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PROTOCOL

Title: NIDA CTN-0068 Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) for Methamphetamine Use Disorder

Version 6.0

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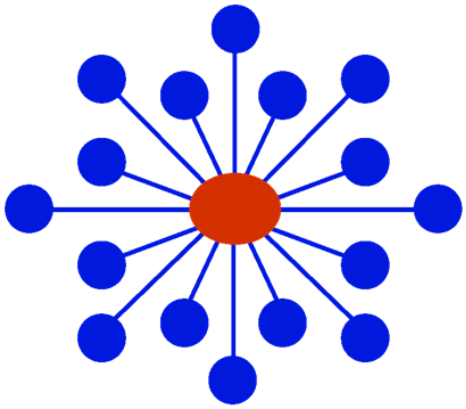

NIDA CTN Protocol 0068

Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) for Methamphetamine Use Disorder

Lead Investigator (LI): Madhukar Trivedi, MD

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Details regarding the timing of re-randomization and related statistical analysis (as it contains information about the timing of re-randomization) are omitted from the Protocol to protect the double blind. These details are contained in the confidential Statistical Analysis Plan. The Lead Team will provide the Statistical Analysis Plan directly to the site Institutional Review Board(s) or Independent Ethics Committee.

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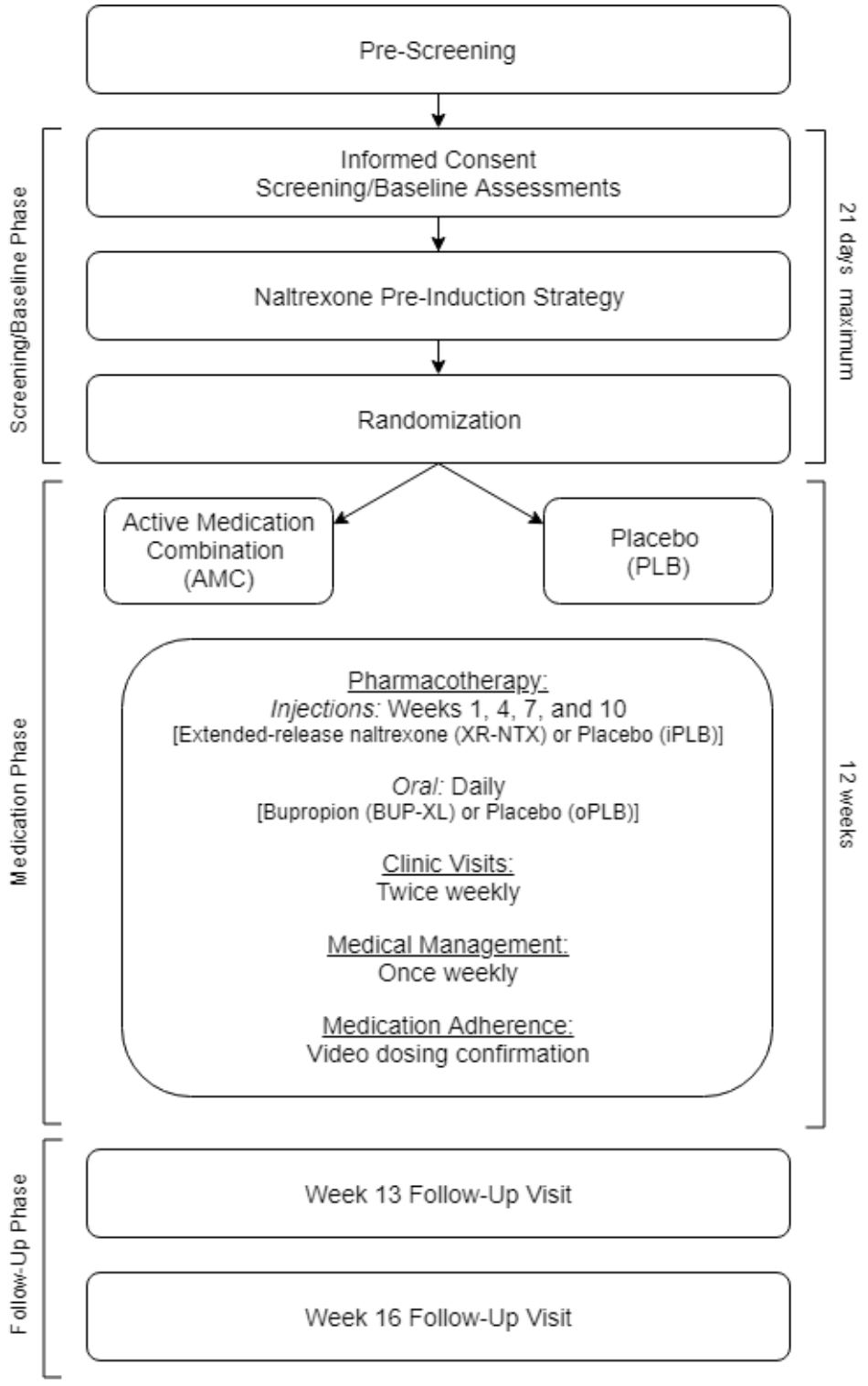
1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AMC	Active Medication Combination
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BL	Blood levels of bupropion and/or metabolite
BUP-XL	Extended-release Bupropion
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
CCTN	Center for the Clinical Trials Network
CHRT	Concise Health Risk Tracking
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
CRF	Case Report Form
CTN	Clinical Trials Network
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
EDC	Electronic Data Capture system/Advantage eClinical
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
HIV	Human Immunodeficiency Virus
ICH	International Council on Harmonisation
IM	Intramuscular
IRB	Institutional Review Board
IND	Investigational New Drug
iPLB	Injectable Placebo
LFT	Liver Function Test
LN	Lead Node
MA	Methamphetamine
Mg	Milligrams
NAL	Naloxone
NDA	New Drug Application
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
oPLB	Oral Placebo
PCM	Prior and Concomitant Medications
PDSQ	Psychiatric Diagnostic Screening Questionnaire
PI	Principal Investigator
PLB	Placebo Medication Combination
RAP-C	Research Advisory Panel of California
SRB	Sexual Risk Behaviors
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TEA	Treatment Effectiveness Assessment
TES	Treatment Effectiveness Score
TLFB	Timeline Followback
UDS	Urine Drug Screen
VAS	Visual Analog Scale
XR-NTX	Extended-Release Naltrexone (as Vivitrol®)

2.0 SCHEMA



Randomization to AMC or PLB occurs the day of successful completion of the naltrexone pre-induction strategy. During the medication phase, participants may or may not be switched (re-randomized) to another arm, as determined by the a priori adaptive aspect of the study design. Participants appearing to respond well to their original treatment assignment will not be switched.

3.0 SYNOPSIS

STUDY OBJECTIVE: The primary objective of this study is to evaluate the efficacy of extended-release naltrexone plus bupropion as a combination pharmacotherapy for methamphetamine use disorder. Secondary objectives include assessing the safety of naltrexone plus bupropion and determining the efficacy of the combination pharmacotherapy on other substance use outcomes, on depression symptom scores, and on quality of life ratings.

STUDY DESIGN: This is a double-blind, placebo-controlled, adaptive randomized clinical trial in which 400 individuals with moderate or severe methamphetamine use disorder will be randomly assigned to the 1) active medication combination (AMC) arm in which injections of extended-release naltrexone (XR-NTX; as Vivitrol®) plus once daily oral extended-release bupropion (BUP-XL) tablets will be provided or the 2) matching placebo (PLB) arm in which injections of placebo (iPLB) and once daily oral placebo (oPLB) tablets will be provided. During the course of the study, participants may or may not be switched to another arm, as determined by the a priori adaptive aspect of the study design. Participants appearing to respond well to their original treatment assignment will not be switched. Overall, approximately 50% of the participants will receive the AMC. After establishing eligibility during a maximum 21-day screening period, participants will begin the 12-week medication phase. Randomization will be stratified by site. At the end of the 12-week medication phase, participants will complete a follow-up phase, including an oral medication taper. Post-medication phase follow-up visits will occur during Weeks 13 and 16.

STUDY PARTICIPANTS: The study sample consists of 400 males and non-pregnant, non-lactating females, ages 18 to 65 years old, who have met all eligibility criteria, including DSM-5 criteria for moderate or severe stimulant use disorder (methamphetamine type), who report using methamphetamine 18 or more days during the 30 days prior to signing consent, and who provide at least 2 methamphetamine-positive urine specimens during screening. Potential participants have up to 3 weeks to meet eligibility criteria after signing consent.

INTERVENTION: The study intervention consists of a 12-week medication phase. Participants randomized to the AMC arm will receive injections of extended-release naltrexone (Vivitrol®) plus 450 mg of once-daily oral extended-release bupropion tablets while participants randomized to the PLB arm will receive placebo injections plus once-daily oral placebo tablets. Injectable study medication will be administered every three weeks (weeks 1, 4, 7, and 10). Take-home oral study medication will be dispensed once weekly for dosing on non-clinic days. Once weekly medical management sessions with the study medical clinician will be provided. Medication adherence procedures will include smartphone app-based videos of daily dosing. Participants will be asked to attend clinic twice weekly for observed oral study medication dosing, collection of urine drug screening samples, and self-report assessments. Compensation will be provided for visit attendance and dosing adherence.

ASSESSMENTS: Screening/baseline assessments include safety and medical measures including a medical and psychiatric history, a physical examination, clinical lab tests (blood chemistry, hematology, and urinalysis), 12-lead electrocardiogram, vital signs, and pregnancy tests (for females). Screening/baseline assessments also include psychological and drug use measures. Methamphetamine use outcome assessments include Urine Drug Screens (UDS), self-reported use via the Timeline Followback (TLFB), and Visual Analog Scale (VAS) craving scores. Other outcome assessments include UDS and TLFB (i.e., alcohol, tobacco, and/or illicit drugs), depression (Patient Health Questionnaire-9), quality of life (QOL), functioning (Treatment Effectiveness Assessment), and clinic attendance. Safety measures include monitoring vital signs, adverse events (AEs), concomitant medications, clinical lab results, and assessments of suicidality. Oral study medication adherence will be assessed by self-report, quantitative blood levels of bupropion and its primary metabolite, and smartphone app-based dosing confirmation procedures.

A blood sample for genetic analysis will be collected from randomized participants who consent to this procedure and the de-identified sample will be sent to a cell and DNA repository.

ANALYSES: The primary analysis will evaluate the impact of the AMC arm, relative to PLB, on methamphetamine use. The primary efficacy outcome is a measurement of treatment response based on MA-negative urine drug screen results obtained during weeks 5 to 6 and weeks 11 to 12 of the medication phase. Outcome variables will be analyzed using appropriate statistical methods for the intention-to-treat (ITT) population and for the evaluable population.

4.0 BACKGROUND AND RATIONALE

4.1 Background

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-Lindström et al., 2008b). Development of a safe and effective pharmacotherapy is an important objective with considerable public health significance.

For many medical conditions, combinations of medications may be routine in clinical practice but are emerging only recently for methamphetamine pharmacotherapy. Well-publicized combination pharmacotherapy studies have tested combination medications for depression (CO-MED, Zisook et al., 2011; STAR-D, Trivedi et al., 2006) made possible by the availability of a number of medications approved for depression. Two notable attempts within the National Institute on Drug Abuse National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) include the *Cocaine Use Reduction with Buprenorphine* (CTN-0048 CURB) trial, a Vivitrol+Suboxone combination trial for cocaine dependence (Ling et al., 2016; Mooney et al., 2013), and the *Accelerated Development of Additive Pharmacotherapy Treatment* (CTN-0054 ADAPT) pilot trial completed in early 2015 that examined the combination pharmacotherapy naltrexone plus bupropion for MA use disorder in an open-label design (Mooney et al., 2016). Findings from the ADAPT pilot study provided a signal sufficient to advise the development of a fully powered, placebo-controlled study to test the efficacy of the combination in producing sustained abstinence from methamphetamine at the end of the study (see below).

4.1.1 Treatment of Stimulant Use Disorder (Amphetamine-type) with Naltrexone

There is modest research to support the individual constituents of the combination pharmacotherapy of naltrexone and bupropion as a putative treatment for MA use disorder.

Naltrexone mechanism of action: An early human laboratory study 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., 2005). 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. A retrospective pooled data analysis of three studies examining alcohol dependent participants with single nucleotide polymorphism (SNP) A118G (heterozygous or homozygous) found that participants treated with naltrexone were substantially less likely to relapse (Oslin et al., 2003). However, one small randomized trial showed no difference in outcomes along this SNP (A118A vs. A118G) when prospectively assigning individuals to open-label injectable naltrexone treatment for methamphetamine dependence (Pal et al., 2015). More recent controlled human laboratory data show that compared to placebo, steady state naltrexone at 50 mg per day significantly blunted cue-induced craving for methamphetamine and attenuated several of the hedonic subjective effects of methamphetamine, including craving, during administration of 30 mg IV methamphetamine challenge. Specifically, naltrexone decreased subjective ratings of "crave drug," "stimulated," and "would like drug access," decreased the post methamphetamine administration time course of "anxious," and increased ratings of "bad drug effects," as compared to placebo (Ray et al., 2015). There is no aversive response to administration of opioids or alcohol while naltrexone is present at clinical dosages.

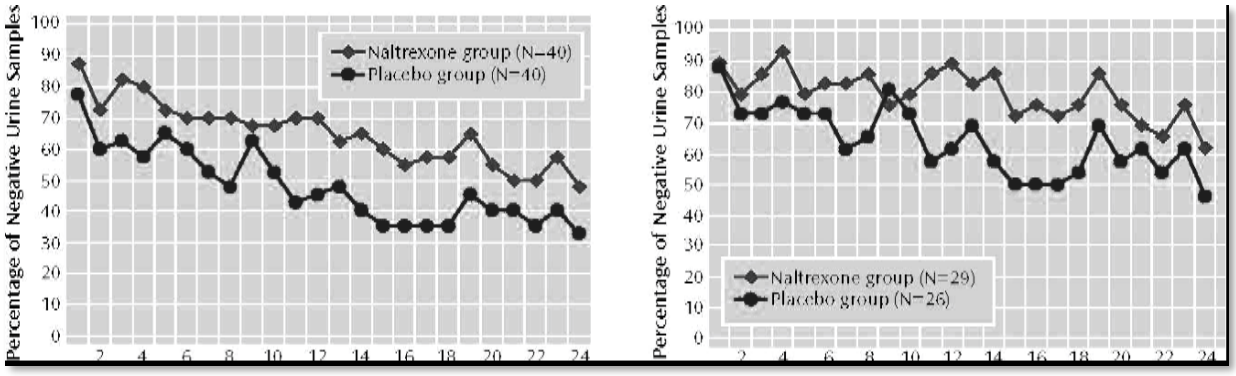
Efficacy of naltrexone in treating stimulant use disorders: A study conducted in Sweden (Jayaram-Lindström, 2008b) indicated that naltrexone reduced amphetamine use among human

subjects, though this efficacy was tested only for patients who could achieve two weeks of abstinence during the baseline screening period. Previously, efficacy of naltrexone for stimulant use disorder was found by Schmitz et al. (2001), reporting cocaine use decreased over time among cocaine-dependent patients taking 50 mg 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 50 mg/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 384 mg of sustained-release naltrexone, virtually the same dosage of the extended-release formulation to be used 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 quantity of amphetamine use during treatment than before naltrexone treatment. Furthermore, in a double-blind trial, the same Swedish group (Jayaram-Lindström et al., 2008a) found that naltrexone reduced subjective effects of amphetamine. Subsequent work (Jayaram-Lindström et al., 2008b) found that oral naltrexone was effective in suppressing relapse to stimulant use among individuals meeting DSM-IV criteria for amphetamine dependence. While the current study protocol was being developed, a double-blind, randomized, placebo-controlled trial (NCT01449565) of the injectable form of naltrexone was being conducted in San Francisco among methamphetamine dependent men who have sex with men (Coffin et al., 2017). Participants were assigned to extended-release injectable naltrexone (n=50) or matched placebo (n=50), administered every 4 weeks for a 12-week period. All participants reduced their methamphetamine use, as evidenced by urine drug screens, during the primary outcome evaluation period of intervention weeks 2 to 12; however, there were no significant differences by intervention arm. Therefore, this recent study does not provide support for the clinical benefit of the use of naltrexone alone as a treatment for methamphetamine dependence in men who have sex with men and who use methamphetamine during sex. Notably, study participants had excellent medication adherence, which lends support to the acceptability and tolerability of this medication in a methamphetamine dependent sample.

Figure 1, from Jayaram-Lindström et al. (2008b), shows percentages of urine samples negative for MA, presented in the figure on the left in the intention-to-treat sample—for the naltrexone group (diamonds) versus the placebo group (circles)—and for the completer group in the right figure.

4.1.2 **Figure 1.** Percentages of Urine Samples Negative for MA



The rationale for including extended-release injectable naltrexone (XR-NTX) in the original CTN-0054 trial was 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., 2011a), 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-Lindström et al., 2008a), and prevent relapse to amphetamine in a double-blind, placebo-controlled trial (Jayaram-Lindström et al., 2008b). The progression of work logically extends from research on preclinical effects of opiate antagonists, to a clinical pharmacology demonstration of attenuation of amphetamine by naltrexone, to an outpatient efficacy study, then to the CTN-0054 combination medication trial on which the present trial is based.

4.1.3 Treatment of Stimulant Use Disorder (Amphetamine-type) with Bupropion

Bupropion is an antidepressant with stimulant properties that has been proven effective for the treatment of nicotine dependence (Richmond & Zwar, 2003). The antidepressant effects of bupropion may be related to its noradrenergic and dopaminergic mechanisms of action. 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, Guernsy, & Ingram, 1983). Bupropion has been studied as an attractive candidate medication for the treatment of stimulant use disorder, which is associated with dopaminergic dysregulation that may contribute to craving and drug seeking. Restoration of dopamine deficit states, combined with bupropion's ability to alleviate dysphoria observed in early abstinence from stimulants (Newton et al., 2004), may in turn reduce craving and help prevent relapse.

Bupropion has been investigated as a treatment for cocaine use disorder. 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-maintained 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-maintained patients indicated efficacy of bupropion for the subgroup of patients with depression at study entry (Margolin et al., 1995).

The results of preclinical 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. 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 reduction of relapse.

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 XL (150 mg twice daily) or placebo control and a series of 3 infusions of saline or MA. The first and second infusions were randomized to be either 0 mg or 15 mg of either saline or MA, and the last infusion was always 30 mg of saline or MA (Newton et al., 2006). Of the 26 subjects 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 (Newton et al., 2005).

Pharmacokinetic analysis revealed that bupropion treatment reduced the plasma clearance of MA and lowered plasma concentrations of the metabolite amphetamine in the plasma (Newton et al., 2005). MA administration did not alter the peak and trough plasma concentrations of bupropion or its metabolites.

A NIDA 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 (Elkashef et al., 2008). 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 a trend, albeit statistically non-significant, favoring bupropion over placebo for the entire population (GEE, $p = 0.09$).
- Bupropion showed a statistically significant effect for MA-free weeks in participants who used MA $\leq$18 days in the 30 days prior to the start of screening (GEE, $p = 0.03$).
- 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, $p = 0.02$).

Participants were randomized to receive thrice-weekly CBT and either 150 mg twice daily bupropion SR or placebo. Randomization was balanced by frequency of self-reported MA use 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; and 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.

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

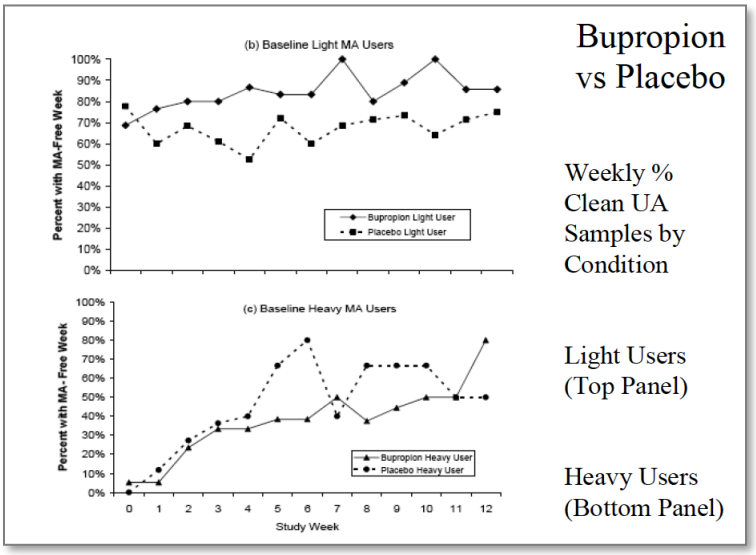
	Abstinence Last 2 Weeks		
Group	**Fail (%)**	**Success (%)**	**Total**
Bupropion	48 (76.2%)	15 (23.8%)	63
Placebo	50 (94.3%)	3 (5.7%)	53
	98	18	116

P = 0.01 (Chi-Square test)

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 not related to the study drug.

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

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



To conclude, this study suggested efficacy of bupropion only in participants who had used methamphetamine relatively infrequently at baseline. However, in the Mooney et al. (2016) study, the medication combination of once-daily 450 mg bupropion XL and extended-release injectable naltrexone resulted in a clinically-meaningful outcome in terms of proportion of methamphetamine dependent participants who met "responder" criteria. Unlike in the Elkashef et al. (2008) study,

these “responders” were participants who had used methamphetamine frequently, having self-reported at least 20 days of MA use in the 30 days prior to consent, and having submitted 3 MA-positive urine drug screens out of 4 collected during screening. Thus, the 450 mg dose of bupropion XL used in the Mooney et al. (2016) trial merits further evaluation in a sufficiently powered, randomized, placebo-controlled trial.

4.2 Study Rationale

Interest in the combination of naltrexone with other medications, 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-Lindström et al., 2008b). Still, the medication is not wholly effective (e.g., Coffin et al., 2017), 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, as examined in CTN-0054, 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) also substantiate the utility of naltrexone for reducing MA use. The combination of naltrexone and bupropion had also been studied in research on the efficacy of the combination pharmacotherapy for controlling obesity (e.g., Greenway et al., 2010; Wadden et al., 2011) leading to the marketing of Contrave® for weight management. In a small (n = 7) clinical pharmacology trial, however, steady state naltrexone (50 mg per day), bupropion (300 mg per day), and their combination showed no statistically significant effect on behavioral responses or subjective effects following 0 mg, 10 mg or 30 mg intranasal methamphetamine (Stoops, Hays, Glaser, & Rush, 2015).

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® allowed 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. 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.

Some of the best evidence in support of this protocol is from the CTN-0054 pilot trial that was conducted as an open-label study of 49 participants at three sites in two CTN Nodes (Nexus Recovery Center, Inc., Texas Node; Integrated Substance Abuse Programs (ISAP) and University of Hawaii (UH), Pacific Region Node). Treatment-seeking, severe MA users (using an average of 27 days out of the previous 30 prior to enrollment) were given bupropion XL (450 mg) daily and XR-NTX every 4 weeks for 8 weeks. Many procedures being proposed for this phase III RCT

were developed and evaluated in the initial pilot trial, including collection of data regarding the tolerability and titration procedures for the 450 mg bupropion in the AMC condition. The intent-to-treat (ITT) analysis in the pilot trial defined the primary efficacy endpoint as the number of responders, with responders 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. Out of 49 participants, 9 responders were required to indicate that the medication combination has sufficient potential efficacy to warrant a fully-powered phase III, placebo-controlled trial. Findings from the 49 participants included in the analysis of the primary efficacy endpoint indicated that 11 were responders, which met the a priori specified criterion requiring 9 or more responders ($p = 0.0075$). The unbiased estimate of the responder rate was 24%, and the 95% lower confidence limit was 13%. There were no significant site, sex, race or ethnicity differences by responder status. The responder rate was highest at the ISAP site (27.8%) and lowest at the Nexus site (15.8%). Seven (26.9%) males and 4 females (17.4%) were responders. Four (16.7%) whites and 7 others (4 multiracial and 3 others) were responders. Seven responders were not Hispanic or Latino, and 4 were Hispanic or Latino.

These data were used to support development of the current phase III randomized, double-blind, placebo-controlled trial of this combination pharmacotherapy to produce abstinence for participants with methamphetamine use disorder. It is intended that participants randomized to the active medication arm receive the maximum safe dose of both bupropion and naltrexone to maximally enable them to become abstinent within the treatment phase of this study. The recommended dosing regimen of Vivitrol® is every four weeks; however, plasma levels of naltrexone and its metabolite are at a plateau during the first three weeks after administration but fall off in the fourth week. Replenishment of the depot supply of naltrexone at the beginning of the fourth week by re-injecting Vivitrol® should prevent that decline and allow evaluation of the maximum safe dose of the combination medication.

4.3 Significance of the Project to the Field

Identifying an effective medication, or combination of medications, to help achieve abstinence and to prevent relapse to MA use is an important objective with considerable public health significance. The proposed placebo-controlled trial, based on preliminary evidence established in the CTN-0054 ADAPT pilot trial, will advance medication research and potentially confirm the naltrexone plus bupropion combination as the first effective pharmacotherapy for the treatment of stimulant use disorder involving MA.

5.0 OBJECTIVES

The objective of this study is to evaluate an active medication combination (AMC) that comprises extended-release naltrexone (XR-NTX) plus bupropion (BUP-XL) as a potential pharmacotherapy for methamphetamine use disorder.

5.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy of the AMC arm, compared to a matched placebo (PLB) arm, in reducing methamphetamine use in individuals with moderate or severe methamphetamine use disorder seeking to stop or reduce methamphetamine use. It is hypothesized that the AMC arm will be associated with a greater number of "responders," defined as participants who provide a pre-specified number of MA-negative UDS tests obtained during the evaluation period (i.e., weeks 5 to 6 and weeks 11 to 12) of the 12-week long medication phase, relative to the PLB arm.

5.2 Secondary Objectives

Secondary objectives include evaluating the effect of the AMC arm, compared to the PLB arm, on safety, other substance use outcomes, depression scores, quality of life, overall functioning, clinic attendance, and medication adherence.

6.0 DESIGN

6.1 Overview of Study Design

The primary objective of this study is to assess the efficacy of extended-release naltrexone plus bupropion as a combination pharmacotherapy for methamphetamine use disorder. There will be 400 individuals randomized into the study across 7 -10 clinical sites. Eligibility will be determined during a maximum 21-day screening period. To document an appropriate level of current methamphetamine use, prospective participants must submit at least 2 urine samples positive for methamphetamine of a possible 3 tests to occur within a 10-day period during which clinic visits occur with at least 2 days between visits. In addition, participants must self-report MA use on 18 or more days in the 30-day period prior to consent using the Timeline Followback (TLFB) and meet diagnostic criteria for moderate or severe methamphetamine use disorder per DSM-5 (4 or more criteria) at screening. After screening is completed and eligibility is confirmed, participants will begin the 12-week medication phase of the trial. Participants will be randomized to either the 1) AMC arm and receive injections of extended release naltrexone (XR-NTX; as Vivitrol®) plus once-daily oral extended-release bupropion tablets (BUP-XL) or the 2) matching placebo (PLB) arm and receive injections of placebo (iPLB) plus once-daily oral placebo (oPLB) tablets. This protocol will utilize a sequential parallel comparison design (SPCD), originally proposed by Fava et al. (2003), and later revised by Chen et al. (2011). A feature of this design is that it can reduce the overall placebo response rate. One advantage of the adaptive aspect of the design is that it requires a smaller sample size compared to a standard two group randomized trial design. During the course of the study, participants may or may not be switched to another arm, as determined by the a priori adaptive aspect of the study design. Participants appearing to respond well to their original treatment assignment will not be switched. Overall, approximately 50% of the participants will receive the AMC. Injections will be provided in weeks 1, 4, 7, and 10. Take-home oral study medication will be dispensed weekly for dosing on non-clinic days. Participants will be asked to attend the clinic twice weekly for observed oral medication dosing, assessments, collection of urine samples, and once-weekly medical management. On non-clinic days, participants will participate in smartphone app-based medication adherence activities. Participants will be asked to complete assessments as indicated on the schedule of assessments (see Section 8.0). Following the 12-week medication phase, participants will complete a follow-up phase, including a medication taper and post-medication phase follow-up visits during weeks 13 and 16.

6.2 Duration of Study and Clinic Visit Schedule

Participants will be involved in the study for approximately 19 weeks, including a screening/baseline period of up to 3 weeks (i.e., 21 days), 12 weeks of medication, and a post-medication follow-up phase. The screening phase may differ by participant in the length of time needed to complete preliminary eligibility assessments. Confirmation of opioid-free status (urine drug screen test(s) and optional naloxone challenge) before randomization and medication induction will take approximately 1.5 hours. Twice-weekly visits during the medication phase will range from about 20 to 90 minutes in length depending on scheduled assessments. Once-weekly medical management sessions will require an additional 20 minutes. Medication injection visits will take approximately 2 hours. The post-medication phase follow-up visits will take approximately 1 to 2 hours to complete. A 12-week medication period was selected based on expected time needed to observe clinical benefit and for pragmatic issues related to medication dosing.

Enrollment is expected to take place over a period of approximately 18 months.

6.3 Participant Selection

A total of 400 males and females who meet eligibility criteria will be randomized. 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. The study sites should attract a diverse study population. Efforts will be made to recruit a study sample that reflects, or exceeds, the proportion of minorities in the community where the site is located. Recruitment procedures aiming to enhance enrollment of women and/or minorities will be conducted, including linkages with medical sites and/or treatment programs that serve a large number of women and/or minorities, and advertising in media outlets with high female/minority audience. Participants will not receive other formal addiction treatment services while they are participating in the study. Thus, at the time of randomization participants must be willing to have the study intervention serve as their sole treatment during study participation. Mutual help support group attendance will be encouraged throughout the trial. Upon study completion, participants may enroll in behavioral or pharmacological addiction treatment services.

6.3.1 Inclusion Criteria

Study participants ***must***:

1. Be 18 to 65 years of age;
2. Be interested in reducing or stopping methamphetamine use;
3. Be able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study;
4. Meet DSM-5 criteria for moderate or severe methamphetamine use disorder (4 or more criteria);
5. Self-report methamphetamine use on 18 or more days in the 30-day period prior to consent using the Timeline Followback (TLFB);
6. Provide at least 2 urine samples positive for methamphetamine out of a possible 3 tests to occur within a 10-day period during which clinic visits occur with at least 2 days between visits;
7. If female, agree to use acceptable birth control methods and have periodic urine pregnancy testing done during participation in the study unless documentation of hysterectomy provided;
8. Meet subjective and objective measures of being opioid-free prior to naltrexone induction per study medical clinician’s determination;
9. Be willing to comply with all study procedures and medication instructions;
10. Agree to use a smartphone app (downloaded for free to own device or on a study provided smartphone device) to take daily videos of medication dosing.

6.3.2 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 suicidal or homicidal ideation that requires immediate attention;
3. Have a history of epilepsy, seizure disorder, or head trauma with neurological sequelae (e.g., loss of consciousness that required hospitalization); current anorexia nervosa or bulimia; or any other conditions that increase seizure risk in the opinion of the study medical clinician;
4. Have evidence of second or third degree heart block, atrial fibrillation, atrial flutter, prolongation of the QTc, or any other finding on the screening ECG that, in the opinion of the study medical clinician, would preclude safe participation in the study;
5. Have Stage 2 hypertension as determined by the study medical clinician (e.g., greater than or equal to 160/100 in 2 out of 3 readings during screening);
6. Have any elevated bilirubin test value per laboratory criteria OR any other liver function test (LFT) value > 5 times the upper limit of normal per laboratory criteria;
7. Have a platelet count <100 x 10^3/μL;
8. Have a body habitus that precludes gluteal intramuscular injection of XR-NTX in accordance with the administration equipment (needle) and procedures;
9. Have a known allergy or sensitivity to bupropion, naloxone, naltrexone, PLG (polyactide-co-glycolide), carboxymethylcellulose or any other component of the XR-NTX diluents;
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. Have been prescribed and taken naltrexone or bupropion within 30 days of study consent;
13. Be concurrently enrolled in formal behavioral or pharmacological addiction treatment services;
14. Be receiving ongoing treatment with tricyclic antidepressants, xanthines (i.e., theophylline and aminophylline), systemic corticosteroids, nelfinavir, efavirenz, chlorpromazine, MAOIs, central nervous system stimulants (e.g., Adderall, Ritalin, etc.), or any medication that, in the judgment of the study medical clinician, could interact adversely with study medications;
15. 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;
16. Require treatment with opioid-containing medications (e.g., opioid analgesics) during the study period;
17. Have a surgery planned or scheduled during the study period;

18. Are currently in jail, prison or any inpatient overnight facility as required by court of law or have pending legal action or other situation (e.g., unstable living arrangements) that could prevent participation in the study or in any study activities;

19. If female, be currently pregnant, breastfeeding, or planning on conception.

Although not targeted for recruitment, this study obtained authorization from the Office for Human Research Protections (OHRP) to follow-up with study participants who happen to become incarcerated during the trial, as needed and feasible at the individual study sites. Study staff may work with institutions to arrange research visits, and any needed assessments and procedures the institution will allow may be completed. Study medications will be discontinued during incarceration.

6.4 Site Selection

The trial will include 7 -10 sites with each site randomizing approximately 30-70 participants.

6.4.1 Site Characteristics

Participating sites ***must***:

1. Have a physician who can commit the time necessary to take a leadership role and oversee all medical aspects of the study, perform medical assessments, confirm participant eligibility, order and dispense or administer study medications, review adverse events, and appropriately evaluate 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, order and dispense or administer study medications, review adverse events, and appropriately respond to adverse reactions that may occur during the course of the study.

3. Have standard operating procedures 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 qualified personnel to complete blood draws.

6. Have the ability to meet storage and dispensing requirements for all study medications, including access to adequate storage space, equipment, and appropriately qualified staff, as directed by the protocol and in accordance with local regulations and NIDA stipulations.

7. Have access to, or the ability to contract with, a local laboratory to process biological specimens (e.g., blood and/or urine) in a timely manner during screening.

8. Have adequate facility space available to conduct study procedures.

6.4.2 Rationale for Site Selection

The sites selected for participation in this trial will be selected, in part, based on the node's interest in participating in the trial, the availability of a sufficient pool of potential study participants in the area, and the presence of an existing team of experienced personnel at the site knowledgeable in clinical trial operations and trained in core CTN assessments. Information on site readiness and capacity will be gathered via a site survey and a coordinated site/investigator selection process will confirm the following:

1. An ability to recruit and randomize 3-4 eligible individuals with methamphetamine use disorder each month.
2. Experienced regulatory personnel capable of the timely preparation of necessary regulatory documents and having the ability to facilitate an expeditious IRB submission, approval, modification, and continuing review processes.
3. Medical staff who can commit the time necessary to oversee all medical aspects of the study, perform medical assessments, confirm participant eligibility, order and administer or dispense study medications, and appropriately respond to possible adverse reactions that may occur during the course of the study.
4. Staff familiar with web-based Electronic Data Capture systems and who have the capacity and discipline to conform to protocol-required direct data entry procedures.
5. Adequate and available space that is suitable for the performance of study procedures.

6.5 Randomization Plan

Eligible participants will be randomized to the AMC and PLB treatment arms, stratifying by site. During the course of the medication phase, participants who provide sufficient UDS for evaluation of outcomes may or may not be switched to another arm. Switching, or re-randomization parameters, were determined a priori and are based on a combination of original treatment assignment, availability of data, and treatment response. Participants appearing to respond to their original treatment assignment will not be switched. Re-randomization will be implemented automatically by computer and will be stratified by site. Overall, approximately 50% of the participants will receive the AMC.

The randomization process will be conducted centrally and electronically by the CTN Data and Statistics Center (DSC) via the Advantage eClinical Electronic Data Capture (EDC) system, and randomization assignments will not be conveyed to staff or participants to maintain the double blind. To ensure the lack of predictability while maintaining the designed randomization fraction, an urn scheme similar to one described in Wei and Lachin (1988) will be used. The DSC statistician will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization slot, once used, will not be re-allocated.

6.6 Study Intervention

The study intervention consists of 12 weeks of pharmacotherapy, medical management, and medication adherence procedures. Participants randomized to the AMC treatment arm will receive an injection of extended-release naltrexone (XR-NTX; as Vivitrol®) plus 450 mg of once-daily oral extended-release bupropion tablets (BUP-XL). Participants randomized to the PLB treatment arm will receive matched placebo in the form of injections of placebo (iPLB) plus once-

daily oral placebo (oPLB) tablets. Injections of study medications (XR-NTX or iPLB) will be administered in weeks 1, 4, 7, and 10. All randomized participants will receive weekly medical management sessions with the study medical clinician and will utilize smartphone app-based medication adherence procedures.

6.7 Outcome Measures

The primary outcome measure, as described below, is based on urine drug screen (UDS) test results and is considered a clinically significant improvement in methamphetamine use in this study population. The primary outcome (UDS) has been chosen because it is an objective measure of methamphetamine use. Secondary outcome variables are intended to explore various aspects of response to this medication combination and to identify factors that may be associated with treatment response or non-response. Some of the secondary outcome variables add a measure of clinical relevance to the reduction of use by assessing sustained abstinence, reduced frequency of methamphetamine use, reduction in craving that may be a prelude to relapse, and improvements in mood, quality of life, and overall functioning.

6.7.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is a composite of MA-negative UDS test results obtained during weeks 5 to 6 and weeks 11 to 12 of the medication phase and will be compared by treatment group (AMC versus PLB).

6.7.2 Primary Safety Outcome Measure

The safety and tolerability of the AMC arm, relative to the PLB arm, will be determined using participants' reports of adverse events (serious and non-serious) collected at clinic visits or via other contact.

6.7.3 Secondary Outcome Measures

Secondary outcome measures for the impact of the AMC, relative to the PLB arm, on other substance use outcomes, depression scores, quality of life, overall functioning, clinic attendance, and medication adherence will be evaluated as follows:

1. Alternate measures and composites of methamphetamine use including:

   a) The Treatment Effectiveness Score (TES), as measured by UDS results, during the medication phase;

   b) Frequency of MA use, as measured by self-report, during the medication phase;

   c) Severity of MA craving, as measured by Visual Analog Craving Scales (VAS), during the medication phase;

   d) MA use, as measured by UDS and self-report, during the follow-up period.

2. Quantity and frequency of alcohol, tobacco, and other drug use, as measured by self-report, during the medication phase;

3. Change in depressive symptoms, as measured by the PHQ-9, during the medication phase;

4. Changes in quality of life, as measured by the Quality of Life (QoL), during the medication phase;

5. Changes in overall functioning, as measured by the Treatment Effectiveness Assessment (TEA), during the medication phase;

6. Percentage of participants retained in treatment during the medication phase;

7. Ratings of participant and staff satisfaction with study procedures, including use of the medication adherence app, compensation, and medication.

7.0 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 domains. Screening and baseline assessments will be conducted as shown in Table 2 in section 8.0. Participants who do not complete all screening/baseline assessments within 21 days of signing consent, including the naltrexone pre-induction strategy, or who are otherwise found to be ineligible for participation in the study, will be considered screen fails. With Lead Node approval, screen fails may be allowed to return at a later date to repeat the screening process.

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., 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) 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 and before any assessments are administered, qualified study personnel will conduct the informed consent process with prospective participants. The informed consent process will begin with a description of the study, including study procedures and study medications. Potential study participants will be given a copy of the IRB-approved consent form to review either on site or at home, in accordance with IRB requirements. Potential study participants who remain interested after review of the consent form will answer written comprehension questions to ascertain their understanding of the study, including its purpose, procedures involved, and the voluntary nature of participation. For participants who do not correctly answer all comprehension items, research staff will re-explain the study, with a focus on aspects candidates did not understand. Participants may attempt the consent comprehension questions a maximum of three times before they are deemed unable to comprehend the study. Any participant who cannot demonstrate appropriate understanding of the study to research personnel will be ineligible to participate and will be assisted in finding other treatment resources if desired. Study participants who demonstrate understanding of the study and who voluntarily agree to participate will be asked to sign the IRB-approved consent form and, if the consent form is signed, will proceed with the screening assessments. As part of the informed consent process, participants also will be asked if they consent to (1) be contacted for future studies and (2) provide a blood sample for genetic testing.

7.1.3 Screening and Baseline Assessments

Upon signing the IRB-approved consent form, participants enter a maximum 21-day screening phase to complete assessments to determine eligibility and to collect baseline data. Screening/baseline assessment procedures must be completed across at least two screening visits.

During the screening phase, participants must submit at least 2 urine samples positive for methamphetamine out of a possible 3 tests to occur within a 10-day period during which clinic visits occur with at least 2 days between visits. Therefore, all screening visits will have at least 2 days elapse between visits. In addition, participants must self-report MA use on 18 or more days

in the 30-day period prior to consent using the Timeline Followback. These criteria will be used to confirm current MA use and further substantiate a diagnosis of moderate or severe methamphetamine use disorder.

Once the participant completes all screening and baseline assessments, submits 2 MA-positive UDS tests, and is found otherwise eligible for continued participation, the participant may begin the naltrexone pre-induction procedure (see below). All consented participants who do not complete all screening assessments within the 21-day screening period or who are otherwise found to be ineligible for study participation will be considered to be screen fails. Demographic data and the reasons for not meeting eligibility criteria must be documented for all screen fails.

7.1.4 Naltrexone Pre-Induction Strategy

The screening/baseline phase includes a naltrexone pre-induction strategy to be conducted on the final screening visit after all other eligibility criteria have been met. The naltrexone pre-induction strategy is designed to ensure participants meet subjective and objective measures of being opioid-free, per the study medical clinician's determination, on the day of and prior to randomization and induction on the injectable study medication. Required and optional procedures are outlined below:

1. Subjective measures of opioid-free status. 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 naltrexone administration) in the 7-10 days prior to the day of randomization, as measured using the TLFB and the Prior and Concomitant Medications (PCM) assessment.
2. Objective measures of opioid-free status. To objectively evaluate opioid-free status, a urine sample must be provided and tested on the day of anticipated randomization. Individuals must have negative results for opioids (on the OPI 2000 and the OPI 300 tests) prior to randomization. Individuals with a positive opioid result on these tests may provide an additional urine sample on a subsequent day if the study medical clinician determines that a second screen is appropriate. The study medical clinician must determine suitability for continuing the pre-induction process for individuals positive for opioids on other opioid tests that may be conducted during Screening.
3. *Optional* naloxone challenge. A naloxone challenge is not required but may be administered for definitive determination of opioid free status at the discretion of the medical clinician. If a naloxone challenge is administered, a minimum 0.8 mg bolus must be given before determining the outcome of the challenge. The study medical clinician will use clinical judgment to determine if the participant passes the naloxone challenge and is safe to continue on to randomization and subsequent XR-NTX or iPLB induction. Evidence of withdrawal signs or symptoms following naloxone administration will result in postponement of randomization until a negative naloxone challenge result is achieved. In other words, if a clinician opts to administer a naloxone challenge and withdrawal is precipitated, a second naloxone challenge must be administered, with no withdrawal observed immediately prior to randomization.

   Participants who experience withdrawal symptoms following a 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 Confirmation of Eligibility

After completing all screening and baseline assessments, including the naltrexone pre-induction strategy, the study physician must review and approve safety and eligibility assessments in order to confirm participant eligibility prior to randomization. Randomization will occur on the day the naltrexone pre-induction strategy is completed (i.e., the participant is determined to be opioid-free) after study eligibility has been confirmed and documented.

7.2 Medication Phase

7.2.1 Randomization

Immediately following the naltrexone pre-induction strategy and final assessment and documentation of eligibility, eligible participants will be randomly assigned to the AMC arm or the matching PLB arm. The randomization procedure will be conducted electronically by the Advantage eClinical system. The switching or re-randomization procedure described previously will occur seamlessly by the electronic system, based on data routinely collected and entered.

7.2.2 Pharmacotherapy

Participants will receive the first intramuscular gluteal injection of study medication (XR-NTX or iPLB) on the day of randomization (Day 1), following confirmation of opioid-free status and final confirmation of study eligibility by the study physician. Subsequent intramuscular gluteal injections (XR-NTX or iPLB) will be administered at the beginning of Weeks 4, 7, and 10 and shall be administered following guidelines in the XR-NTX package insert. Study medical clinicians will evaluate participants to ensure continued suitability for injectable study medication administration. Urine drug screening procedures will help clinicians evaluate participant opioid-free status at the time of study medication injection. A naloxone challenge may be administered prior to any study medication injection at the discretion of the study medical clinician.

Take-home oral study medication will be dispensed weekly. The first dose of oral study medication (BUP-XL or oPLB) will be taken on the day of randomization (Day 1) immediately following administration of the injectable study medication. For each clinic visit, participants will be asked to refrain from taking their dose at home and to bring their oral study medication for in-clinic dosing. On the days in which injectable study medication is administered, oral study medication self-administration will occur immediately following the injection. All in-clinic self-administration of oral study medication will be observed by study staff. Participants will take a dosing video using the study app for all in-clinic and non-clinic self-administrations of oral study medication.

If a participant reports intolerable symptoms or side effects at the full 450 mg dose, ancillary medications may be used and/or a dose reduction may occur if deemed appropriate by the study medical clinician. The study medical clinician, in collaboration with the study physician and site principal investigator, is encouraged to consult with the Lead Investigator(s) in making the decision to reduce a participant's dose. The dose may be reduced to 300 mg daily. Medication packaging will allow for dose reductions without re-dispensing; participants will be instructed to take only the tablets in the first two wells for each day they are on a reduced dose. If intolerable adverse effects continue, the participant may be withdrawn from further medication administration. If intolerable adverse effects resolve after an initial dose reduction or are appropriately addressed with the use of ancillary medications, and if deemed appropriate by the study medical clinician, titration to the full 450 mg target dose may be attempted (i.e., participants will be instructed to take all three tablets for each day) on any visit except visits in which injectable study medication is administered.

7.2.3 Medical Management

Medical management procedures will be conducted as follows. Participants will meet with a study medical clinician once weekly for an individual medical management session that utilizes a structured adherence enhancement manual designed for pharmacotherapy trials with subjects with substance use disorder (adapted from Carroll et al., 1996). The goal of medical management sessions is to achieve high quality supportive treatment that reinforces adherence to study procedures and the study medication regimen. A session will be approximately 20 minutes and focus on:

1. Setting abstinence from methamphetamine as a goal,

2. Participant adherence with study medications and procedures,

and

3. Current functioning.

Medical clinicians will also review 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 symptoms such as anxiety, nausea, vomiting, diarrhea, muscle pain, and insomnia. At all medical management sessions, the medical clinician will remind participants about the importance of adhering to the study procedures, including attending scheduled clinic visits and complying with smartphone app-based dosing confirmation procedures. Mutual help support group attendance will be encouraged.

7.2.4 Medication Adherence

Medication adherence procedures will be conducted as follows. To encourage and monitor adherence to oral study medication, procedures include discussing adherence during medical management sessions and twice-weekly observed dosing in the clinic as described previously. Procedures also include the use of a smartphone app to take dosing videos to document oral study medication self-administration on non-clinic days and during clinic visits (while staff observe), including on the taper days in the post-medication follow-up phase. Participants will access the app on either a study provided smartphone device or by downloading the app to their personal device. Further details are outlined in Appendix C. Dosing will be assessed by automated visual recognition software during the video capture to ensure the videos clearly show dosing adherence based on assessment criteria. Participants will be compensated for dosing videos (see section 7.5).

7.2.5 Participant Medication Withdrawal

Participants will be withdrawn from further study 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 study medication administration. Likewise, women who become pregnant during the medication period will be immediately withdrawn from study medication administration. Participants reporting use of medications that may interact with naltrexone or bupropion will be withdrawn based on clinical judgment. Participants who experience intolerable adverse 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 to the extent that now taking study medication may be possibly unsafe or unwise. Examples of clinical deterioration that might trigger a decision to withdraw the participant from study 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 a pre-existing psychiatric or medical condition that would preclude continued safe participation in the study;
- Worsening of substance use disorder or overdose such that a higher level of care is indicated;
- Increase in LFT or decrease in platelet test results at week 6 that may increase participant health risks. This includes any of the following: AST/ALT results > 5 times ULN, total bilirubin > 2 times ULN, or platelets below 75 x 10^3/μL.

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 in making the decision to withdraw a participant from study medications. Also, participants may decide at any time that they no longer wish to continue to receive medication or participate in the study.

In most cases, a taper is not indicated if the study medical clinician determines medication discontinuation is warranted for medical or psychiatric reasons. Generally, a taper of bupropion is not medically necessary as there is no evidence of a physiological dependence or increased incidence of adverse events when this medication is discontinued. However, as down titration is common in clinical practice, clinicians are guided to follow this convention for the majority of study participants. 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 on how to best proceed.

In the event a participant becomes pregnant during the medication period, a taper is not indicated as bupropion is a pregnancy category C medication and the risks of taper outweigh the benefits in pregnant women. The pregnant participant will be immediately discontinued from further study medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

A taper is also not indicated for participants who become incarcerated or for participants who lose study medication during the medication phase of the study. Participants who lose study medication will resume their dosing schedule at the appropriate next study visit; no medication should be dispensed earlier than scheduled.

As the primary aim of this study is to evaluate the efficacy of XR-NTX plus BUP-XL as a combination pharmacotherapy, withdrawal from either study medication will typically lead to discontinuation of the other medication. With Lead Node and Study Medical Monitor approval, participants may be allowed to continue on one medication if discontinued from the other. In the event a participant is withdrawn from further study medication administration, referrals to treatment programs or recommendations for medical care will be provided. Unless consent is officially withdrawn, study staff will encourage participants who are withdrawn from study medications or who opt out of study medications to continue attending twice weekly clinic visits and complete study assessments throughout the duration of the medication phase (weeks 1 – 12) and the follow up phase (weeks 13 and 16).

7.2.6 Medication Phase Visits

Given the requirements across study visits (e.g., meeting with medical clinician, blood draws, injections, assignment of oral medication only after the participant arrives, physical exam, ECG, etc.), the study was designed with the expectation that all visits occur at the study site. However, there may be cases in which off-site visits may be possible with Lead Team approval.

7.3 Follow-up Phase

7.3.1 Oral Study Medication Taper

A taper will occur during the first four days of Week 13 (Days 85 – 88) for participants continuing on oral study medication (BUP-XL or oPLB) through the end of the medication phase. The daily dose will be 300 mg for Days 85 and 86 and 150 mg for Days 87 and 88. This taper schedule will apply to all participants, including any participants already taking a reduced dose.

7.3.2 Post-Medication Phase Follow-up Visits

All enrolled participants will be asked to complete post-medication phase follow-up visits in weeks 13 and 16 according to the schedule of assessments (see Table 2, section 8.0). There may be cases in which off-site visits may be possible with Lead Team approval. Tracking and locating strategies will be used to ensure the highest possible follow-up rates.

7.4 Study Medication Management/Drug Accountability

As set forth in the protocol agreement signed by each site principal investigator (see Section 14, Signatures), study sites are required to observe local, state, and federal regulations regarding receipt, custody, dispensing, administration, and associated documentation of all medications used in this study. Medications used in the study include extended-release bupropion, extended-release injectable naltrexone, oral placebo, and injectable placebo provided by the NIDA contractor as well as naloxone purchased and maintained by each site.

7.4.1 Documentation

Upon receipt, the investigator, pharmacist, or authorized designee at each site is responsible for maintaining written inventory of the investigational agents and naloxone obtained for the study. Appropriately trained and qualified personnel will maintain an accurate and real-time accounting of all medications, which will be available for verification by study monitors. Medication accountability records, including perpetual inventory, will document the amount of study medication ordered, received, transferred between areas of the study site (e.g., from pharmacy to clinic), and medications administered to or dispensed to and returned by an individual participant. Documentation will also record unused medications destroyed on site or returned to the NIDA contractor for destruction. As with all study documentation, medication accountability records must be maintained in accordance with Good Documentation Practices and must be attributable, legible, contemporaneous, original, accurate, and complete.

7.4.2 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 and iPLB injectable kits

will be stored in a secure, limited access refrigerator. Temperature logs will show a daily record of medication storage temperature for all medications.

7.4.3 Packaging

Intramuscular gluteal injections (XR-NTX and iPLB) will be supplied in single use kits marked with medication kit numbers which will be used for tracking and inventory purposes. Each active injectable medication kit 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. Each injectable placebo medication kit will be prepared to look identical and will contain the same contents as the active medication kits but with no active medication.

Participants will receive once-daily oral study medication (BUP-XL or oPLB). BUP-XL blister cards will contain a daily dose of 300 mg for the up titration days and a daily dose of 450 mg for all other days in the medication phase. BUP-XL blister cards for the taper days (Days 85-88) will contain a daily dose of 300 mg (Days 85 and 86) and 150 mg (Days 87 and 88).

Oral study medication (BUP-XL and oPLB) will be pre-packaged in weekly blister cards that contain 3 tablet wells for each day. The packaging will be designed such that participants will take all 3 tablets each day, including during the up titration and taper periods.

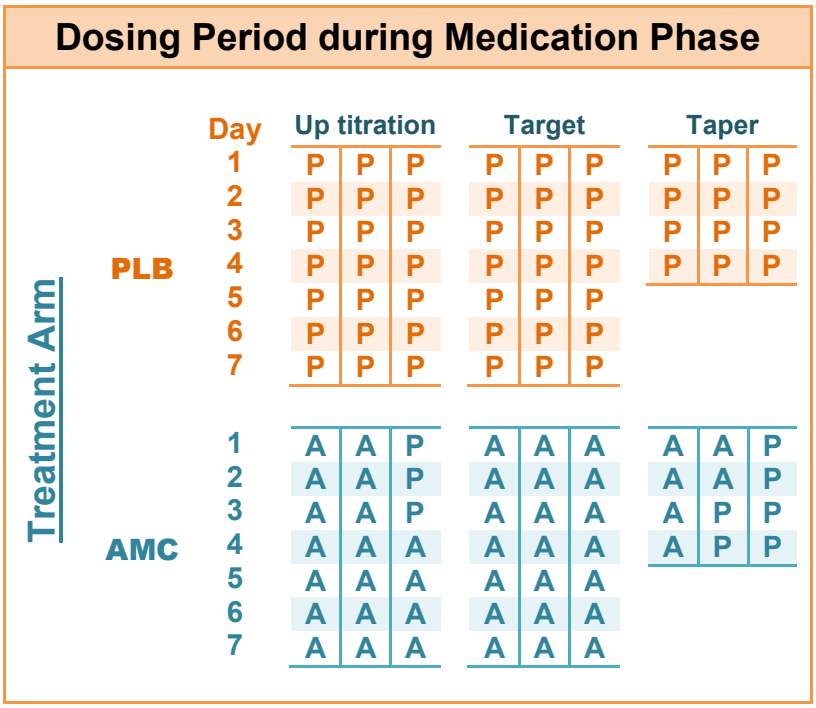
There will be five types of blister cards manufactured to appear identical for both treatment arms. There will be three types of 7 day cards for use in weeks 1 to 12—one for up titration (for AMC only) and two for target dosing (AMC and PLB). Two types of cards will contain a 4-day supply for the week 13 taper period (AMC and PLB).

The up titration AMC card will be dispensed twice during the study: in week 1 for participants randomized to AMC and again when some participants may be re-randomized and assigned to receive AMC. Therefore, the up titration card will be manufactured to contain 3 tablets for each day of the titration in order to appear identical to the target dosing card. The up titration card will contain two active and one placebo tablet each day for days 1 - 3, and it will contain three active tablets each day for days 4 - 7. Packaging the up titration card in this way will help protect the double-blind throughout the trial.

The target dosing cards will contain either active medication or placebo. The AMC taper card will contain two active and one placebo tablet for the first two days and one active and two placebo tablets for the last two days. The PLB taper card will contain three placebo tablets for each of the four days.

Weekly blister cards dispensed to participants will be labeled to include protocol number, study drug information, and blister card number. The label will also include blister card contents, “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.

Below, the medication packaging plan is summarized visually, whereby P indicates placebo tablet and A indicates active tablet. Weekly blister cards for each treatment arm by the dosing period (up titration, target dosing, and taper) will be dispensed as follows:



Key: A - Active medication tablet **P** - Placebo tablet

7.4.4 Ordering and Dispensing

All study medications shall be ordered only by delegated licensed medical staff and dispensed by research staff appropriately trained to do so. Injectable medications will be administered by qualified staff during Weeks 1, 4, 7, and 10. Oral medications will be dispensed to the participant weekly in labeled blister cards that will include both in-clinic observed doses and self-administered doses for non-clinic days.

7.4.5 Used/Unused Medication

Unused study medication will be returned and logged into a perpetual inventory. Returned, damaged, expired or otherwise unused study medications will be accurately labeled, securely stored, kept separately, and shall be accounted for prior to disposition. Any unused or expired investigational agent shall be accounted for at all times. Expired naloxone and other ancillary medications obtained for this study will be destroyed on site or sent for destruction per local institutional policies.

7.4.6 Lost Medication

There will be no replacement of any dispensed study medications.

7.4.7 Maintaining and Breaking Blind

This is a double-blind, placebo-controlled trial. With the exception of the data management group overseeing the random assignment schedule and the NIDA-contracted research pharmacist preparing study medications, all other study personnel and participants will remain blinded to medication status until nationwide completion of the trial. A Data and Safety Monitoring Board (DSMB) will review study data throughout the course of the trial. In rare cases, it may be

necessary to break the blind for a particular study participant before completion of the trial (e.g., pregnancy or other medical necessity). A request to break the study blind for an individual participant must be made by the study physician after consultation with the Lead Investigator. Unblinding the participant should only be done in cases of medical emergency when knowledge of the treatment group assignment may be necessary for clinical management and decision making. The decision to break the blind for a participant will be made jointly by the CCC Medical Monitor and at least one of the Lead Investigators. Any requests for unblinding will be responded to within one business day or less.

7.5 Participant Compensation

Study participants will be provided with study medications, medical management, and a study medication adherence app for use on his/her own device at no cost. Alternatively, a study smartphone device pre-loaded with the medication adherence app will be provided if needed. In addition, participants will receive gift cards or cash (based on local requirements) as compensation for time, travel, parking, and other costs borne by the participant. A total of up to $50 will be provided for completion of screening/baseline assessments (divided among at least two screening visits). Ten dollars ($10) will be provided for each additional eligibility phase clinic visit to provide a urine sample. During the medication phase, $10 will be provided for completion of assessments including a urine sample ($5 will be provided for assessments without a urine sample); $5 for bringing the study medication on clinic days and taking a self-dosing video via the smartphone app while staff observe; and $25 for each injection visit. Participants will be compensated an additional $40 per visit for completion of the mid-treatment visit (visit 602) and the end of treatment visit (visit 1202), and $30 for each follow-up visit in weeks 13 and 16. In addition, participants will be compensated $5 for each dosing video taken on non-clinic days, including the taper in week 13 (see Appendix C for details). Participants may earn a visit attendance bonus of $20 (received up to 6 times) when they attend each visit expected to occur within each 2-week block of the medication phase. For example, a participant could earn $20 for attending four visits in weeks 1-2, $20 for weeks 3-4, and so on until weeks 11-12. Participants may also receive up to $40 to offset the cost of additional data service needed for the dosing app on their personal device or for return of the study smartphone device (see Appendix C for details). Total compensation possible is $1,160 as outlined below.

7.5.1 **Table 1.** Compensation Schedule

Visit/Assessment	Amount	# of Payments	Total
Screening Assessments	$50	1	$50
Eligibility Phase Clinic Visits	$10	4	$40
Injection Visits	$25	4	$100
Clinic Visits (12-week Medication Phase)	$10	23	$230
In-clinic dosing/med return (2x/wk)	$5	24	$120
Mid-Treatment Visit (visit 602) and End-of-Treatment Visit (visit 1202)	$40	2	$80
Dosing video (5x/wk+4 taper days)	$5	64	$320
Attendance Bonus (attending all expected visits in each 2-week block)	$20	6	$120
Follow-up Visits (Weeks 13 and 16)	$30	2	$60

Visit/Assessment	Amount	# of Payments	Total
Additional data service for dosing app on personal device OR smartphone device return	$40	1	$40
Maximum Compensation Possible			**$ 1,160**

8.0 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 also selected to obtain information typically assessed in medication studies, including assessments of drug abuse and dependence diagnoses, psychological status, and measures of craving. Safety is assessed at each visit. Additional forms will be 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 (http://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. Table 2 provides the schedule of study assessments. On average, screening and eligibility assessments will be completed in 6-8 hours. Twice-weekly assessments during the medication phase will be completed in approximately 30 to 90 minutes. Once-weekly medical management sessions will require an additional 20 minutes. The post-medication phase follow-up visits will take approximately 1 to 2 hours.

8.1 Table 2. Schedule of Assessments

Study Phase	Screening/ Baseline	Medication Phase												Follow-up	
Study Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	16
Screening Measures															
Pre-Screening Interview Form	X*														
Informed Consent	X*														
Demographics Form	X*														
Alcohol and Substance Use History	X*														
DSM-5 Checklist	X*														
Psychiatric Diagnostic Screening Questionnaire	X*														
Sexual Risk Behaviors	X*						X^2						X^2		
Self-Report of HIV Testing	X*														
Medical and Psychiatric History	X*														
Safety Measures															
Physical Examination	X*												X^2		
Electrocardiogram	X*												X		
Injection Site Examination		X^2			X^2			X^2			X^2				
Injection Site Abnormality Log[A]															
Clinical Laboratory Tests	X*												X		
Liver function tests & platelet lab tests							X								
Concise Health Risk Tracking	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test	X^E														
Pregnancy and Birth Control Assessment	X*	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs	X^C	X	X	X	X^C	X	X	X^C	X	X	X^C	X	X		
Prior and Concomitant Medications	X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X
Adverse Events and Serious Adverse Events	X^D	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X
Naloxone Challenge Form	X^E				X^E			X^E			X^E				
Efficacy Measures															
Urine Drug Screen	X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X
OPI 300	X**				X**			X**			X**				
Timeline Followback	X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X
Visual Analog Craving Scale	X+	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Health Questionnaire-9	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Effectiveness Assessment	X*						X^2						X^2		
Tobacco Use History	X*						X^2						X^2		
Quality of Life	X*						X^2						X^2		
Blood draw for genetic testing	X^F														
Adherence Measures															
Study Medication Dosing Logs	X^E	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	
Injection Administration Form		X			X			X			X				
Oral Medication Dispensation Form		X	X	X	X	X	X	X	X	X	X	X	2X	X^E	
Bupropion Blood Levels					X^B			X^B			X^B		X^2		
End of Medication Form[E]														X	
Administrative and Other Forms															
Locator Form	X*			X			X			X			X		
Eligibility - Randomization	X*														
Missed Visit Form[E]															
Protocol Deviation Form[E]															
Protocol Satisfaction Surveys														X	
Study Completion Form															X

NOTES: X* = once during screening/baseline

X** = required prior to randomization and injectable study medication administration, may be collected at other times per Medical Clinician discretion.

X+ = at each screening/baseline visit

X= a procedure or assessment performed once per week and on the first visit of the week, unless otherwise noted.

2X= a procedure or assessment performed twice per week.

X^2 = collected at the second visit of the week.

[A] Completed in the event an injection site reaction is reported by a participant or an abnormality is identified during an injection site examination.

[B] Collected according to schedule of assessments, but must be prior to administration of ANY medications (e.g., naloxone; injectable or oral study medication) in a given visit.

[C] Collected according to schedule of assessments, including BEFORE and AFTER administration of naloxone challenge(s) as well as BEFORE and AFTER administration of the study medication combination.

[D] Collected at each visit after consent (i.e. SV02 through the final follow-up visit)

[E] Completed as applicable

[F] If consent is provided, collect genetic sample at the end of the day of randomization if possible. Otherwise, collect during any future visit in which a blood draw occurs.

8.2 Screening Measures

8.2.1 Pre-Screening Interview Form

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-Screening Interview, staff will provide a brief overview of the study and will obtain and document verbal consent. The Pre-Screening Interview consists of questions to assess essential information in determining potential eligibility.

8.2.2 Informed Consent

Prior to beginning any study assessments, all participants will review and sign an IRB-approved consent form and any other related documents in accordance with IRB requirements. The date the IRB-approved consent form was signed will be entered into the electronic data capture system.

8.2.3 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.

8.2.4 Alcohol and Substance Use History

The Alcohol and Substance Use History 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/or various substances as well as his/her age when the substance was first used. The intent of this measure is to document any alcohol use, illicit drug use (e.g., illegal, more than prescribed, not prescribed), and any marijuana use.

8.2.5 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.

8.2.6 Psychiatric Diagnostic Screening Questionnaire

The Psychiatric Diagnostic Screening Questionnaire (Zimmerman, 2002) is a self-report questionnaire used primarily as a psychiatric disorder screener administered in primary care. The Psychiatric Diagnostic Screening Questionnaire will evaluate symptoms of common psychiatric disorders and will be administered during the screening phase.

8.2.7 Self-Report of HIV Testing

HIV testing status will be assessed via self-report questionnaire using PhenX Core Tier 1 items. Items will assess whether the participant has ever had an HIV test, when the most recent test occurred, the test result, and, if the participant was not tested in the past 12 months, and the most important reason the participant was not tested. This will be administered during the screening phase.

8.2.8 Medical and Psychiatric History

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

8.3 Safety Measures

8.3.1 Physical Examination

A physical examination will be completed at screening to ensure there are no exclusionary medical conditions and to gather baseline information. The physical at screening will also include an examination of the participant's body habitus and the planned injection site(s) to assess appropriateness for intramuscular gluteal injections. The physical examination will be repeated at the end of the medication phase (week 12 visit 2).

8.3.2 Electrocardiogram (ECG)

A 12-lead ECG will be administered at screening to assist in determination of participant eligibility and again at study exit (i.e., week 12 visit 1) to assess safety at termination. The ECG tracings will be reviewed by a qualified medical clinician for accuracy and transmitted to be read by a central cardiologist. Results from the central cardiologist's interpretation will be assessed by a qualified medical clinician at the site.

8.3.3 Injection Site Examination

Appropriate medical personnel will examine the injection site on the visit following each intramuscular gluteal injection. These examinations will usually occur at visits 0102, 0402, 0702, and 1002 but should occur at the next attended visit if any of the aforementioned visits are missed. Additional monitoring may also be required. Well-developed precautionary procedures will be followed to avoid adverse events associated with injectable study 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 may increase the likelihood of injection site reactions. Individuals whose body habitus precludes a gluteal intramuscular injection using the needles provided will be excluded from the study.

8.3.4 Injection Site Abnormality Log

Participants will be asked to immediately report any injection site reactions to allow evaluation, monitoring, and possible referral, as needed. A log entry is completed in the event an injection site reaction is reported by a participant or an abnormality is identified during an injection site examination. All injection site reactions should be documented on the Injection Site Abnormality Log. If the abnormality results in a Serious Adverse Event (SAE), the Adverse Event forms must also be completed.

8.3.5 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. At week 6 visit 1, clinical lab tests to assess LFTs and platelet counts will be repeated for safety monitoring. Clinical labs completed at screening (chemistry, LFTs, hematology, and standard urinalysis) will be repeated during the final week of the medication phase (week 12 visit 1). An accredited local laboratory (College of American Pathologists or

equivalent) that meets CLIA guidelines will perform testing, provide normal values, and provide proof of lab certifications.

8.3.6 Concise Health Risk Tracking - Participant Rated Module

The Concise Health Risk Tracking measure will assess aspects of suicidal ideation and behavior using 16 questions scored on a 5-item Likert scale, 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. The Concise Health Risk Tracking measure will be used at screening, every week during the medication phase, and at the week 13 and 16 follow-up visits. Participants who report a significant suicidal/homicidal risk will be assessed by a qualified clinician before leaving the clinic.

8.3.7 Pregnancy and Birth Control Assessment

For females, urine pregnancy test administration, test results, and self-reports of birth control method(s) will be documented during screening unless documentation of hysterectomy is provided. A urine pregnancy test will be performed prior to the naltrexone pre-induction strategy in the screening/baseline phase and may be performed at any other time if clinically indicated or if a woman suspects she is pregnant. If a woman is found to be pregnant at any point during the study, she will be allowed to continue in the study but will be withdrawn from study medications, given an appropriate referral, and followed until resolution of the pregnancy. Self-reports of birth control method(s) will be documented every week during the medication phase.

8.3.8 Vital Signs

Vital signs (e.g., body temperature, blood pressure, pulse, respiration rate) will be collected at least once during screening, as well as before and after any naloxone challenge conducted during the study. During study medication injection clinic visits, vitals will be collected before and after participants receive the combination of the study medications. On non-injection clinic visits, vitals will be collected weekly before oral medication self-dosing. Vital signs can be repeated to confirm the reading or on more frequent intervals, as clinically indicated.

8.3.9 Prior and Concomitant Medications

At screening, the Prior and Concomitant Medications form will collect information about prescription and over-the-counter medications used by participants in the prior 30-day period. At other visits, the form will document medications taken since the previous data collection visit. Participants may be excluded based on medications reported during screening. 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.

8.3.10 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.

8.3.11 Naloxone Challenge Form

The Naloxone Challenge Form will document the time of administration, total dose, route of administration, and result of each naloxone challenge administered during the study. A naloxone challenge may be conducted at the discretion of the medical clinician prior to any injection of study medication; the Naloxone Challenge Form will be completed for each naloxone challenge.

8.4 Efficacy Measures

8.4.1 Urine Drug Screen

Urine samples will be collected at every clinic visit. Urine drug screen (UDS) testing will be performed on site using an FDA-cleared for use one-step urine drug dip card and/or dipstick following all the manufacturer's recommended procedures.

The UDS will test for the presence of opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamine, marijuana (THC), methadone, and ecstasy (MDMA). Prior to drug screening, a temperature and validity assessment will be performed on all urine samples collected. The validity assessment will be performed using a commercially available adulterant test strip that indicates normal ranges for creatinine, pH (at minimum), nitrate, glutaraldehyde, specific gravity, bleach and pyridinium chlorochromate. If the temperature or adulterant test falls outside the normal range, the first urine specimen will be considered adulterated and will not be screened. In this case, the first urine sample will be discarded, and the participant will be asked to provide another sample following oral hydration. If the only out of range value from the second sample is a high specific gravity on the adulterant test strip and there are no visible precipitants, this sample may be considered not adulterated and can be drug tested. Any other out of range value on either the temperature strip or adulterant test indicates adulteration and the second sample should not be tested. Study teams at each site may opt to observe the urine collection process either at each collection or as deemed necessary (e.g., recommend observing urine collection if specimen tampering is suspected) according to clinic standard operating procedures.

Throughout the study, urine will be tested to evaluate urine opiate levels at 2000 ng/mL. At Screening/Baseline and prior to each injection of XR-NTX or iPLB, urine will be tested to evaluate urine opiate levels at 300 ng/mL. Additional onsite urine drug testing may occur at Screening/Baseline and during the medication phase to detect urine metabolites of other drugs that are not detected by the previously described tests. Results from any urine drug test intended for forensic use only, or otherwise not cleared by the FDA for use in clinical settings, may not be used in any clinical evaluation and is collected for data purposes only.

8.4.2 Timeline Followback

The Timeline Followback (TLFB) procedure (Sobell & Sobell, 1992; Fals-Stewart, 2000) will be used to elicit the quantity and frequency of the participant’s self-reported use of cigarettes, e-cigarettes, alcohol and illicit drug use. 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 medication phase and the post medication phase follow-up visits to document the participant’s self-reported use of substances for each day since the previous TLFB assessment. Adherence to this procedure will ensure that self-reported substance use for the entire study period is documented without gaps.

8.4.3 Visual Analog Craving Scale

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). The VAS will be completed at each screening visit, once weekly throughout the medication phase, and at the week 13 and 16 follow-up visits.

8.4.4 Patient Health Questionnaire-9

The Patient Health Questionniare-9 (Kroenke et al., 2001) is a well validated self-report tool that measures diagnostic criteria for major depression, severity and frequency of depressive symptoms, presence of suicidal ideation, and functional impairment related to depression. The Patient Health Questionniare-9 will be collected during screening, weekly during the medication phase, and at the week 13 and 16 follow-up visits.

8.4.5 Treatment Effectiveness Assessment

The Treatment Effectiveness Assessment (Ling, 2012) 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 community. The Treatment Effectiveness Assessment will be collected at screening, mid-treatment (week 6 visit 2) and end-of-treatment (week 12 visit 2).

8.4.6 Tobacco Use History

The Tobacco Use History assessment will be administered at screening, mid-treatment (week 6 visit 2), and end-of-treatment (week 12 visit 2) to incorporate PhenX Core Tier 1 items. Tobacco use items assessed include lifetime use, 30-day quantity and frequency, and age of first tobacco use.

8.4.7 Quality of Life

Quality of Life will be assessed using items from the 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, mid-treatment (week 6 visit 2), and end-of-treatment (week 12 visit 2).

8.4.8 Sexual Risk Behaviors

The Sexual Risk Behaviors assessment will be administered at screening, mid-treatment (week 6 visit 2), and end-of-treatment (week 12 visit 2) to assess engagement in risky sexual related behaviors in the 30 days prior to each assessment. Participants will answer questions about the number and sex of sexual partners, HIV status of partners, and use of condoms as well as the use of drugs and alcohol during sex.

8.4.9 Genetic Sampling

The NIDA CCTN has requested that blood samples for genetic analysis be obtained for all new CTN pharmacotherapy trials. Randomized participants who consented to the optional genetic testing will have approximately 30 mL (2 tablespoons) of blood drawn at the end of the day of randomization, after all medication administration and monitoring has been completed. However, if the sample cannot be collected on the day of randomization, the sample may be collected at any subsequent visit, ideally at a visit in which a blood draw is scheduled to occur. The blood samples will be coded and only the local investigators will know the identity of the participant

providing the sample. The blood sample will be sent to the Rutgers University Cell and DNA Repository for storage and future analysis.

8.5 Adherence Measures

8.5.1 Study Medication Dosing Logs

Dosing logs will document medication administered in-clinic and dispensed for take-home dosing. Medications to be recorded on dosing logs include naloxone, injectable study medication, and oral study medication. A dosing log will also document return of oral medication blister cards and the participant's self-report of doses taken. Logs will be completed at each visit when medications are dispensed or administered throughout the study.

8.5.2 Injection Administration Form

The Injection Administration Form(s) will document whether injectable study medication is to be administered, it will automatically assign (in real time) an injection kit number for administration, and it will document information related to the administration of the medication (e.g., time of injection). The form is to be completed only after the participant appears in clinic. This form will be completed at each visit in which injectable study medication is administered (i.e., weeks 1, 4, 7, and 10).

8.5.3 Oral Medication Dispensation Form

The Oral Medication Dispensation Form(s) will document whether oral study medication is to be dispensed and it will automatically assign (in real time) a blister card number for dispensation. The first question on this form is to be completed only after the participant appears in clinic, even if oral study medication is not being dispensed.

8.5.4 Oral Study Medication Blood Levels

One of the methods used to evaluate medication adherence requires collecting blood to test for bupropion and hydroxybupropion levels at a central bioanalytical laboratory. Blood will be collected for this purpose prior to study medication administration at visits 0401, 0701, and 1001 and again at the final medication phase visit (week 12 visit 2).

8.5.5 Video Based Adherence to Oral Study Medication Database

Dosing adherence will be assessed in part by automated visual recognition software during the video capture within the AiCure app. The software converts adherence information into data that is automatically entered and stored in the database maintained by AiCure for this study. This database will contain data indicating whether a video was submitted, whether the dosing was deemed valid (i.e., the study participant is clearly ingesting study medication), and whether the dosing was self-reported as opposed to documented via video. Study staff will help ensure information in the AiCure dashboard (the visual representation of the database) is accurate. No additional logs or forms are required for documenting video based adherence.

8.5.6 End of Medication Form

An End of Medication Form will be completed any time a decision is made to discontinue a participant from further medication administration or at the post-medication phase follow-up assessment in Week 13.

8.6 Administrative and Other Forms

8.6.1 Locator Form

A locator form will be used to obtain information to assist in tracking participants during treatment and at follow-up. The locator form will collect information such as participants' current address, email address, social media accounts, and phone numbers, as well as names, addresses, and phone numbers of family/friends who may know how to reach the participants if direct contact efforts are unsuccessful. This information will be collected at screening and updated in weeks 3, 6, 9, and 12 and whenever the participant reports a change in locator information. No identifying information from this form will be used in data analyses.

8.6.2 Eligibility - Randomization

The Enrollment form lists all the study inclusion and exclusion criteria and must be completed for every participant who has signed consent and entered the screening/baseline phase. Eligibility is assessed on an ongoing basis during the screening phase. Only participants who continue to meet study eligibility criteria will be allowed to continue in the screening phase, including the naltrexone pre-induction procedures (e.g., naloxone challenge). The Enrollment form is to be completed in the electronic data capture system after all screening and baseline procedures are complete. Eligible participants will be randomized; ineligible participants will be excluded and deemed screen failures.

8.6.3 Missed Visit Form

This form is designed to capture the reason any study visit was missed. Once the visit window closes without completion of the visit, this Missed Visit Form will be completed directly in the electronic data capture system. Completing this form will remove the requirement for most assessments scheduled for that missed visit. Active tracking and follow-up should be performed for all missed visits.

8.6.4 Protocol Deviation Form

This form should be entered into the electronic data capture system whenever a protocol deviation occurs. This form will document a description of the deviation, how it occurred, the corrective action taken to resolve the specific deviation, as well as a description of the plan implemented to prevent future occurrences of similar deviations.

8.6.5 Protocol Satisfaction Surveys

Satisfaction with medication components, smartphone app, and other study procedures will be recorded on the Protocol Satisfaction Survey completed at the week 13 visit. 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 smartphone app-based technology for improving and monitoring medication adherence.

8.6.6 Study Completion Form

Information regarding when and why study visits were stopped for each participant, including whether a participant completed the final follow-up visit in week 16, will be recorded on this form.

9.0 TRAINING

The study staff will be trained as specified in the 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 will also be identified as part of the training (e.g., who to contact for aid, questions, resources). All study staff will also complete any additional training per their study site and IRB requirements. An Operations Manual will be provided for this study that will outline study 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.

10.0 STATISTICAL ANALYSES

10.1 General Design

10.1.1 Study Hypothesis

The primary hypothesis is that the combination of extended-release depot naltrexone plus extended-release bupropion medication (AMC), relative to the PLB, will be associated with greater MA non-use. Participants will be randomized to one of two conditions, PLB or AMC. Randomization will be stratified by site.

10.1.2 Sample Size

A sample size of 400 is chosen for this study to detect the difference between the two treatment arms. A total of 7 - 10 sites will participate in the trial. It is anticipated that each site will randomize approximately 30 - 70 participants over the recruitment period.

10.1.3 Primary Outcomes

The primary efficacy outcome measure is MA-negative urine drug screen (UDS) test results obtained during weeks 5 to 6 and weeks 11 to 12, which will be compared by treatment group (AMC versus PLB). Participants will be defined as a “responder” if there are at least 75% MA-negative UDS tests during the pre-specified evaluation period. The treatment groups will be compared as to the proportion of responders using a Z test. All treatment comparisons will be performed under the Intent-to-Treat (ITT) criteria.

10.1.4 Secondary Outcomes

Secondary outcomes include methamphetamine and other substance use outcomes in the pre-evaluation period, in the evaluation period, at the follow-up assessment, and any combination of these periods, for responders, non-responders, and other sub-groups. Secondary outcomes also include depression scores, quality of life, overall functioning, clinic attendance, and ratings of participant and staff satisfaction with study procedures, including use of the smartphone app, compensation, and study medication. Secondary safety outcomes will be participants’ reports of treatment emergent adverse events including serious adverse events collected at scheduled clinic visits or via other contact.

Drug use will be measured by several outcomes including but not limited to the Treatment Effectiveness Score (TES; Ling et al., 1997), days of self-reported drug use, number of consecutive negative UDS, and UDS as a binary outcome (positive or negative) across time. The TES 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 the models, we will control for baseline MA use and other key demographic and participant variables. Additional analyses will include assessment of drug use in the pre-evaluation period, 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. A two-sided test of significance will be used with a p-value less than 0.05 indicating significance.

Analyses of secondary outcomes will be primarily performed on all individuals who are randomized and inducted onto study medications. Secondary analyses will also be performed by

examining responses in subgroups with varying characteristics. Adherence with oral study medication dosing will be measured by participant self-report, smartphone device app dosing videos, and in-clinic observation. A dosing adherent per-protocol analysis will be performed by evaluating response rates in the medication-adherent group. Because per-protocol analyses may be biased (Sheiner and Rubin, 1995) an unbiased complier-adjusted-causal-effects analysis (Jo and Stuart, 2009) may also be used to adjust for adherence. Multiple testing will not be adjusted for in the secondary analyses, since these are not part of the study's primary objective. When multiple tests are conducted, the chance of finding a significant difference in one of the tests, when in fact no difference exists, is greater than the stated Type I error rate. The investigators are aware of the issues associated with multiple testing and will interpret results with caution.

All the above mentioned secondary analyses (except staff satisfaction ratings) will be performed in a similar way as the primary analysis. For continuous outcomes, ordinary least squares and mixed effects model for repeated measures (MMRM) will be used and for binary outcomes, a logistic regression will be used. These will be described in the protocol Statistical Analysis Plan (SAP).

10.2 Interim Analyses

In coordination with the centralized Data and Statistics Center, a DSMB will monitor the progress of the trial. As requested by the DSMB, interim analyses of sample size re-estimation and monitoring of the efficacy and safety data will be performed. However, if ADAPT-2 has a rapid recruitment such that the proportion of Week 12 outcomes realized is small when recruitment is completed or nearly completed, discussion with the DSMB will take place about whether sample size re-estimation and interim analysis of efficacy data is warranted.

10.2.1 Sample Size Re-estimation

Sample size re-estimation analysis will be conducted when approximately half of the participants have been enrolled. This analysis will not reveal the treatment effect observed in the trial at the time of this interim analysis. A sample size re-estimation will be performed to assess the adequacy of the projected study sample size and whether a sample size increase is warranted.

The timing of the sample size re-estimation is based on a number of factors: recruitment rate, timing of the primary outcome, amount of loss to follow-up, and time to perform the sample size re-estimation. The sample size re-estimation will be done only once, and done before any interim analysis of the primary outcome is performed. The results of the sample size re-estimation analysis would be presented in a closed session of the DSMB, who will then provide a recommendation to the NIDA CCTN regarding whether the target sample size should be modified. A decision regarding any such modification would be made subsequently by the CCTN, taking into consideration the recommendation of the DSMB.

Update to the sample size:

The NIDA CTN DSMB reviewed the sample size re-estimation report dated July 23, 2018, prepared by the DSC. Based on the results, the DSMB and NIDA CCTN recommended increasing the originally planned sample size of 370 by 30 additional participants to maintain the targeted 90% power. The CCTN approved the increase in sample size to 400 participants in a letter to the Lead Investigator dated August 13, 2018.

10.2.2 Interim Monitoring of Primary Efficacy Endpoint

Interim monitoring for efficacy will be performed. There will be no interim efficacy monitoring before a sample size re-estimation is performed (or a determination that re-estimation is not needed) because sample size re-estimation could change the target sample size, affecting the alpha spending function used in the interim efficacy monitoring. After sample size re-estimation, interim efficacy monitoring will be performed only once during the recruitment period.

All interim monitoring will use an O'Brien-Fleming-type boundary with information fraction equal to the proportion of the target sample size with primary outcome. This approach spends very little alpha at the interim look, therefore the impact of an interim monitoring on the sample size is negligible. The only criterion for early stopping for efficacy will be based on Z-scores and its relation to O'Brien-Fleming-type boundary.

Before recommending early termination, the DSMB will consider:

- Internal consistency of primary and secondary results.
- Internal consistency of primary and secondary results by subgroups defined by baseline characteristics (e.g., severity of MA use, tobacco use history, treatment effectiveness assessment and visual analog craving scale).
- Distribution of baseline prognostic factors among the two groups.
- Consistency of primary and secondary results across clinical sites and among clinical sites enrolling larger numbers of participants.
- Possible impact of missing data from missed participant visits for assessment of the primary and secondary response variables.
- Possible differences in concomitant interventions or medications.

10.2.3 Safety Interim Analyses

Safety interim looks will be performed for the regular DSMB meetings or at unscheduled times per the DSMB's request. These will include analysis of adverse events and narrative reports on serious adverse events.

Simultaneous with primary interim efficacy monitoring analysis, a "poor efficacy" statistic will be calculated to assess whether the combination of extended-release depot naltrexone plus extended-release bupropion medication (AMC), relative to the PLB, is associated with greater MA use. This analysis will be conducted after the sample size re-estimation. If the "poor efficacy of AMC" statistic crosses its boundary, defined as the response rate for PLB minus AMC being greater than 10%, the DSMB will consider whether to stop the trial early because of poor efficacy of AMC relative to PLB.

10.2.4 Conditional Power and Futility

Unless otherwise requested, a futility/conditional power calculation will be performed every time interim monitoring is performed. If at any DSMB meeting the conditional power falls below 0.3, this will stimulate a discussion among the DSMB members about whether we should stop for futility.

10.3 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for participants randomized and inducted on study medications. 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.

10.4 Description of Plans to Conduct Analyses of Study Results by Sex and Race/Ethnicity

The association between specific demographic characteristics and outcome will be studied. The demographic characteristics of potential importance include: age, sex, race, and ethnicity. In accordance with NIH guidelines, analyses will be completed to determine whether treatment response was significantly affected by participant minority/sex status using an interaction term for treatment, time and minority/sex as appropriate.

10.5 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, REPORTING AND MONITORING

11.1 Statement of Compliance

This study will be conducted in compliance with the current version of the study protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, consistent with current International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements.

11.2 Institutional Review Board Approval

Participating sites must obtain written approval of the study protocol, consent form(s), other supporting documents, any materials given to the participant, and any advertising for participant recruitment from their Institutional Review Board (IRB) of record or Independent Ethics Committee (IEC) to participate in the study. Prior to initiating the study, site investigators will obtain written IRB approval to conduct the study at their respective site. Any amendments to the protocol or consent must be approved by the Lead Investigator and IRB before implementation. Progress reports, and any required post-approval reports will be submitted to the IRBs either 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 copies of all performance site(s)' current IRB approval notice(s) and IRB-approved consent document(s), including approvals for all protocol and consent modifications. These materials must be received by the Lead Investigator prior to the initiation of research activities at a given site, must be maintained by the Lead Investigator throughout the course of the trial, 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, 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 to maintain continuing study approval. Protocol amendments must also be submitted, and it is required that the Panel be notified of any significant study drug related adverse events that may emerge during conduct of the study at the California sites only.

11.4 Informed Consent

All potential candidates for the study will be given a current IRB-approved consent form in English to read. In accordance with IRB policies, appropriately trained and qualified study personnel will explain all aspects of the study in lay language and answer all the study candidates' questions. Participants who remain interested after receiving an explanation of the study will be given a short quiz to test their understanding of the project including the purpose, procedures involved, and the voluntary nature of participation. Those who cannot successfully answer all 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 IRB-approved consent

form. Participants will not be administered any assessments or participate in study procedures in any way prior to signing and dating the IRB-approved consent form.

Informed consent is a process and not just a document. The informed consent process is a means of providing study information to each prospective participant in understandable language and taking all the time needed to answer all questions to allow for an informed decision about study participation. The IRB-approved consent form must be revised whenever important new information becomes available including whenever the protocol is amended in any way that may affect a study participant's willingness to continue participating in the trial. All study sites must have the study consent forms approved by their IRB(s). Sites must maintain the original signed IRB-approved consent forms for all study participants in a locked, secure location that is in compliance with IRB and institutional policies. Signed/dated IRB-approved consent forms must be accessible for quality assurance review and regulatory compliance at all times. Every study participant will be provided with a copy of the signed/dated consent form that can be used as continual reference for study information including procedures, possible risks and/or side effects, and contact information for questions and/or emergencies. California site participants will also be provided with a California Research Subjects' Bill of Rights. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

11.5 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 laws and regulations, 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.

11.6 Investigator Assurances

Each participating site must file (or have previously filed) a Federalwide Assurance (FWA) with the HHS Office for Human Research Protections setting forth the commitment of the organization to adhere to appropriate policies and procedures for the protection of human research subjects. The site's 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 OHRP-registered IRB designated 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.

11.7 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. All study personnel with decision-making responsibilities regarding the protocol must comply with their institution's policy regarding conflict of interest.

11.8 Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state law and regulations. 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 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 obtained a federal Certificate of Confidentiality (CoC) and distributed it to all sites when it was received. A CoC helps researchers protect the privacy of human research participants enrolled in biomedical, behavioral, clinical and other forms of sensitive health-related research (e.g., drug use). Certificates protect against compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a research participant. The department that issues the CoC will be advised of any changes in the CoC application information that may occur during the study, as required. Participating sites will be notified if CoC revision is necessary.

Participant records will be kept confidential by using 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. All laboratory specimens, eCRFs, reports, and other data records will be identified by the participant identification study code that includes the site number, node number, and participant number. Research records will be stored in a locked cabinet. Only authorized individuals will have access to the study records. Participant information will not be released without written permission, except as necessary for monitoring by the FDA, NIDA-contracted monitors, local node monitors, lead node staff, or NIDA. By signing the protocol signature page, 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.

11.9 IND Requirements

A request for IND exemption was submitted to FDA for this protocol, as described in title 21 of the Code of Federal Regulations, part 312 (21 CFR 312) and the Agency determined that the ADAPT-2 study was exempt from FDA IND regulations, as per Title 21 of the Code of Federal Regulations, Part 312.2.

Though exempt from IND regulation, this study will be conducted in accordance with International Council on Harmonisation Good Clinical Practices (ICH GCPs), all applicable FDA and OHRP Guidance documents, and any state and institutional requirements applicable at the clinical site level.

11.10 Regulatory Files

Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. Regulatory files should be maintained throughout the lifecycle of the trial and should contain all required regulatory documents, study-

specific documents, and all important study-related 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.

11.11 Study Documentation

Study documentation includes, but is not limited to, all data-related forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, signed protocols including amendments, Ethics Review Committee or Institutional Review Board/Committee correspondence, 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.

11.12 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 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.

11.13 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 described herein. At the completion of the trial, the Lead Investigator will provide a final report to the sponsor.

11.14 Safety Monitoring

11.14.1 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 examinations or laboratory evaluations. 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 adverse events.

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

11.14.2 Definitions of Adverse Events and Serious Adverse Events

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

11.14.3 Reportable Adverse Events and Serious Adverse Events

For the purpose of this study, all AEs and SAEs will require reporting in the electronic data system. Reporting of AEs and SAEs is described in Appendix A. The local site is responsible for reporting all their local AEs and SAEs to their IRBs per IRB guidelines.

11.14.4 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.

11.14.5 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). The Safety Monitor will review all Serious Adverse Events (SAEs) within one business day of their reporting in eClinical 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 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.

11.15 Protocol Deviations: Reporting and Management

Any divergence from procedures and requirements outlined in the protocol will be classified a protocol deviation. 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.

11.16 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 Texas Node; the National Institute on Drug Abuse Center for the Clinical Trials Network (NIDA CCTN, the study sponsor); NIDA’s contracted agents, monitors or auditors; and other agencies, such as the Department of Health and Human Services (HHS), the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), and the sites’ Institutional Review Boards may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

11.17 Quality Assurance 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. Monitoring of the study sites will be conducted on a regular basis using a combination of NIDA-contracted monitors, local node monitors, and lead node staff.

Site investigators will host periodic visits by monitors who will ensure all study procedures are appropriately conducted, and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), and corresponding source documents for each participant. NIDA-contracted 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 signed/dated consents, eligibility for study 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 visits and forwarded to the site principal investigator, the Lead Investigator and NIDA CCTN.

Qualified node personnel (Node Protocol Managers and/or QA monitors) will provide site management for each site during the trial to encourage and assess compliance with the study protocol, Good Clinical Practice guidelines, and to ensure the integrity of the trial progress. These visits will take place as specified by the local protocol team, Node PI or Lead Team, and visits will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will ensure that study procedures are properly followed and that site staff are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training.

12.0 DATA MANAGEMENT AND PROCEDURES

12.1 Design and Development

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

12.2 Site Responsibilities

The data management responsibilities of each site 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 Case Report Forms in electronic (eCRF) and paper (CRF) format, and Participant Reported Outcome forms in electronic (ePRO) and paper (PRO) format for the collection of all data required by the study, 3) develop data dictionaries for each CRF and PRO form that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of forms, 5) conduct ongoing data validation and cleaning activities on study data collected from all participating sites, and 6) perform data validation and 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 on the form in Advantage eClinical, or will be collected via direct entry into the eCRF by the site or direct entry into the ePRO by the participant. In the event that Advantage eClinical is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into Advantage eClinical in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC. Data entry into the forms 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 forms for each research participant.

12.5 Data Monitoring, Cleaning, and Editing

Data will be entered into the DSC automated data acquisition and management system (Advantage eClinical). Forms 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

Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within forms and between forms and post data clarification requests or queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into Advantage eClinical.

The CCC will conduct regular visits to sites, during which audits comparing source documents to the data entered will be performed. Any discrepancies identified between the source document and the eCRF or ePRO 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 follow-up visits, regulatory status, and data quality, will be generated routinely and posted to a secure website. These reports will be available to the site, the corresponding Local Node, the Lead Investigator, the coordinating centers, and NIDA, to monitor the sites' progress on the study.

12.6 Database Transfer and Lock

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 to NIDA, as requested, for storage and archive.

13.0 PUBLICATIONS AND OTHER RIGHTS

Protocol development and implementation in the NIDA CTN is a collaborative process. The planning, preparation, and submission of publications will follow the policies of the CTN Publications Committee. Individuals making substantive contributions to the protocol development and implementation will have opportunities to participate in publications. Other contributors will also be acknowledged. Per NIH policy, the results of the trial are to be made available to the research community and to the public at large. The project will adhere to stipulations in accord with the NIH Public Access Policy (for any articles based on 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)

Udi Ghitza, PhD		
Printed Name	**Signature**	**Date**

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 6.0 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**

Site Name _____

Node Affiliation _____

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16.0 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 baseline 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/baseline 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 IRB, per IRB's guidelines.

Site staff is required to enter AEs and SAEs in the eClinical 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 of 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 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 help 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.

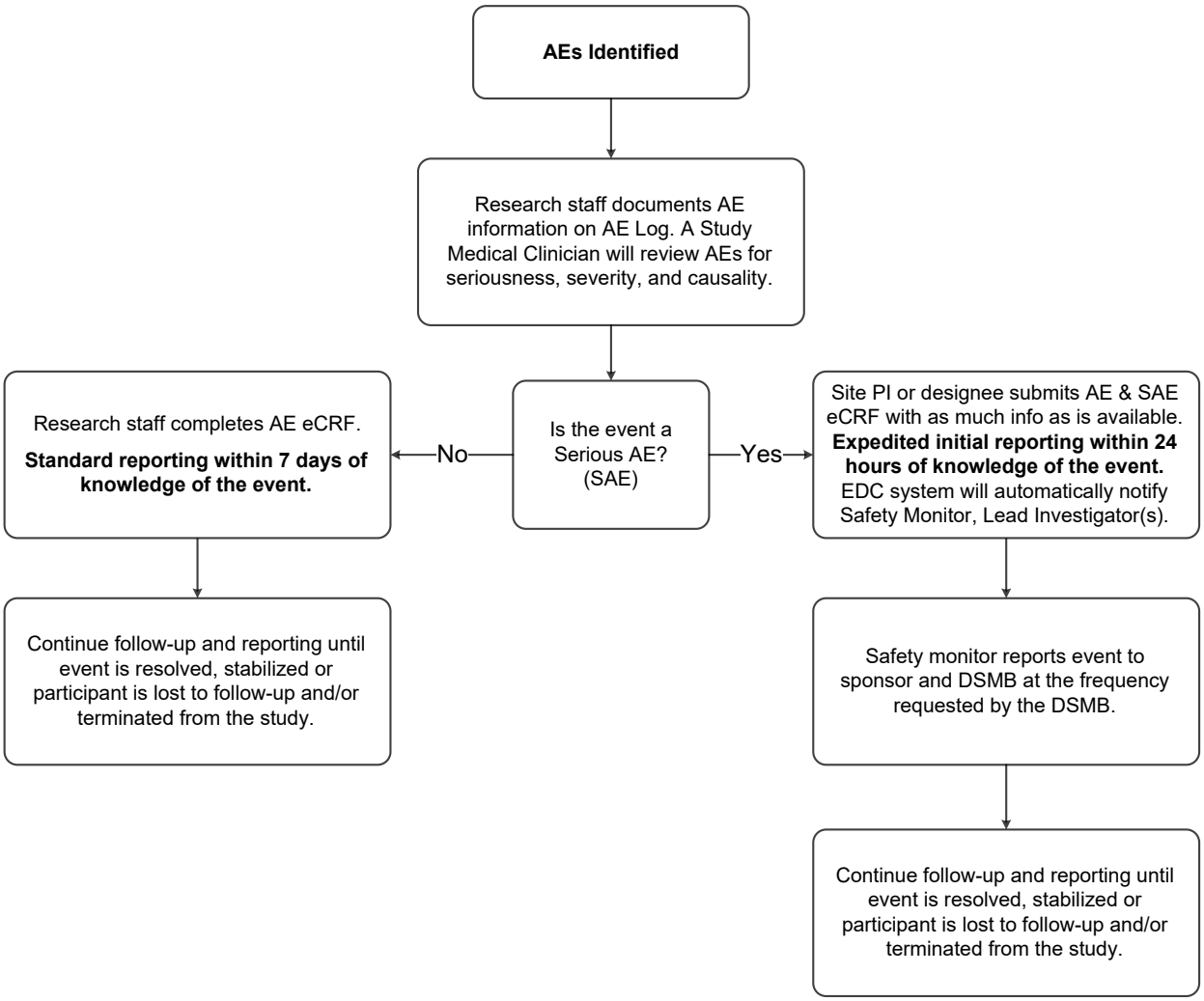
Reporting to the Data and Safety Monitoring Board

The DSMB will receive a 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. If voluntary withdrawal is requested, the participant will be asked to complete an end-of–medication visit to assure safety and to document end-of–medication outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary. Other reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons.

AE Chart



17.0 APPENDIX B - DATA AND SAFETY MONITORING PLAN

BRIEF STUDY OVERVIEW

This double-blind, placebo-controlled, randomized clinical trial will investigate a combination medication, extended-release injectable naltrexone plus extended-release bupropion, compared to placebo as a potential pharmacotherapy for MA dependence. Screening will occur over a maximum of 21 days. Study medications will be provided during a 12-week medication phase. Participants will be randomized to either the active medication combination (AMC) arm in which injections of extended-release naltrexone (XR-NTX; as Vivitrol®) plus 450 mg / day oral extended-release bupropion (BUP-XL) tablets will be provided or the matching placebo (PLB) arm in which injections of placebo (iPLB) and once daily oral placebo (oPLB) tablets will be provided. Injections will be provided in weeks 1, 4, 7, and 10. Participants will be asked to attend clinic twice weekly for observed oral medication dosing and provision of take-home oral medication, collection of urine samples, assessments, and medical management. Following the 12-week medication phase, participants will complete a follow-up phase, including a medication taper and post-medication phase follow-up visits during Weeks 13 and 16.

Details for the definitions and reporting of safety events are found in 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 all study visits. Study staff will follow-up on the status of any AEs that remain for up to 30 days after the last planned study visit in week 16.

The occurrence of AEs and Serious Adverse Events (SAEs) will be assessed at each clinic visit after consent. All adverse events will be followed until resolution, stabilization or study end. 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 eClinical. The Medical Monitor will also indicate concurrence or not with the details of the report provided by the site. Where further information is needed the Safety Monitor/Medical Monitor will discuss the event with the site. Reviews of SAEs will be conducted

in the Advantage eClinical data system and will be a part of the safety database. All AEs will be reviewed on a regular 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 is 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. The DSMB will receive listings 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.

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 node 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 site staff to identify issues and re-train the site staff 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 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 using 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. All study data will be stored in a secure location with limited access. Only research staff will have access to the study records. Other parties with access to study data, such as local or central IRBs, will be specified

to the participants per HIPAA regulations. No identifying information will be disclosed in reports, publications or presentations.

Participants' information will not be released without their written permission, except as necessary for monitoring or suspected abuse or violence. The Lead Investigator (LI) will apply for a Certificate of Confidentiality that will cover all sites participating in the study. By participating in this protocol, the local site investigator agrees that within local regulatory restrictions and ethical considerations, any regulatory agency may consult and/or copy study documents to verify study data.

By participating in this protocol, the local site investigator affirms that information furnished to the investigator by the Lead Investigator will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committees, affiliated institutions, and employees only under an appropriate understanding of confidentiality with such boards or committees, affiliated institutions, and employees.

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.

Participant Protection

The study physician will evaluate all pertinent screening and baseline assessments prior to participant randomization 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. Study personnel will request that the participant complete an end-of-medication visit to assure safety and to document end-of-medication outcomes.

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 30 minutes following the naloxone challenge, and at least 15 minutes following each medication induction (co-administration of injectable and oral study medications).

BUPROPION Extended Release: Possible side effects include elevated blood pressure, agitation, irritability, restlessness, sleeplessness, dry mouth, headache/migraine, nausea, vomiting, constipation, and shakiness. At doses of 450 mg daily, there is 1 chance in 1000 that a participant taking bupropion will experience a seizure. Individuals with a history of epilepsy or seizure disorder, current 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.

NALTREXONE for Extended Release (Vivitrol®): 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 injection. 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.

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 (Advantage eClinical) 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 Case Report Forms in electronic (eCRF) and paper (CRF) format, and Participant Reported Outcome forms in electronic (ePRO) and paper (PRO) format for the collection of all data required by the study, 3) develop data dictionaries for each CRF and PRO form that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of forms, 5) conduct ongoing data validation and cleaning activities on study data collected from all participating sites, and 6) perform data validation and 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 on the form in Advantage eClinical, or will be collected via direct entry into the eCRF by the site or direct entry into the ePRO by the participant. In the event that Advantage eClinical is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into Advantage eClinical in accordance with the instructions provided during project-specific training and guidelines established by the DSC. Data entry into the forms shall be performed by authorized individuals. Selected eCRFs may also require the site 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 site investigator is responsible for ensuring the timely completion of forms for each research participant.

Data Monitoring, Cleaning and Editing

Data will be entered into the DSC automated data acquisition and management system (Advantage eClinical). Forms will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms will be available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within forms and between forms and post data clarification requests or queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into Advantage eClinical.

The CCC will conduct regular visits to sites, during which audits comparing source documents to the data entered will be performed. Any discrepancies identified between the source document and the eCRF or ePRO 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 follow-up visits, regulatory status, and data quality, will be generated routinely and posted to a secure website. These reports will be available to the site, the corresponding Local 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.

18.0 APPENDIX C - SMARTPHONE APP-BASED MEDICATION ADHERENCE PROCEDURES

The smartphone app will be provided by AiCure and will be referred to as the "app" or "study app."

Technology Training

After eligibility has been established and the participant has been randomized, staff will provide training on the use of the medication adherence app that will monitor and encourage adherence. The AiCure app will be downloaded onto the participant's personal smartphone or, if unable to be downloaded, a study provided smartphone device will be provided with the app pre-loaded on it. Training will include using the app features and capabilities, security features (e.g., encryption), and taking practice dosing videos.

Medication Adherence App on Participant Personal Smartphone

Participants who choose to use their own smartphone must own a device that is camera-equipped and capable of SMS text messaging and taking videos. Participants who download the app on their personal smartphone devices will be provided an additional $10 at the beginning of each study month to offset the costs for additional data services needed due to use of the app. Participants who require a study provided smartphone device at any point during the study may be provided one. However, to ensure that participants are compensated equitably, no participant will receive more than $10 per study month for using either the app or a study provided smartphone device.

Study Provided Smartphone Device

Participants who do not have a personal device or are unable to download the AiCure app will be provided with a smartphone device (and battery charger). Service plans will be included to allow participants to receive text messages and reminders from study staff through the study app and to take dosing videos. The smartphone device equipment will be retained by participants through the end of their participation in the study. A replacement device may be available in the event of unintentional damage or loss. Sites are encouraged to consult with the Lead Team when considering providing replacement study devices for participants who are withdrawn from study medications. If the participant does not require a replacement smartphone device during the course of the study, the participant will be provided up to $40 payment (i.e., $10 for each study month) for the safe return of the smartphone device and, ideally, all accompanying accessories (e.g., charger, carrying case). Replacement smartphone devices will be returned at the end of study participation, but no payment will be provided to those participants requiring a replacement device.

Set-up and Maintenance of App (and Smartphone Device, if applicable)

Study staff will activate the AiCure app on participant smartphones or prepare the study provided smartphone for the participant. If a participant is using a study provided smartphone device, study staff will provide appropriate training on how to use the device.

Smartphone Device-Based Procedures and Compensation

Prior to randomization, study personnel will request a signed agreement from participants regarding the use of the smartphone app or study provided device for the purposes of the study. Participants will be informed of the medication adherence procedures, including the requirement to take daily videos of oral study medication ingestion. If a participant fails to bring his/her oral study medication to the clinic so that self-administration of the dose can be observed and a video

can be taken, the participant will be asked to take a video of him/herself taking the dose for that day at home (if the dose has not already been taken). Participants will be compensated $5 for each dosing video taken on non-clinic days, including the taper in week 13. “Red Alerts” are triggered by AiCure when there is a pattern of problematic behaviors observed during video dosing. AiCure staff will guide site staff in how to re-train participants to appropriately use the app. If a pattern of recurring Red Alerts are triggered by AiCure, this indicates repeated problematic dosing behaviors are occurring, indicating non-adherence to oral study medication. Recurring Red Alerts may result in a participant not being compensated for dosing videos; sites should consult with the Lead Team when repeated Red Alerts occur.

Lost/Stolen/Inoperable Smartphone Devices

The purpose of providing a study smartphone device (to participants unable to use their own) is to monitor and improve medication adherence on non-clinic days as well as provide a means of study staff contacting participants. Participants will be notified that study provided devices will have a tracking tag on the back which allows for lost or stolen devices to be retrieved via a nationwide network and that removal of the tracking tag reveals a “stolen property” embossing on the device. Study provided smartphone devices are operational for study purposes only and are locked down to any other use. A one-time replacement of a lost, stolen, or inoperable study provided smartphone device may be permitted. Study staff should consult with the Lead Team should a second loss/theft of a study smartphone device occur.

Protection of Participant Privacy

Participants will be advised on how to secure their devices with passwords and how the software application will be used to transmit dosing videos to the secure server as an encrypted file. Research staff will only access smartphone device settings as needed to help troubleshoot a problem with the AiCure app and when requested by the participant.

Staff-to-Participant Contact

Staff will send texts from a list of pre-determined messages to participants through the app regarding reminders for clinic visits or dosing requirements. If a participant has not taken 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 medication dose via the app as soon as possible.