed that the low rate use group administered bupropion had a statistically significant increase (GEE, $p<0.04$) in the slope of weekly proportion of participants with MA negative urines compared to the low rate use group administered placebo. The high

rate of MA use appears to reduce the bupropion effect when examining the entire study population.

Figure 2 illustrates the frequency of abstinence over the last two weeks in non-daily MA users in the bupropion study in which 15 of 63 subjects (23.8%) achieved abstinence as compared to 3 of 53 (5.7%) in the placebo group. This finding was shown to be statistically significant (Chi-square, $p=0.01$). Although there was a fairly high dropout rate over the course of the study (approximately 50% of the participants completed the study), it is important to note that there were no significant differences in the rate of dropout between the two groups.

Bupropion was well tolerated in this study. The only significant treatment emergent adverse event was nausea. Participants receiving bupropion had a significant increase (Chi-square, $p=0.019$) in the incidence of nausea over the intervention period. One participant (a 31 year old female) in the bupropion group temporarily discontinued taking bupropion during the study due to an adverse event four weeks after commencing study drug, but the investigator determined that the adverse event was definitely not related to the study drug.

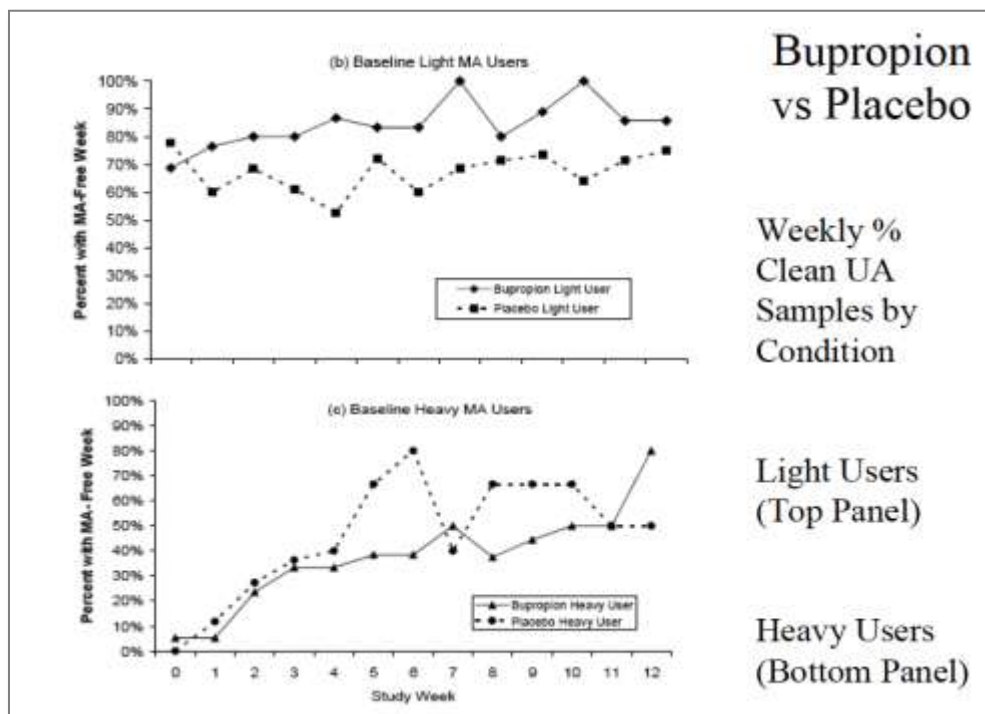
Figure 2. Abstinence for the last two weeks among non-daily MA users

<i>Group</i>	Abstinence Last 2 Weeks		
	Fail (%)	Success (%)	Total
Bupropion	48 (76.2%)	15 (23.8%)	63
Placebo	50 (94.3%)	3 (5.7%)	53
	98	18	116

P = 0.01 (Chi-Square test)

Figure 3 is from Elkashef et al., 2008, showing the relative effects on MA use comparing participants who had reported greater than 18 days of use per month at baseline (“light users”) against participants who had used more than 18 days per month (“heavy users”).

Figure 3. Weekly Abstinence Rates for Light Users versus Heavy Users



11.27.2 Naltrexone Treatment for MA Dependence

Clinical research findings substantiate the potential role of naltrexone as a treatment for MA dependence.

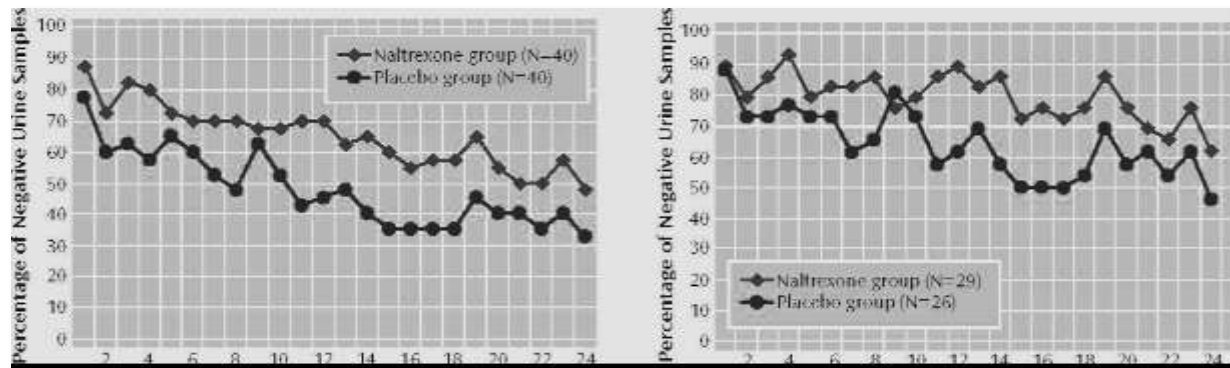
Naltrexone mechanism of action. Human laboratory studies have provided some evidence for modulation of the opioid system as the mechanism of action of naltrexone in its ability to reduce reinforcing effects of amphetamine (Jayaram-Lindström et al., 2004). Although not completely clear, the action of naltrexone that may work to reduce the reinforcing effects of alcohol and other drugs appears to derive from a blockade of effects of endogenous opioid peptides by occupation and binding of opioid receptors. There is no aversive response to administration of opioids or alcohol while naltrexone is present at clinical dosages.

Efficacy of naltrexone in treating stimulant use disorders. As noted, a study conducted in Sweden (Jayaram-Lindström, 2007) indicated that naltrexone reduced amphetamine use among human subjects. This study is described below, following the rather limited work involving naltrexone for treatment of stimulant use disorders. Efficacy of naltrexone for stimulant abuse has been found by Schmitz et al. (2001), in which cocaine use decreased over time among cocaine-dependent patients taking 50mg oral naltrexone compared to placebo. A question persists as to whether similar reductions can be expected among polydrug users, as the same authors subsequently found no effect on drug use among a sample of alcohol- and cocaine-dependent individuals treated with 50mg/day (Schmitz et al., 2004). In contrast, Comer et al. (2006), in a study of combination opioid and stimulant abusers, found that cocaine use was reduced among the portion of the sample randomized to 384mg of sustained-release naltrexone, virtually the same dosage of the extended-release formulation to be used in the trial described in this protocol.

Efficacy of naltrexone in treating amphetamine-dependent individuals. The clinical data emerging from research examining oral naltrexone in amphetamine-dependent humans in Sweden provide convincing rationale for the exploration of naltrexone for MA dependence. Jayaram-Lindström and colleagues (2005) established tolerability and feasibility of naltrexone in an open-label trial, finding mild and transient side effects (nausea, headache, abdominal pains) and documenting reduced frequency and amount of amphetamine use during treatment than before naltrexone treatment. Furthermore, in a double-blind trial, the same Swedish group (Jayaram-Lindström et al., 2007) found that naltrexone reduced subjective effects of amphetamine. Subsequent work published by the Karolinska Institute as a dissertation (Jayaram-Lindström, 2007) and as an article (Jayaram-Lindstrom et al., 2008) found that oral naltrexone was effective in suppressing relapse to stimulant use among individuals meeting DSM-IV criteria for amphetamine dependence.

Figure 4, from Jayaram-Lindstrom et al., 2008, shows percentages of urine samples negative for MA are presented in the figure on the left in the intent to treat sample—for the naltrexone group (triangles) versus the placebo group (circles)—and for the completer group in the right figure.

Figure 4. Percentages of Urine Samples Negative for MA



12.0 DATA MANAGEMENT AND PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture system (AdvantageEDC) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld.

12.1 Operations Manual

An Operations Manual will be provided for this study that incorporates procedures from this protocol with those procedures in more detail as necessary for the day-to-day conduct of the trial. The Operations Manual will be used to train study staff, to provide reference for study procedures, and to support quality management activities.

12.2 Site Responsibilities

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

12.3 Data and Statistics Center Responsibilities

The DSC will 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of AdvantageEDC and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all study sites, 6) perform data cleaning activities prior to any interim analyses and prior to the final study database lock.

12.4 Data Collection and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in AdvantageEDC, or will be collected via direct entry into the eCRF. In the event that AdvantageEDC is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into AdvantageEDC in accordance with the instructions provided during project-specific training and guidelines established by the DSC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

The investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

12.4.1 Data Monitoring, Cleaning, and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in AdvantageEDC. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in AdvantageEDC on a scheduled basis.

Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into AdvantageEDC.

The CCC will conduct regular on-site and remote visits, during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcome, treatment exposure, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding RRTC (node), the lead node, the coordinating centers, and NIDA to monitor study progress overall and at each individual participating site.

12.5 Data Transfer and Lock

At the conclusion of data collection for the study, the DSC will perform final cleaning activities and will “lock” the study database from further modification. The final analysis dataset will be returned to the Lead Investigator and to NIDA, as requested, for storage and archive.

12.6 Confidentiality

12.6.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration (FDA) under the Freedom of Information Act providing, in part, that proprietary information furnished to investigators and Institutional Review Boards will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and Institutional Review Board (IRB).

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

12.6.2 Confidentiality of Participant Records

To maintain participant confidentiality, all laboratory specimens, eCRFs, reports, and other records will be identified by a participant identification code that includes the site number, node number, and participant number. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Participant information will not be released without written permission, except as necessary for monitoring by the FDA if under IND, the NIDA monitoring contractor, local node monitors, lead node staff, or NIDA.

By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations, NIDA or any regulatory agency may consult and/or copy study documents in order to verify eCRF data.

13.0 PUBLICATIONS AND OTHER RIGHTS

Per NIH policy, the results of the proposed trial are to be made available to the research community and to the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN. The project will adhere to stipulations in accord with the NIH Public Access Policy (for any articles based work supported by NIH funding) required for Applications, Proposals, or Reports Submitted After July 1, 2013, as set forth in:

<http://publicaccess.nih.gov/>

<http://publicaccess.nih.gov/FAQ.htm#792>

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-119.html>

14.0 SIGNATURES

SPONSOR'S REPRESENTATIVE (CCTN DESIGNEE)

Printed Name	Signature	Date
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ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 5.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- 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 personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date
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Site Name _____

Node Affiliation _____

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16.0 APPENDICES

APPENDIX A

Adverse Event Reporting Definitions and Procedures

Each participating site's principal investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

Definition of Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related, which occurs during the conduct of a clinical trial. Any change from a baseline pre-existing condition based on clinical status, ECGs, lab results, x-rays, physical examinations, etc., that is considered clinically significant by the study medical clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

An **adverse event, suspected adverse reaction, or adverse reaction** is considered "**serious**" (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study medical clinician or sponsor, it:

1. Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study drug/intervention, must be reported.
2. Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Is a congenital abnormality or birth defect.
6. Seizure.
7. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the investigator brochure or the package insert or is not listed at the specificity or severity that has been observed. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy

Any pregnancies that occur to a participant enrolled in the study will be captured on a pregnancy case report form (CRF) and not separately reported as an AE or SAE. Women who become pregnant during the medication period will be discontinued from further medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

Medical and Psychiatric History

A thorough medical and psychiatric history during the screening 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.

Site Staff's Role in Eliciting and Reporting Adverse Events

All adverse events (medical and/or psychiatric) occurring during the course of the study will be assessed, documented, and reported. Appropriately qualified and trained medical personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs (i.e., the first visit following informed consent and at every visit thereafter). Study staff will follow-up on the status of any AEs that remain at the post-medication phase follow-up visit assessment for up to 30 days post last study visit. Study personnel will obtain as much information as possible about the reported AE/SAE in order to complete AE/SAE documentation (i.e., log and CRFs) and will consult with medical clinicians and the study medical monitor as necessary.

Standard reporting, within 7 days of the site staff becoming aware of the event, is required for AEs. Expedited reporting, within 24 hours of their occurrence and/or site staff's knowledge of the event is required for SAEs (including death and life-threatening events). Site staff is responsible for reporting SAEs to the local IRB, per IRB's guidelines.

Site staff is required to enter AEs and SAEs in the EDC system as soon as they become aware of the event. The AE log and CRF are used to capture AEs (as defined in the protocol). Additional information may need to be gathered to evaluate serious adverse events and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

Site Staff's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained medical personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event.

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.

Guidelines for Determining Causality

The study medical clinician will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study drug/intervention caused the event?

Quality Assurance Staff's Role in Monitoring Adverse Events

Quality assurance monitors (from the RRTC node staff and the CRO contract monitor staff) will review safety documentation on a regular basis and will promptly advise site staff to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting.

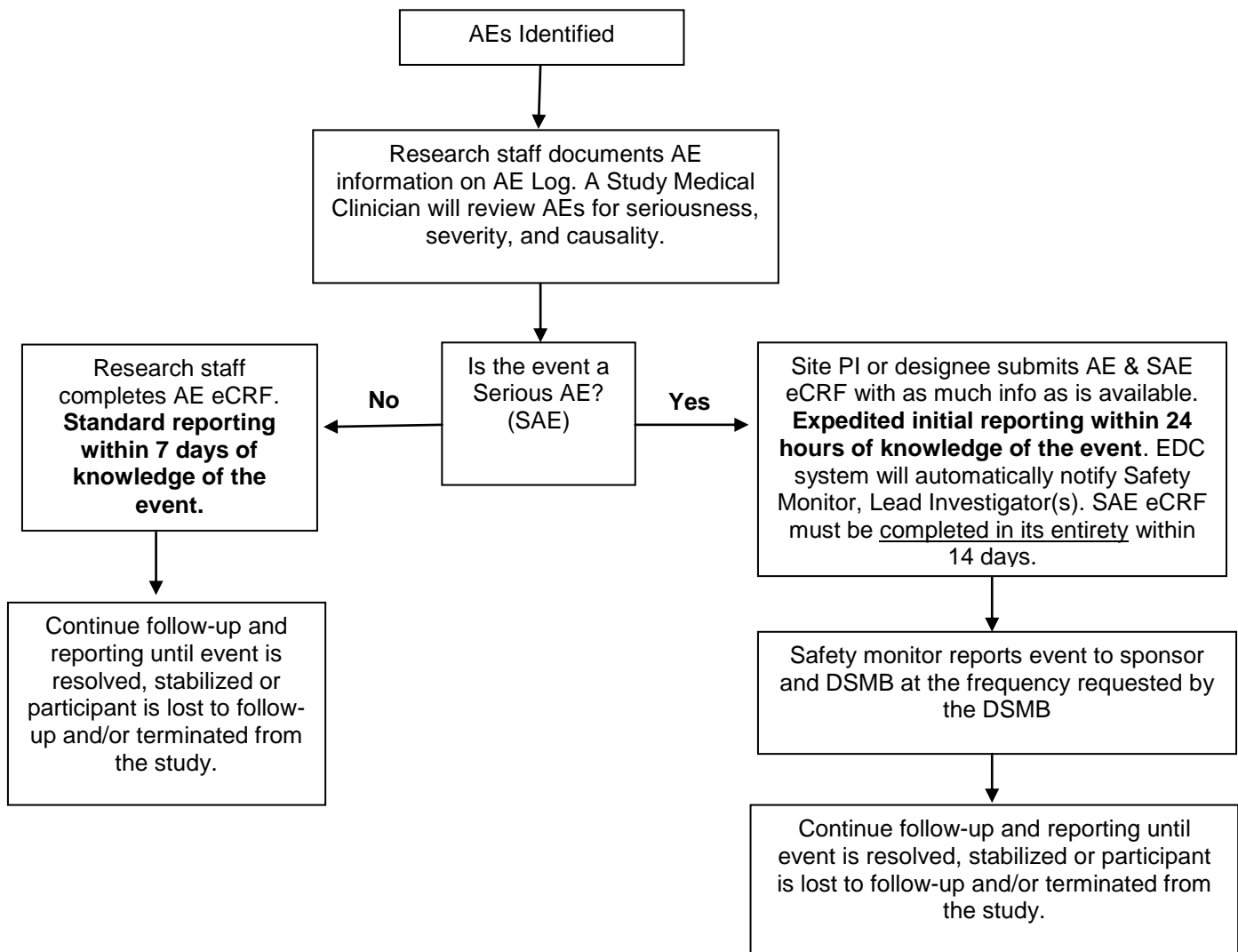
Sponsor's Role in Safety Management Procedures of AEs/SAEs

A NIDA-assigned medical monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the medical monitor, Lead Investigator, and designees. All SAEs will be reviewed by the medical monitor and, if needed, additional information will be requested. The medical monitor will also report events to the sponsor, the Data and Safety Monitoring Board (DSMB), study drug manufacturers, and regulatory authorities. The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA assigned medical monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the medical monitor in writing for review by the sponsor and DSMB. Subsequent review by the Medical Monitor, DSMB, and 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 the DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Reporting to the Data and Safety Monitoring Board: The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Participant Withdrawal

The study medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant is withdrawn from further study medication administration. The study medical clinician should consult with the study physician, site principal investigator, the lead investigator and/or medical monitor as needed. If necessary, a study medical clinician may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason.



APPENDIX B

Data and Safety Monitoring Plan

BRIEF STUDY OVERVIEW

This study will investigate a combination medication, extended-release depot naltrexone plus extended-release bupropion as a potential pharmacotherapy for MA dependence. Stage 1 will include 20 methamphetamine (MA) dependent participants at three study sites. Screening will occur over a maximum of 30 days to include a maximum 2-week eligibility phase to collect and test urine samples for methamphetamine to ensure an appropriate level of current severe MA use disorder. Participants will receive a monthly injection of sustained release depot naltrexone (XR-NTX; as Vivitrol®) plus 450mg/day oral extended-release bupropion (BRP; as WellbutrinXL®) for 8 weeks. Participants will be asked to attend clinic twice weekly for observed BRP dosing and take-home provision of BRP, collection of urine samples, assessments, and medical management. Following the 8-week active medication phase, participants will complete a follow-up phase, including a medication taper and post-medication phase follow-up visit during Week 9. Success in at least three participants will allow the conduct of Stage 2 to utilize the same protocol as in Stage 1, to enroll an additional group of 29 participants.

Details for the definitions and reporting of safety events are found in the Appendix A of the protocol.

OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's 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.

Regarding safety, all Adverse Events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the protocol. The assessment of Adverse Events (medical and/or psychiatric) will commence the visit after consent and will continue through 30 days post last study visit.

The occurrence of AEs and Serious Adverse Events (SAEs) will be assessed at each clinic visit after consent. Serious adverse events will be followed until resolved or considered stable, with reporting to the CCC Safety Monitor/Medical Monitor through the follow-up period.

Standard reporting, within 7 days of the site becoming aware of the event, is required for 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).

B. Medical Monitor/Safety Monitor

The NIDA Clinical Coordinating Center (CCC) Safety Monitor/Medical Monitor is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed at the time they are reported in the EDC. The Medical Monitor will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed the Safety monitor/Medical monitor will discuss the event with the site. Reviews of SAEs will be conducted in AdvantageEDC data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

The CCC Safety Monitor/Medical Monitor will in turn report events to the sponsor, study drug manufacturers, and regulatory authorities if the event meets the definition of an expedited event. All SAEs that meet expedited reporting based on federal regulations will be reported to the DSMB in writing within 15 calendar days of notification of the CCC. If the SAE meets the criteria for death or immediately life-threatening, the CCC will notify the DSMB electronically, by phone or by fax as soon as possible but no later than 7 calendar days of notification of the CCC, with a follow-up written report within 15 calendar days of notification of the CCC. The CCC will prepare an expedited report and copies will be distributed to site investigators.

Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings.

C. Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. The DSMB will make recommendations to NIDA as to whether there is sufficient support for continuation of the trial, that study procedures should be changed, or that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, including DSMB recommendations, in writing to the study Lead Investigator. Study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

Monitoring of study sites will be conducted on a regular basis using a combination of NIDA CCC contract monitors, the local RRTC site managers, and lead node staff. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. Areas of particular concern will be the review of Inclusion/Exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and Principal Investigator supervision and involvement in the trial. The Monitors will interact with the sites to identify issues and re-train the site as needed to enhance research quality.

QA Site Visit Reports will be prepared by the NIDA CCC contract monitors following each site visit. These reports will be and forwarded to the site Principal Investigator, the study Lead Investigator and NIDA.

E. Management Of Risks To Participants

Confidentiality

Confidentiality of participant records will be secured 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. No identifying information will be disclosed in reports, publications or presentations.

Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required to be reported and the fact that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Subject Protection

The study physician will evaluate all pertinent screening and baseline assessments prior to participant enrollment to ensure that the participant is eligible and safe to enter the study. Adverse events (AEs) and concomitant medications will be assessed and documented at each

clinic visit. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration and provided referrals for other treatment or to specialized care.

Pregnancy

Pregnancy is an exclusion criterion for study participation. A positive pregnancy test post-enrollment will result in the cessation of study medication. Participants who discontinue medications will be expected to continue with study visits. Pregnancy test results and related outcome information will be collected on a Pregnancy and Outcome CRF. The site staff will follow the participant until an outcome of the pregnancy is known.

Expected Risks of the Study Medication

For anyone who has opioids in their system, naloxone and naltrexone may cause opioid withdrawal symptoms. As with any study drug, there is also the possibility of an allergic reaction. Participants will be monitored for at least one hour following the naloxone challenge, Vivitrol study drug injection, and bupropion dose.

NALTREXONE: Possible side effects include nausea, vomiting, headaches, dizziness, insomnia, dry mouth, and depressed mood. In rare cases people who received naltrexone developed suicidal thoughts, or a type of pneumonia (lung inflammation) caused by an excess of a certain type of white blood cells in the lungs. The most serious side effect of naltrexone is liver (hepatocellular) injury, which has almost always occurred with oral doses of 1400 to 2100 mg per week. Recent study findings show that no evidence of liver injury was found in people receiving once-monthly Vivitrol® injections. For safety, participants with acute symptomatic hepatitis or liver failure will not be allowed to participate.

Vivitrol injections may cause pain, tenderness, hardening or damage of body tissues, swelling, redness, bruising, itching, or infection at the injection site. Such injection site reactions have been the most common side effects associated with Vivitrol. The injection site will be monitored after each of the two injections. Participants will be instructed to report any injection site reactions immediately to the study team. Any participants showing signs of injection site reactions such as a localized infection (abscess), skin infection (cellulitis), body tissue damage, or extensive swelling will be monitored by the study medical staff and treated accordingly.

BUPROPION: Possible side effects include agitation, irritability, restlessness, sleeplessness, dry mouth, headache/migraine, nausea, vomiting, constipation, and shakiness. At doses of 450mg daily, there is 1 chance in 1000 that a participant taking bupropion will experience a seizure. Individuals with a seizure disorder, acute eating disorder, or who are taking certain medications will not be allowed to participate. Although bupropion is used to treat depression, a small percentage of people who take antidepressants have increased thoughts of suicide, particularly during the early weeks of medication.

Data management procedures

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture system (AdvantageEDC) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

Data and statistics center responsibilities

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report

Forms (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of AdvantageEDC and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, 6) perform data cleaning activities prior to any interim analyses and prior to the final study database lock.

Data collection and entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in AdvantageEDC, or will be collected via direct entry into the eCRF. In the event that AdvantageEDC is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into AdvantageEDC in accordance with the instructions provided during project-specific training and guidelines established by the DSC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

The principal investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

Data monitoring, cleaning and editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in AdvantageEDC. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in AdvantageEDC on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into AdvantageEDC.

As described above, the CCC will conduct regular visits to sites, during which, audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding RRTC (node), the Lead Investigator, the coordinating centers, and NIDA, to monitor the sites' progress on the study.

Data lock and transfer

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final analysis dataset will be returned to the Lead Investigator and NIDA, as requested, for storage and archive.