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Protocol and Statistical Analysis Plan

Title: NIDA CTN Protocol 0110 Randomized, double-blind, placebo-controlled trial of monthly injectable buprenorphine for methamphetamine use disorder (MURB)

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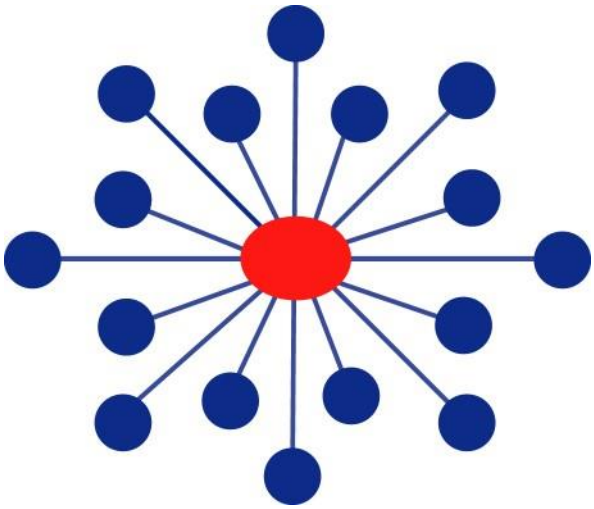

NIDA CTN Protocol 0110

Randomized, double-blind, placebo-controlled trial of monthly injectable buprenorphine for methamphetamine use disorder (MURB)

Lead Investigator: Steven Shoptaw PhD, UCLA
Co-Lead Investigator: Madhukar H. Trivedi, MD, UT Southwestern

Sponsor: Madhukar H. Trivedi, MD, UT Southwestern
Funded by: National Institute on Drug Abuse (NIDA)

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Lead Investigator (LI):	**Steven Shoptaw, PhD** Big South/West Node UCLA
Sponsor/Co-LI:	**Madhukar H. Trivedi, MD** Big South/West Node UT Southwestern Medical Center
Protocol Development Team:	**Andrew Herring, MD** Alameda Health System **Mariah M. Kalmin, PhD** UCLA **Steven Nieto, PhD** UCLA **Thomas Carmody, PhD** UT Southwestern Medical Center **Angela Casey-Willingham** UT Southwestern Medical Center
CCTN Scientific Officer:	**Udi Ghitza, PhD** National Institute on Drug Abuse
Data and Statistics Center (DSC):	**Jennifer McCormack, MS** DSC Principal Investigator Emmes
Clinical Coordinating Center (CCC):	**Eve Jelstrom MBA, CRNA** CCC Principal Investigator Emmes

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AST	Aspartate Transaminase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
BUP	Buprenorphine
BUP-Inj	Extended-Release Injectable Buprenorphine, XR-BUP, BUP-XR, Sublocade™
CAST	Concise Associated Symptom Tracking Scale
CBT	Cognitive Behavioral Therapy
CCC	Clinical Coordinating Center
CCTN	Center for the Clinical Trials Network
CFR	Code of Federal Regulations
CHRT-SR	Concise Health Risk Tracking – Self-Report
CLIA	Clinical Laboratory Improvement Amendments
CoC	Certificate of Confidentiality
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Forms
CRA	Clinical Research Associate
CTN	Clinical Trials Network
CURB	Cocaine Use Reduction with Buprenorphine
DARS	Dimensional Anhedonia Rating Scale
DEA	Drug Enforcement Administration
DM	Data Management
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GAD-7	Generalized Anxiety Disorder Scale-7
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IGT	Iowa Gambling Task
IDS-SR	Inventory of Depressive Symptomology - Self-Report
IND	Investigational New Drug

Abbreviation	Definition
IRB	Institutional Review Board
LFT	Liver Function Tests
LI	Lead Investigator
LN	Lead Node
MA	Methamphetamine
MINI	Mini International Neuropsychiatric Interview
MOP	Manual of Procedures
MOUD	Medication for Opioid Use Disorder
MUD	Methamphetamine Use Disorder
MURB	Methamphetamine Use Reduction with Buprenorphine
MSM	Men who Have Sex with Men
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OUD	Opioid Use Disorder
PBO-Inj	Injectable Placebo
PEBL	Psychology Experiment Building Language
P-FIBS	Pain Frequency, Intensity, and Burden Scale
PI	Principal Investigator
PSS	Perceived Stress Scale
PT	Preferred Term
RAP-C	Research Advisory Panel of California
RCT	Randomized Controlled Trial
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sIRB	Single Institutional Review Board
SOC	System Organ Class
SOP	Site Operating Procedures
SOWS	Subjective Opiate Withdrawal Scale
STI	Sexually Transmitted Infection
SUSAR	Serious Unexpected and Suspected Adverse Reaction
TEA	Treatment Effectiveness Assessment
TES	Treatment Effectiveness Score
TLFB	Timeline Followback
UDS	Urine Drug Screen
UPT	Urine Pregnancy Test
UP	Unanticipated Problem
US	United States
VAS	Visual Analog Craving Scales
XR-BUP	Extended-Release Injectable Buprenorphine, BUP-Inj, BUP-XR, Sublocade™
XR-NTX	Extended-release Naltrexone

2.0 PROTOCOL SUMMARY

2.1 Synopsis

Title	Randomized, double-blind, placebo-controlled trial of monthly injectable buprenorphine (BUP) for methamphetamine (MA) use disorder (MURB)
Study Number	CTN-0110
IND Number	161851
Study Description	This study is a 12-week randomized, double-blind, placebo-controlled trial that will investigate the use of injectable buprenorphine (BUP-Inj) compared to injectable placebo (PBO-Inj) for the treatment of methamphetamine use disorder (MUD) among individuals with mild co-use of opioids.
Objectives	Primary Objective: To evaluate whether assignment to 12 weeks of outpatient BUP-Inj compared to 12 weeks of outpatient PBO-Inj reduces MA use (as measured by twice-weekly urine drug screens (UDS)) during Weeks 9-12 in participants with moderate to severe MUD with co-occurring mild opioid use disorder (OUD) or opioid misuse not warranting medication for opioid use disorder (MOUD). Secondary Objectives: To evaluate whether assignment to 12 weeks of outpatient BUP-Inj compared to 12 weeks of outpatient PBO-Inj among participants with moderate to severe MUD with co-occurring mild OUD or opioid misuse not warranting MOUD improves: 1) outcomes related to alternate measures of MA use including total number of MA negative urine drug screens (UDS) and self-reported days of MA use; 2) measures of opioid use and self-reported frequency of opioid use; and 3) measures of MA and opioid co-use and self-reported days of MA and opioid co-use. Exploratory Objectives: Include exploring whether assignment to BUP-Inj compared to PBO-Inj during the medication phase corresponds with changes in measures of subjective effects of MA including MA withdrawal symptoms and self-reported MA craving; measures of subjective effects of opioids including opioid withdrawal symptoms and self-reported opioid craving; measures of self-reported craving for MA and opioid co-use; measures of mood, stress and pain including self-reported symptoms of depression, anxiety, mood, anhedonia, stress, and pain; retention in the protocol; infectious disease markers, incidence, and Human Immunodeficiency Virus (HIV) transmission risk behaviors; measures of overall functioning; measures of adverse events and fatal and non-fatal overdose events; changes in other substance use or new sexually transmitted infections (STIs) and whether a neurocognitive measure of impulse inhibition predicts treatment outcomes.

Outcome Measures

Primary Outcome Measure: The number of MA-negative UDS obtained during Weeks 9 through 12 of the medication phase as measured for the BUP-Inj and PBO-Inj conditions.

Secondary Outcome Measures:

1) Alternate measures of MA use during Weeks 1-12: total number of MA negative UDS (Treatment Effectiveness Score) and self-reported days of MA use (Timeline Followback, TLFB);
2) Opioid use during Weeks 1-12: Opioid Treatment Effectiveness Score (TES); self-reported frequency of opioid use (TLFB);
3) MA and opioid co-use during Weeks 1-12: total number of MA and opioid negative UDS (TES) and self-reported days of MA and opioid co-use on the TLFB.

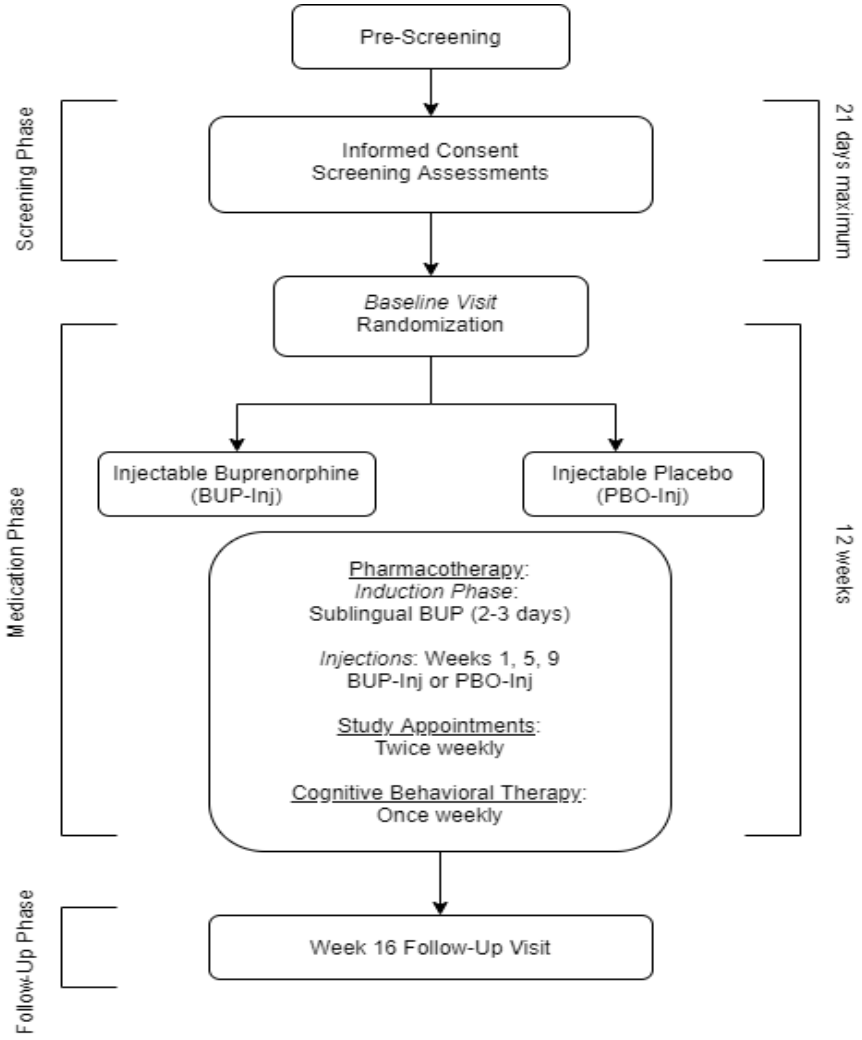
Exploratory Measures:

1) MA subjective effects during Weeks 1-12: Withdrawal symptoms (Amphetamine Cessation Symptom Assessment, ACSA); Self-reported MA craving (Visual Analog Craving Scales, VAS);
2) Opioid subjective effects: Withdrawal symptoms (Clinical Opiate Withdrawal Scale, COWS and Subjective Opiate Withdrawal Scale, SOWS) at Weeks 1, 5, 9, and 12; Self-reported opioid craving (VAS) during Weeks 1-12;
3) Self-reported craving (VAS) for MA and opioid co-use during Weeks 1-12
4) Mood, stress, and pain : Self-reported depressive symptoms (Inventory of Depressive Symptomology - Self-Report, IDS-SR) during Weeks 1-12; Self-reported anxiety symptoms (Generalized Anxiety Disorder Scale-7, GAD-7) during Weeks 1-12; Self-reported anhedonia (Dimensional Anhedonia Rating Scale, DARS) at Weeks 1, 5, 9, and 12; Self-reported mood (Concise Associate Symptom Tracker, CAST-IRR) during Weeks 1-12; Self-reported stress (Perceived Stress Scale, PSS) at Weeks 1, 5, 9, and 12; Self-reported pain (Pain Frequency, Intensity, and Burden Scale, P-FIBS) during Weeks 1-12;
5) Retention in treatment, defined as present and providing urine drug samples during Weeks 1-12;
6) Infectious disease: Biomarkers at Week 12 (remaining HIV negative for participants HIV-negative at screening; remaining Hepatitis C Virus (HCV) negative for participants HCV negative at screening); Self-reported HIV transmission risk behaviors at Weeks 1, 6, and 12 (Sexual Risk Behaviors - number of new sexual partners, number of sexual partners with condomless sex who are serodiscordant or unknown serostatus and whether illicit

	substances were used during sex (chemsex), number of male sexual partners (for men), number of episodes sharing needles, injection equipment or paraphernalia); 7) Measures of functioning: Quality of Life (QoL) at Weeks 1 and 12 and Treatment Effectiveness Assessments (TEA) at Week 12; 8) Measures of adverse events during Weeks 1-12: number and severity of adverse events reported; number and outcomes (fatal, non-fatal) of overdose events reported; 9) Self-reported measures of alcohol, tobacco and other drug use during Weeks 1-12 (TLFB) and UDS results of other substance use not quantified for primary or secondary outcomes; 10) Urinalysis results indicating a new chlamydia or gonorrhea diagnosis at Week 12; 11) Iowa Gambling Task (IGT) performance at screening.
Study Population	The study will consist of approximately 246 males and females who meet eligibility criteria, including Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for moderate to severe MUD and co-occurring mild OUD or opioid misuse not warranting MOUD, supported by urine samples positive for MA and negative for opioids during screening.
Phase or Stage	This is a Phase IIb double-blind, randomized, placebo-controlled trial.
Description of Sites Enrolling Participants	The trial will include 4-8 sites with appropriate staffing and facilities to conduct all study procedures and will not include sites outside of the United States.
Description of Study Intervention	The study intervention is 3 doses of 300mg BUP-Inj delivered by abdominal subcutaneous injection every 4 weeks.
Safety Reporting	Appropriately qualified and trained personnel will elicit participant reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs) at each study visit. Study personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult with the Safety Monitor/Medical Monitor as warranted. Standard reporting, within seven days of the study site becoming aware of the event, will be required for reportable AEs. Expedited reporting, within 24 hours of the site's becoming aware of the event, will be required for reportable SAEs (including death and life-threatening events).
Analyses	Primary Statistical Analysis: Generalized estimating equations will be used to model the log-odds of a MA-negative UDS during Weeks 9-12, assuming an autoregressive lag-1 working correlation matrix. The robust (sandwich) estimator will be used to adjust the covariances for the correlation of UDS from the same participant. Missing UDS are imputed as MA-positive.
Study Duration	The study will be conducted over a period of approximately 20-24 months.

Participant Duration	Participants will complete all study-related tasks over a period of 19 weeks (up to 3 weeks for screening, 12 weeks for the medication phase, and a follow-up safety visit at Week 16; about five months total).

3.0 STUDY SCHEMA



3.1 Key Research Site Roles

Site Principal Investigator (MD; DO; PhD)

Medical Clinician #1 (NP; PA; MD; DO) [May be a shared role with Site PI]

Medical Clinician #2 (NP; PA; MD; DO)

Research Coordinator

Research Assistant

Unblinded Medical Personnel (RN, LVN, MA, or other healthcare provider able to administer Sublocade™ injections per local licensure requirements)

Suggested Additional Roles (not required)

Recruiter/Pre-screener/Retention Specialist

4.0 INTRODUCTION

4.1 Study Rationale

Stimulants are the drivers of the fourth wave of the United States drug overdose epidemic[1]. Although most national attention and resources have been targeted at combating opioid use due to the surge of overdose deaths related to fentanyl, recent reports suggest populations that use opioids are also using methamphetamine (MA) at high rates[2,3]. Indeed, current data show that as many opioid overdose deaths involved psychostimulants as did not[4-6]. These stark epidemiological data underscore the significance of developing one or more broadly efficacious treatments for methamphetamine use disorder (MUD) – especially in the setting of ongoing opioid use.

Most therapeutic trials for MUD have failed, with one notable exception: one small randomized controlled trial (RCT) of mirtazapine tested in San Francisco among men who have sex with men (MSM)[7]; and a larger replication RCT in a larger sample of MSM with MUD that showed that 30 mg mirtazapine reduced MA use by 27% at week 36[8]. A recent RCT completed by the CTN (CTN-0068; ADAPT-2; Trivedi Lead Investigator) tested injectable naltrexone plus high-dose oral bupropion 450 mg/day compared to placebo and reported statistically significant reductions in methamphetamine use in a broad sample of people with MUD (in review). This combination pharmacotherapy is impossible to use among those with MUD who use opioids as the opioid antagonist naltrexone precipitates immediate opioid withdrawal, further underscoring the impact of evaluating a broad pharmacotherapy strategy that does not include an opioid antagonist.

As a monotherapy, buprenorphine (BUP) has sufficient rationale for evaluation as a medication for MUD in the setting of opioid co-use. Findings from the CTN-0048 Cocaine Use Reduction with Buprenorphine (CURB) study showed that extended-release Naltrexone (XR-NTX) plus oral BUP (4mg and 16 mg), produced modest, though statistically significant, reductions in cocaine use (urine-verified) among those adherent to oral BUP (verified with BUP blood levels) compared to placebo[9]. These findings provide initial support for a kappa antagonist approach to treating stimulant use disorder, in this case MUD, as the combination pharmacotherapy used in the CURB study left only a kappa antagonist working at the opioid receptor[10]. Kappa antagonists are potent antidepressants, elevating mood while also producing an overall sense of “well-being”[11]. While there are no placebo-controlled RCTs of buprenorphine for MA addiction, a recent clinical report showed patients treated for OUD using buprenorphine showed a 15% reduction in MA use from baseline to follow-up[12].

The recent approval of Sublocade™ and the pending final approval of Brixadi™, both BUP extended-release injection formulations for subcutaneous use, provide renewed interest in using BUP to treat stimulant-use disorders. The availability of injectable formulations of BUP eliminates problems regarding medication adherence that plague MA medication trials. With medication adherence virtually assured (all study products after induction are injectable), the confidence in a definitive test of the pharmacotherapy is greatly increased.

This rationale is the foundation for this protocol, which will investigate the use of BUP-Inj compared to placebo for treatment of MUD among individuals with co-use of opioids. This study

will apply findings learned from prior studies to a population that has been understudied to date, but who are at risk for overdose due to both MA and opioids. Elimination of medication adherence problems allows evaluation of safety and efficacy of BUP-Inj compared to placebo for reducing MA use and of subjective reports of dysphoria and stress. Positive findings would support additional evaluation of BUP-Inj as a treatment for those with mild OUD or opioid misuse.

4.2 Background and Significance to the Field

Current levels of MA use in the United States (US) are at historic levels with endemic levels in the Southwestern US, including California[13]. In 2017, the Drug Enforcement Administration reported that MA was the greatest drug threat in the Pacific, Southwest, West Central, and Southeast regions of the United States[14]. MA use is a leading cause of drug overdose in the US, particularly in the West, South, and Midwest[15,16]. The use of MA provides a number of positive attributes for the user, including focused attention, enhanced body states, diminished appetite, increased attention and mood and euphoria at high doses. With repeated use, addiction develops. Negative effects of continued frequent use of MA include cardiovascular problems (including myocardial infarction and stroke)[17], psychiatric problems (depression, hypomania, anxiety, panic)[18], criminal justice involvement[19], problems with friends and family members, and employment difficulties.

MA use also is associated with increased risk for HIV and other STIs, especially among men who have sex with men (MSM). Increasing rates of STIs also are reported among women and heterosexual men linked to increased MA use[20,21]. For people living with HIV, MA use challenges sustained viral suppression, creating opportunities for onward HIV transmission and related morbidity and mortality[22].

4.2.1 Buprenorphine mechanism of action

BUP is an opioid partial agonist originally approved for the treatment of cancer pain and approved as a treatment for OUD in 2002[23,24]. BUP competitively binds at the mu-opioid receptor sites, displacing opioid mu agonists with its partial agonist action protecting against respiratory depression in opioid overdose[25,26]. The kappa antagonist property of BUP reduces dysphoric mood and produces a sense of well-being[27].

4.2.2 Efficacy of buprenorphine in stimulant-dependent individuals

The data supporting evaluation of BUP for the treatment of MUD are promising. In the CURB combination trial for cocaine addiction, XR-NTX plus high dose (16 mg/d) or low dose (4 mg/d) oral BUP compared to placebo did not significantly reduce cocaine use days (urine verified)[9]. However, when the urine drug screen results were analyzed as secondary outcomes, high dose BUP (16 mg/d) plus XR-NTX significantly reduced cocaine use measured by proportion of urine samples negative for cocaine (p=0.022) and by proportion who achieved ≥75% negative urine samples during the trial (p=0.008) compared to placebo. Using blood levels assessing the “as-treated” population, both low (4 mg/d) and high (16 mg/d) dose BUP conditions produced significantly more cocaine negative urine samples compared to placebo (p=0.02; p=0.01, respectively)[28]. These consistent signals using biomarkers of outcome, and especially in the “as-treated” group with measurable blood levels of BUP, provide the clearest signal yet favoring

investigation of BUP. The availability of an injectable BUP product to eliminate medication adherence problems builds the rigor and significance for conducting this study now.

4.2.3 Support for buprenorphine in treating individuals with methamphetamine use disorder

Despite the biological rationale for using BUP as a pharmacotherapy for MUD, there has been limited exploration for evaluating this medication for treatment. One study conducted in Iran studied the effects of BUP in reducing MA cravings during withdrawal. When added to an existing behavioral treatment approach, BUP resulted in individuals experiencing fewer MA cravings compared to those receiving placebo[28]. Perhaps the strongest uncontrolled data yet, a recent report in the State of Washington shows that among people who remained in treatment for OUD, BUP also significantly decreased MA use over time[12].

In order to isolate focus on the kappa antagonist action of buprenorphine in this trial, it is not desirable to combine a mu antagonist with a long-acting partial agonist, such as using combined XR-NTX plus Sublocade™. This is because for those with moderate to severe methamphetamine use disorder who co-use opioids, induction onto XR-NTX may cause opioid withdrawal symptoms and contribute to screen fails and lack of interest in screening for the study from the population. This is a significant sub-group of people with moderate to severe methamphetamine use disorder. There is substantial epidemiological evidence documenting the increasing prevalence of Americans who simultaneously use opioids and methamphetamine[29]. Data documenting contemporaneous shifts in exposure to fentanyl and co-use of methamphetamine are observed nationwide and in the West, Southwest[30]. This issue is now observed in West Virginia[31], where methamphetamine and opioid co-use is measured as a significant contributor to the ongoing overdose crisis in the US[32]. Given the substantial opioid exposure (up to and including potential episodic use of oral buprenorphine), there is rationale for the use of an extended-release buprenorphine (Sublocade™) medication tested against an injectable placebo condition, a design feature that would provide the kappa antagonist effect as well as strongly bind at the opioid mu receptor in the active medication condition.

This study was designed to specifically evaluate BUP-Inj as a pharmacological monotherapy for individuals with moderate to severe MUD and co-occurring use of opioids. This therapy will be tested using the Sublocade™ product donated by Indivior, which will provide 300 mg of BUP extended-release via a monthly subcutaneous injection administered in clinic by qualified and licensed study personnel. This dose of BUP was informed by multiple sources of data to support our choice for 3 injections, each at 300mg dose. The data supporting Sublocade™'s efficacy in trials for OUD showed initial dosing of 300mg with subsequent injections at 300mg showing comparable efficacy to an initial injection of 300mg with subsequent injections at 100mg, with no increased risk for AEs at the higher dose[33,34]. Furthermore, this dosing strategy was more effective for getting to steady-state concentrations after repeated dosing. However, due to the novel use of this medication in this dual substance using population with less opioid use than what was evaluated in these primary Sublocade™ trials, we undertook consultation with clinicians actively working with these injectable products, with experts in clinical trial design and consulted the literature. Clinical experts were supportive of the higher dose, given the opioid experienced

population that were under study as well as supporting rigorous trial design. Results from the original CURB study indicated a poorer efficacy outcome using the lower 4mg dose of BUP as compared to the higher 16mg dose[9]. This higher dose produced superior outcomes of cocaine abstinence and higher blood level data, suggesting to us that there is a risk for underdosing using the lower formulation of buprenorphine-extended release based on these data.

We further reviewed the literature for relevant experiences of initiating BUP in those who are currently using opioids, but not at levels that warrant MOUD. In the original development of BUP in humans, participants were experienced users of opioids who had a substantial break from opioid use, i.e., not tolerant or dependent on opioids at the time of BUP initiation3[5]. These participants reported minimal adverse effects and repeated dosing over 2 weeks did not induce further toxic effects. Laboratory values for blood samples and urinalysis did not show clinically significant changes. Additional literature supports the use of BUP in a broad range of patients for pain management in comprehensive reviews[36,37]. These build confidence that we will not induce iatrogenic opioid use disorder for those assigned to the active condition in this research as all participants in the protocol will be opioid experienced. The Jasinski study also provided data detailing mild withdrawal symptoms following cessation of BUP[35]. These symptoms were noted to be of gradual and slow onset. For those participants in this protocol who desire to continue with treatment at the end of the study, referrals will be made for care at the conclusion of their participation in the study.

The decision to maintain 3 doses of 300 mg/1.5 mL instead of reducing the third dose to 100mg, as recommended on the package insert, at Week 9 is justified by several reasons. Most importantly, the study is 12 weeks in length with the primary outcome variable defined as the comparison of the number of methamphetamine-negative urine drug screens collected in Weeks 9 through 12 of the study. Changing the Sublocade™ dose at the beginning of this critical period, the efficacy window, risks invalidating the entire study. The risk of under-dosing is enhanced further in the measurement of the primary outcome variable and complicated by a lack of information regarding pharmacokinetic blood levels for Sublocade™ activity as a kappa antagonist for individuals with moderate to severe methamphetamine use disorder. While pharmacokinetic levels are well known for individuals with OUD[38], and were used to advise recommended Sublocade™ dose on the package insert, this information is limited to using Sublocade™ as a treatment for OUD.

Following these considerations, we elected to avoid possible underdosing and save cost by not testing both doses of medication. We therefore chose to maximize the probability to detect a signal in this trial by using three 300mg injections, matching a study design utilized by the manufacturer in the initial OUD efficacy trials and supported by our interpretation of the existing data that the higher 300mg injections would not cause undue risk to our opioid experienced participant population. The 12-week timeframe is in accordance with the pharmacokinetic data indicating increased circulating drug approaching steady state, as well as persistence of the medication in the body for 4-6 weeks. Following an induction onto BUP using sublingual BUP film, participants will then receive 3 study injections over the course of the 12-week medication phase. Participants will be randomized 1:1 to either this active product or placebo condition to test the

efficacy of this medication to stop or reduce MA use in this population. Opioid use will be monitored and evaluated as secondary outcomes for this study.

4.2.4 Ethical considerations of placebo for mild OUD or opioid misuse

The issue of implementing an ethical placebo control condition in this trial of BUP-Inj for persons with moderate-to-severe MUD who co-use opioids (mild OUD or opioid misuse) requires careful consideration. First, participants to be included in this trial will have moderate-to-severe MUD as the primary substance use disorder being treated. We have included procedures to ensure that participants who have moderate-to-severe OUD co-occurring with moderate-to-severe MUD will instead be assisted in seeking medication for OUD and not enrolled in this research project. To support the diagnosis of mild OUD or opioid misuse, participants are required to produce at least one urine sample negative for opioids during the screening phase and a second urine sample negative for opioids on the day of randomization, and self-report at least two days of opioid use in the 30-day period prior to written consent using the TLFB. Potential participants who under-represent the severity of their OUD during screening and present with opioid withdrawal symptoms will be excluded and referred to medication for OUD. Severity of withdrawal symptoms will be evaluated by the COWS. An inclusion criterion requires all participants report a score of ≤8 at both a screening assessment when the participant tests negative for opioids and on the day of randomization. The protocol has an inclusion criterion requiring participants to meet moderate-to-severe MUD and co-use opioids at a level that meets criteria for mild OUD or opioid misuse demonstrated by self-report of any use on the TLFB. Note that in the context of potential participants having moderate-to-severe MUD, any opioid use is considered misuse. Included participants may report physical symptoms of opioid tolerance and withdrawal, though cannot have criteria signaling severe opioid addiction. These procedures ensure selection of participants with moderate-to-severe MUD and mild opioid use disorder or opioid misuse as these participants do not warrant treatment with medication for OUD under standard clinical care. Potential participants whose opioid use does not allow for 48-72 hours without using opioids are excluded and instead referred to medication for opioid use disorder in their communities.

It is not possible to use a matched placebo for the 2-3 lead-in days prior to the first long-acting injection as placebo available from the manufacturer is not packaged to look or to taste like the marketed SL-BUP product, which has markings on the packaging attesting to its active status. The only available placebo medication appears with completely different package markings and tastes completely different compared to the SL-BUP product. Comparison of take-home medications by participants risks dismantling the masking for the study. As well, given the opioid experienced nature of the group, many participants will be familiar with SL-BUP, both in product appearance and taste. For those assigned to placebo, the risk of breaking study masking to conditions is high.

There is no possibility for placebo medication that would meet criteria for fully double-blinded sublingual lead-in products. It was recognized that using an active SL-BUP lead-in for all participants would be consistent with the procedures conducted in the phase 3 trial of Sublocade™[39]. As such, the procedures of using an active lead-in using SL-BUP for participants in both conditions is parallel to that used by Indivior. We recognize that this group of participants with moderate-to-severe methamphetamine use disorder who co-use opioids (have mild OUD or

opioid misuse) is distinctly different from that studied in the Sublocade™ trial who had moderate or severe OUD and were being treated with opioid agonists. In Haight et al., 2019[39] placebo-assigned participants were given a much greater exposure to active SL-BUP during a much longer lead-in period (up to 2 weeks). Opioid withdrawal symptoms for placebo participants in the current study resulting from the 2 or 3 days of SL-BUP are expected to be mild and transitory and participants can be offered palliative medications for any symptoms they experience. In sum, we believe the regimen proposed allows ethical treatment, does not represent substantial exposure to SL-BUP for those assigned to the placebo condition, and protects the study masking to condition.

This research protocol is specifically designed to evaluate BUP-Inj as a broad treatment for reducing methamphetamine use in this co-using group, therefore a placebo condition is necessary to measure the signal size for BUP-Inj. A key issue is that it is not possible to use an active medication control condition, such as injectable naltrexone and high-dose bupropion, as all participants regularly use opioids, which prevents the use of naltrexone-containing products. Thus, placebo compared to BUP product formulations will allow both scientific and ethical rationale as a condition for comparing outcomes to the experimental BUP-Inj condition.

One final ethical consideration involves addressing withdrawal symptoms for participants assigned to the placebo condition, as participants assigned to the placebo condition will not benefit from the partial agonist feature of BUP-Inj, which protects against opioid overdose. To address differential reduction of overdose risks, all participants will be provided naloxone reversal kits and will be instructed to inform their family and friendship members of this increased sensitivity to opioids and the risk of overdose, as well as of how to use the kits in the setting of opioid overdose. Monitoring of ongoing opioid use is an integral part of this trial and we describe procedures for increased clinical attention for signs of escalating opioid use during the trial period (Section 10.7, Considerations Regarding Ongoing Opioid Use).

4.2.5 Significance of the project to the field

From 2012 to 2018, overdoses associated with stimulants including MA have increased nearly five-fold[40]. Aside from MA's detrimental health effects, its use also has severe social consequences: interactions with the criminal justice system[19], homelessness[19], and increased domestic violence[41]. Pharmacologic options for MUD treatment are urgently needed. The potential treatment of BUP-Inj is hoped to have a broad impact on the MA epidemic in the US, uniquely so in the Southwest and Western US.

Identifying a broadly effective medication to help achieve abstinence, to prevent relapse to MA use – and importantly, to prevent overdose and potential deaths – is a key objective with considerable public health significance. This placebo-controlled trial will advance medication research and potentially confirm the use of injectable buprenorphine as the first effective pharmacotherapy for the treatment of stimulant use disorder involving MA in the context of mild OUD or opioid misuse.

4.3 Risk/Benefit Assessment

The use of BUP-Inj, as Sublocade™ in this trial, has not yet been directly evaluated as mono-pharmacotherapy in those with MUD. Overall, the risks of using Sublocade™ for MUD are low. Further reducing risks, participants in this study will not be opioid naïve, will likely combine opioid use with methamphetamine use and meet criteria for mild OUD or demonstrate opioid misuse, which increases acceptability of this putative mono-pharmacotherapy strategy. The study will be conducted under an IND (Investigational New Drug) application, which strengthens oversight and monitoring of the study, with emphasis on evaluating safety and early efficacy. Other than the primary substance used by this population, no other existing differences are believed to increase the risks of using this medication as all other safety guidelines for use of BUP-Inj will be followed as detailed in the package insert for Sublocade™.

There is a risk to untreated MUD, especially in the setting of opioid co-use, particularly ongoing risks for opioid overdose[6]. For participants assigned to the BUP-Inj condition, risks for opioid overdose will be reduced due to the partial agonist properties of BUP. Naloxone overdose reversal kits will be provided to participants in both conditions with instructions to participants and their friends/family members on their use in the setting of overdose in order to address opioid overdose risks. There remain risks for MA overdose for participants in both conditions; however, the risks for opioid overdose are reduced substantially for participants assigned to BUP-Inj and for participants in both conditions who are given naloxone reversal kits. Regular monitoring of ongoing opioid use during the trial allows for identification of those who warrant discontinuation of trial participation and immediate referral to treatment for their opioid use.

Ongoing risks for opioid overdose, adverse events related to BUP-Inj and for events related to ongoing MA use will be assessed at a safety follow-up visit during Week 16 of the study.

There are serious risks for overdose and death should BUP-Inj be injected intravenously. A chain of custody will be maintained and documented detailing transfer from the manufacturer to the study pharmacy to the site staff who will administer the BUP-Inj product to participants assigned to the BUP-Inj condition, under the oversight of the Medical Clinicians with DEA Registrations. No take home injectable medications will be provided – all study products will be prepared and administered to study participants at the research clinic. To document safety and drug accountability, the Risk Evaluation and Mitigation Strategy (REMS) procedures will be followed.

There are expected adverse events to the BUP-Inj medication. Medication-related adverse events that occur in more than 5% of subjects when using BUP-Inj include constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain. These are minor, will be treated with ancillary medications, and tolerable in comparison to protection from overdose and potential for treating MUD[42]. BUP-Inj medication is habit forming. The risks to PBO-Inj are mild, including injection site reactions and tolerable withdrawal symptoms. To avoid risks for iatrogenic illness, all participants must meet criteria for moderate to severe MUD and mild OUD or demonstrate opioid misuse. Throughout the study, management of complaints of opioid withdrawal symptoms for all participants will include provision of over-the-counter medications for head and body aches (e.g., ibuprofen), insomnia (e.g., diphenhydramine), diarrhea (e.g., loperamide) and stomach upset (e.g., bismuth subsalicylate) and ongoing opioid

use will be monitored to ensure that any escalation of opioid use that suggests moderate or greater OUD is evaluated by the Medical Clinician.

Participants assigned to the active condition may acquire opioid dependence by the end of the trial, though concern is mitigated somewhat by the requirement for participants to have mild OUD or opioid misuse. To enroll, individuals must be experienced in the use of opioids, perhaps even including buprenorphine. This risk is balanced by several factors:

1. From the Sublocade™ package insert, withdrawal symptoms following discontinuation from Sublocade™ are mild and may not be observed for a month or more following last injection, if at all[43]. We commit to assisting participants in finding Sublocade™ prescribers for those who report unacceptable opioid withdrawal symptoms anytime following their study visit.
2. Participants must have mild OUD or opioid misuse. This requirement ensures substantial experience with opioids, though not enough to warrant ongoing prescribed Sublocade™.
3. For participants assigned to the placebo condition, the two to three days of sublingual buprenorphine will be insufficient to establish severe opioid dependence or moderate to severe OUD. In response, however, participants in both conditions who complain of opioid withdrawal symptoms can be offered medications for symptom relief.
4. The investigator team has consistently consulted with Indivior and NIDA throughout protocol development to discuss the side effect profile and the risks to benefit ratio for the study. All agree that benefits would outweigh risks to participation for all participants in this trial as outlined.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to evaluate whether assignment to 12 weeks of outpatient BUP-Inj compared to 12 weeks of outpatient PBO-Inj reduces MA use as measured by twice weekly UDS during Weeks 9-12 for participants with moderate to severe MUD with co-occurring mild OUD or opioid misuse not warranting MOUD.

5.2 Secondary Objectives

Secondary objectives include evaluation of whether assignment to 12 weeks of outpatient BUP-Inj compared to 12 weeks of outpatient PBO-Inj improves:

1. Alternate measures of methamphetamine use:
    a. Total number of MA negative UDS (Treatment Effectiveness Score, TES) through Weeks 1-12
    b. Self-reported days of MA use (TLFB) through Weeks 1-12
2. Measures of opioid use:
    a. Total number of opioid negative UDS (TES) through Weeks 1-12
    b. Self-reported frequency of opioid use (TLFB) during Weeks 1-12
3. Measures of MA and opioid co-use:
    a. Total number of MA and opioid negative same-day UDS (TES) through Weeks 1-12
    b. Self-reported days of MA and opioid co-use (TLFB) during Weeks 1-12

5.3 Exploratory Objective(s)

Data will be collected to explore whether assignment to BUP-Inj compared to PBO-Inj over the 12 week medication phase corresponds with:

1. Measures of subjective effects of MA:
    a. MA withdrawal, as measured by scores on the Amphetamine Cessation Symptom Assessment during Weeks 1-12
    b. MA craving as measured by the Visual Analog Craving Scales (VAS) during Weeks 1-12
2. Measures of opioid subjective effects:
    a. Observer rating of opioid withdrawal as measured by the Clinical Opiate Withdrawal Scale (COWS) on the day of randomization; each subsequent visit during induction in Week 1, if needed; prior to each injection in Weeks 1, 5, and 9, and at Week 12.
    b. Self-reported rating of opioid withdrawal as measured by the Subjective Opiate Withdrawal Scale (SOWS) on the day of randomization; each subsequent visit during induction in Week 1, if needed; prior to each injection in Weeks 1, 5, and 9, and at Week 12.

c. Self-reported opioid craving, as measured by Visual Analog Craving Scales (VAS), Weeks 1-12

3. Self-reported craving for MA and opioid co-use, as measured by Visual Analog Craving Scales (VAS), Weeks 1-12

4. Measures of mood, pain, and stress:
    a. Self-reported depressive symptoms as measured by the Inventory of Depressive Symptomology - Self-Report (IDS-SR) during Weeks 1-12
    b. Change in self-reported anxiety symptoms as measured by the Generalized Anxiety Disorder Scale-7 (GAD-7) during Weeks 1-12
    c. Changes in self-reported mood symptoms as measured by the Concise Associated Symptom Tracking Scale (CAST) during Weeks 1-12
    d. Changes in self-reported anhedonia as measured by the Dimensional Anhedonia Rating Scale (DARS) during Weeks 1, 5, 9, and 12
    e. Changes in reported pain as measured by the Pain Frequency, Intensity, and Burden Scale (P-FIBS) during Weeks 1-12
    f. Changes in self-reported stress as measured by the Perceived Stress Scale (PSS) during Weeks 1, 5, 9, and 12

5. Retention:
    a. Participants retained in treatment (defined as present and providing urine drug samples) during Weeks 1-12

6. Measures of infectious disease control, incidence, and risk:
    a. Biomarkers measured at Week 12:
        i. HIV-Negative Participants: Remaining HIV-negative
        ii. HCV-Negative Participants: Remaining HCV-negative
    b. Self-Reported HIV transmission risk behaviors measured at Weeks 1, 6 and 12:
        i. Self-reported number of new sexual partners
        ii. Self-reported number of sexual partners with condomless sex who are serodiscordant or unknown serostatus
        iii. Self-reported number of sexual partners with condomless sex who are serodiscordant or unknown serostatus with whom substances were used during sex (chemsex)
        iv. For men, self-reported number of male sexual partners
        v. Self-reported number of episodes sharing needles
        vi. Self-reported number of episodes sharing injection equipment and paraphernalia

7. Measures of functioning:
    a. Self-reported assessment of Quality of Life (QoL) at Weeks 1 and 12
    b. Self-reported overall functioning as measured by the Treatment Effectiveness Assessment (TEA) at Week 12

8. Measures of adverse events:
    a. Number and severity of adverse events reported during Weeks 1-12
    b. Number and outcomes (non-fatal, fatal) of overdose events during Weeks 1-12
9. Changes in other substance use measured by self-report (TLFB) and UDS. Alcohol, tobacco, and other drugs measured via self-report will be collated and counted, and UDS results will quantify the presence of barbiturates, benzodiazepines, cocaine, amphetamines, marijuana (THC), methadone, phencyclidine (PCP) and ecstasy (MDMA).
10. Changes in disease transmission, with new chlamydia or gonorrhea diagnoses measured via urinalysis.
11. Participants will complete the Iowa Gambling Task (IGT) at screening to determine if performance on the IGT predicts treatment response. The IGT is a standard computer-based task with established performance in people receiving treatment for MUD [44].

6.0 STUDY DESIGN

6.1 Overview of Study Design

The primary objective of this study is to assess the efficacy of BUP-Inj as a pharmacotherapy for moderate to severe MUD in those with co-occurring mild OUD or opioid misuse not warranting MOUD by evaluating whether assignment to 12 weeks of outpatient BUP-Inj compared to 12 weeks of outpatient PBO-Inj reduces urine-verified MA use measured during Weeks 9-12 of medication administration. It is hypothesized that BUP-Inj will produce a significantly greater number of MA-negative UDS test results relative to the PBO-Inj during this period. To assess this objective, a phase IIb double-blinded, randomized controlled trial will be conducted. Participants will be randomized in a one-to-one ratio to one of two study arms: BUP-Inj or PBO-Inj. The Data and Statistics Center (DSC) will generate and implement the randomization schema.

There will be approximately 246 individuals randomized into the study across 4-8 clinical sites. Eligibility will be determined during a maximum 21-day screening period. To document an appropriate level of current MA use, prospective participants must have at least two positive UDS for MA out of a possible three tests to occur at clinic visits within a 10-day period, with at least two days between visits. In addition, participants must self-report MA use on 18 or more days in the 30-day period prior to written consent using the TLFB and meet diagnostic criteria for moderate or severe MUD per DSM-5 (four or more criteria) at screening. In addition, prospective participants must also meet diagnostic criteria for mild opioid use disorder per DSM-5 (at least two but no more than three criteria) at screening or demonstrate opioid misuse by self-reporting opioid use on at least two days in the 30-day period prior to written consent using the TLFB. Additionally, participants must also provide a UDS negative for opioids at least once during the screening period and on the day of randomization, to demonstrate the ability to abstain from using opioids for a short period of time and have a COWS score of ≤8 at both a screening visit on which they provide a UDS negative for opioids and on the day of randomization. After screening is completed and eligibility is confirmed, participants will begin the 12-week medication phase of the trial. Participants will be randomized to receive either 1) BUP-Inj or 2) PBO-Inj. Injections will be provided in Weeks 1, 5, and 9. Participants will be asked to submit twice weekly urine samples, and complete once-weekly cognitive behavioral therapy based on a treatment manual adapted for stimulant use disorder specifically for this study. Participants will be asked to complete assessments as indicated on the schedule of assessments (see Section 11).

The experimental treatment and placebo will be in injectable formulation, with the addition of a two- to three-day sublingual buprenorphine induction using a defined dosing strategy for titration prior to initiating the injections. Dosing will be as follows:

6.1.1 Sublingual Buprenorphine Induction

Due to an inability to obtain placebo sublingual medication that is matched to sublingual buprenorphine in appearance and taste, starting on Day 0 of Week 1, participants in both conditions will receive two 4mg doses of sublingual buprenorphine (as Suboxone™, Indivior), followed by two 8mg doses on Day 1 and, if necessary, Day 2 to reach 16mg maximum oral dose.

This is designed to facilitate rapid transition to the injectable formulation while ensuring the safety of the participants and helping to support the blinded injectable phase.

6.1.2 Injectable Formulations

BUP-Inj:

- Beginning in Week 1 and following successful induction, BUP-Inj participants will then transition to injectable buprenorphine 300 mg (as Sublocade™, Indivior) as determined by the Medical Clinician and is expected about Day 3. Subsequent BUP-Inj injections will occur at Weeks 5 and 9.

PBO-Inj:

- Beginning at Week 1 and following successful induction, PBO-Inj participants will then transition to injectable placebo about Day 3 and will receive placebo injections at the same time points as the active medication group. The dose of sublingual buprenorphine in these participants with some opioid experience is not expected to confer risk for precipitated withdrawal once participants transition to the injectable placebo, since participants will be required to have a negative opioid UDS with a COWS score of ≤8 at the time of induction.

6.2 Duration of Study and Visit Schedule

Participants will be involved in the study for approximately 19 weeks, including a screening period of up to 3 weeks (i.e., 21 days) and 12 weeks in the medication phase, plus one follow-up appointment in Week 16. The screening phase may differ by participant in the length of time needed to complete preliminary eligibility assessments.

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

7.0 OUTCOME MEASURES

7.1 Primary Outcome Measure

The primary outcome measure is the number of MA-negative UDS results obtained during Weeks 9 through 12 of the medication phase as measured for the BUP-Inj and PBO-Inj conditions.

7.2 Secondary Outcome Measures

Secondary outcome measures include:

1. Alternate measures and composites of methamphetamine use:
    a. MA Treatment Effectiveness Score (TES), as measured by number of UDS results negative for MA by condition, during Weeks 1-12 (possible 2 per week; score range 0-24)
    b. Self-reported days of MA use on the TLFB during Weeks 1-12 (possible 1 per day; score range 0-84)
2. Measures of opioid use:
    a. Opioid Treatment Effectiveness Score (TES), as measured by number of UDS results negative for opioids by condition, during Weeks 1-12 (possible 2 per week; score range 0-24). Results from radio-immune assay strips will be used to measure opiates (OPI-300), oxycodone/synthetic opioids, fentanyl for each UDS.
    b. Self-reported frequency of opioid use on the TLFB during Weeks 1-12. Reports of any opioid used will be combined into one measure that includes opiates, oxycodone and synthetic opioids, fentanyl and analogues for each report during Weeks 1-12 (possible 1 per day; score range 0-84).
3. Measures of MA and opioid co-use:
    a. MA and Opioid Co-Use compiled using Treatment Effectiveness Score (TES), as measured by number of UDS results negative for both MA and opioids by condition, during Weeks 1-12 (possible 2 per week; score range 0-24)
    b. Self-reported days of MA and opioid co-use on the TLFB during Weeks 1-12 (possible 1 per day; score range 0-84)

7.3 Other Exploratory Measures

Exploratory measures include:

1. Measures of MA subjective effects:
    a. MA withdrawal, as measured by scores on the ACSA during Weeks 1-12
    b. MA craving as measured by the VAS during Weeks 1-12
2. Measures of opioid subjective effects:
    a. Clinician rating of opioid withdrawal as measured by the COWS on the day of randomization; each subsequent visit during induction in Week 1, if needed; prior to each injection in Weeks 1, 5, and 9, and at Week 12

   b. Self-reported rating of opioid withdrawal as measured by the SOWS on the day of randomization; each subsequent visit during induction in Week 1, if needed; prior to each injection in Weeks 1, 5, and 9, and at Week 12
   c. Self-reported opioid craving as measured by VAS, during Weeks 1-12

3. Self-reported craving for MA and opioid co-use as measured by VAS, during Weeks 1-12

4. Measures of mood, pain, and stress:

   a. Changes in self-reported depressive symptoms as measured by the IDS-SR during Weeks 1-12
   b. Changes in self-reported anxiety symptoms as measured by the GAD-7 during Weeks 1-12
   c. Changes in self-reported mood symptoms as measured by the CAST during Weeks 1-12
   d. Changes in self-reported anhedonia as measured by the DARS during Weeks 1, 5, 9, and 12
   e. Changes in reported pain as measured by the P-FIBS during Weeks 1-12
   f. Changes in self-reported stress as measured by the PSS during Weeks 1, 5, 9, and 12

5. Retention:
   a. Participants retained in treatment, defined as present and providing urine drug samples during Weeks 1-12

6. Measures of Infectious disease control, incidence, and risk:
   a. Biomarkers measured at Week 12:
      i. HIV-Negative Participants: Remaining HIV-negative obtained via blood tests
      ii. HCV-Negative Participants: Remaining HCV-negative obtained via blood tests
   b. Self-Reported HIV transmission risk behaviors measured at Weeks 1, 6 and 12:
      iii. Self-reported number of new sexual partners
      iv. Self-reported number of sexual partners with condomless sex who are serodiscordant or unknown serostatus
      v. Self-reported number of sexual partners with condomless sex who are serodiscordant or unknown serostatus with whom illicit substances were used during sex (chemsex)
      vi. For men, self-reported number of male sexual partners
      vii. Self-reported number of episodes sharing needles
      viii. Self-reported number of episodes sharing injection equipment and paraphernalia

7. Measures of functioning:
   a. Changes in self-reported assessment of Quality of Life (QoL) at Week 1 and 12
   b. Self-reported overall functioning as measured by the Treatment Effectiveness Assessment (TEA) at Week 12

8. Measures of adverse events:
    a. Number and severity of adverse events reported during Weeks 1-12
    b. Number and outcomes (non-fatal, fatal) of overdose events during Weeks 1-12
9. Self-reported measures of alcohol, tobacco and other drug use on TLFB at Weeks 1, 5, 9, and 12, and UDS results of other substance use not quantified for primary or secondary outcomes.
10. Urinalysis results indicating a new chlamydia or gonorrhea diagnosis at Week 12
11. IGT performance at screening

7.4 Study Timeline

After receiving Center for the Clinical Trials Network (CCTN) approval of the full and final protocol, approximately 8 months of trial preparation activities will elapse prior to commencing enrollment. Trial preparation will include applying for and obtaining Institutional Review Board (IRB) approval, filing the IND application, developing the data collection systems, developing the Manual of Procedures (MOP), conducting all staff training, collecting required regulatory documents, and endorsing sites. If feasible, the study may be implemented in a single wave; however, sites may launch on a rolling basis. Recruitment is expected to take approximately 18 months, with the medication phase and follow-up continuing for approximately four months post completion of the recruitment phase. Two months will be allowed for data lock after the end of the follow-up period. Therefore, data lock is projected to occur at approximately 32 months after CCTN approval of the final protocol.

8.0 STUDY POPULATION

Approximately 246 males and females who meet eligibility criteria will be randomized. Eligible participants will meet criteria for moderate to severe MUD and have co-occurring mild OUD or opioid misuse not warranting MOUD.

8.1 Participant Inclusion Criteria

Individuals must meet all of the inclusion criteria in order to be eligible to be randomized into the study.

Study participants ***must***:

1. Be 18 to 65 years of age, inclusive;
2. Able to understand and speak English or Spanish;
3. Be interested in reducing or stopping MA use and not interested in pursuing MOUD;
4. Meet DSM-5 criteria for moderate or severe MUD (4 or more criteria);
5. Self-report MA use on 18 or more days in the 30-day period prior to written consent using the TLFB;
6. Provide at least 2 urine samples positive for MA out of a possible 3 tests to occur at clinic visits within a 10-day period with at least 2 days between visits;
7. Meet DSM-5 criteria for mild OUD (at least 2 but no more than 3 criteria) prior to randomization OR opioid misuse demonstrated by self-report of opioid use of at least 2 days in the 30-day period prior to written consent using the TLFB;
8. Provide at least 2 urine samples negative for opioids, at least one during the screening period and again on the day of expected randomization to indicate control over opioid use;
9. Have a COWS score of ≤8 at both the screening visit on which they provide a UDS negative for opioids and on the day of randomization;
10. If female, agree to both of the following: use an acceptable method(s) of birth control, as defined in the MOP, for the duration of study participation and for four months after the last injection of study medication; undergo periodic urine pregnancy tests for the duration of study participation, unless verifiably unable to get pregnant, as defined in the MOP;
11. Be willing and able to provide consent and comply with all study procedures and medication instructions;

8.2 Participant Exclusion Criteria

Individuals meeting any of the exclusion criteria will be excluded from being randomized into the study.

Study participants ***must not***:

1. Have suicidal or homicidal ideation that requires immediate attention;
2. Have evidence of prolongation of the QTc or any other finding on the screening ECG that, in the opinion of the Medical Clinician, would preclude safe participation in the study (e.g., hypokalemia, unstable atrial fibrillation) and be at significant risk for serious cardiac adverse events;
3. Have a laboratory value with total bilirubin ≥1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) ≥3 × ULN, aspartate aminotransferase (AST) ≥5 × ULN, or serum creatinine >2 × ULN;
4. Have been in a study of pharmacological or behavioral treatment for addiction within 6 months prior to written study consent (smoking cessation excepted);
5. Have taken an investigational drug in another study within 30 days prior to written study consent;
6. Have been prescribed or have taken buprenorphine or methadone within 30 days prior to written study consent;
7. Be concurrently enrolled in formal behavioral or pharmacological addiction treatment services or express the desire to initiate MOUD at the time of written consent;
8. Be receiving ongoing treatment of medications that are clinically relevant CYP 3A4 or CYP 2C8 inducers or inhibitors (e.g., rifampicin, azole antifungals, macrolide antibiotics), Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone) at the time of randomization that, in the judgment of the Medical Clinician, could interact adversely with study medications or put them at significant risk for development of serotonin syndrome;
9. Have a current pattern of alcohol, benzodiazepine, or other sedative hypnotic use which would preclude safe participation in the study as determined by the Medical Clinician;
10. Have a surgery planned or scheduled, or other treatment that would require the use of opioid-containing medications (e.g., opioid analgesics) during the study period;
11. Currently or soon to be in jail or prison; currently in any inpatient overnight facility as required by court of law or have pending legal action or other situation that could prevent participation in the study or in any study activities;
12. If biologically female, be currently pregnant, breastfeeding, or planning on conception;
13. Hypersensitivity (e.g., anaphylaxis) to buprenorphine or any component of the ATRIGEL formulation or their excipients;

14. Have an abdominal area unsuitable for subcutaneous injections by the judgment of the Medical Clinician;
15. Have other medical, psychiatric or other factors that in the judgment of the Medical Clinician could make participation difficult or unsafe.

8.3 Strategies for Recruitment and Retention

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 or other gathering areas. Information regarding the method of recruitment that led potential participants reaching out to study personnel will be recorded on the Prescreening Interview eCRF to optimize the most successful recruitment strategies and track the factors that lead to both recruitment of eligible participants and the reasons that others are deemed ineligible for participation.

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 racial/ethnic minorities in the community where the site is located, including persons of African American and Latinx backgrounds. Recruitment procedures aiming to enhance enrollment of women and/or minorities will be conducted, with sites being encouraged to implement strategies such as linkages with medical sites, treatment programs, or community organizations that serve a large number of women and/or minorities, using targeted advertisement in media with a high female and/or minority audience, and partnerships with community organizations who work with these groups. This study aims to enroll a minimum of approximately 25% women in the total study population.

For successfully enrolled participants, efforts will be made to encourage participation in the full duration of the trial. These efforts include regular participant contact, including reminders, to encourage visit attendance, reimbursement for study related activities, and a weekly cognitive behavioral therapy component which also will encourage and reinforce the importance of continuing in the trial as a key way to reduce methamphetamine use.

9.0 SITE SELECTION

9.1 Number of Sites

The trial will include 4-8 sites with each site randomizing approximately a total of 31-61 participants.

9.2 Site Characteristics

Participating sites ***must***:

1. Have a Site Principal Investigator (PI) who can commit the time necessary to take a leadership role and oversee all aspects of the study, perform assessments as licensure allows, confirm participant eligibility (if a MD or DO), review adverse events (if a MD or DO), and appropriately evaluate and respond to adverse reactions that may occur during the study (if a MD or DO).
2. Have at least two Medical Clinicians (i.e., physician, physician's assistant, or nurse practitioner) with a DEA Registration who can, in accordance with the state regulations where the site is located, make independent medical decisions and commit the time necessary to perform medical assessments as licensure allows, determine participant eligibility, confirm participant eligibility prior to randomization (if a MD or DO), order and administer study medication, review adverse events (if a MD or DO), and appropriately respond to adverse reactions that may occur during the study (if a MD or DO). One of these Medical Clinicians can also be the Site PI.
3. Have staff to serve as unblinded medical personnel (RN, LVN, MA, or other qualified personnel trained in the administration of subcutaneous injection). These staff can only participate in study-related activities pertaining to preparing and administering medication injections, evaluating the injection site, and documenting injectable medication administration.
4. Have standard operating procedures (SOPs) in place for handling medical and psychiatric emergencies.
5. Have a Medical Clinician available to provide after-hours clinical back-up for study-related emergencies.
6. Have access to a phlebotomist or other qualified personnel to complete blood draws.
7. Have the ability to meet storage and dispensing requirements for study medication, including access to adequate storage space, equipment, and appropriately qualified staff, as directed by the protocol and in accordance with local regulations and National Institute on Drug Abuse (NIDA) stipulations.
8. 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.
9. Have adequate facility space available to conduct study procedures.

9.3 Rationale for Site Selection

The sites selected for participation in this trial will be selected, in part, based on the Local Node's interest in participating in the trial, the availability of a sufficient pool of potential study participants in the area that includes both male and female participants, 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 characteristics 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 MUD and co-occurring opioid use each month.
2. Ability to rely on a centralized IRB and having personnel experienced with regulatory requirements to support timely preparation of necessary documents and facilitate an expeditious IRB submission, approval, modification, and continuing review processes in accordance with required IRB reliance procedures.
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 study medication, 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 (EDC) 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.

10.0 STUDY PROCEDURES

10.1 PreScreening Assessment

Prescreening assessment will be completed before participants sign the research consent and therefore, verbal consent to prescreening will be obtained. Those 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 and opioid use history, interest in participating in research to investigate medication that has potential to reduce MA use, ability and willingness to participate for the duration of the trial) will determine preliminary eligibility. Appointments to open the consent process and complete full screening appointments will occur for those who meet preliminary eligibility criteria. A waiver of HIPAA authorization will be obtained from the IRB of record for prescreening.

10.2 Screening Visit

Assessments administered during screening (after the participant signs informed consent) will determine whether participants meet eligibility criteria. Screening assessments will be conducted as shown in Table 11.1. Participants who do not complete all screening assessments within 21 days of signing consent or who are otherwise found to be ineligible for participation in the study will be considered screen fails. With Sponsor approval, screen fails may be allowed one additional chance to return at a later date (at least 30 days past initial screen fail date) to repeat and restart the screening process.

10.2.1 Informed Consent Procedures for Participants

Participants will be given a copy of the current, IRB-approved informed consent form(s). The entire consent form(s) including, study procedures and the potential risks and benefits of participating in the trial will be explained by qualified research staff. Staff will be available to answer questions about the consent form while participants are reviewing it. Given the multisite nature of the trial, it is possible that ancillary studies will be proposed before or after the study begins recruitment. For this reason, during the informed consent process, we will also seek permission to contact the participant in the future about other study opportunities.

Prior to signing the consent form, the participant must pass a brief consent quiz to illustrate comprehension of the study activities. For participants who do not correctly answer all comprehension items, the study staff will re-explain the study, or may ask another study staff member to speak with the participant, with a focus on aspects candidates did not understand. The other study staff member may determine that the participant would benefit from coming back after having some time to review the study details and may return at a later date to engage in the informed consent process again. Participants may attempt the consent comprehension questions a maximum of three times before they are deemed unable to comprehend the study. If the participant is unable to comprehend what the study activities require of them, they will be unable to participate in the study. After passing the quiz and signing the consent form, participants will be given a copy of the signed forms to keep for their records. After the participant signs the informed consent, the rest of the screening assessments will be performed.

10.2.2 HIPAA Authorization and Medical Record Release Forms

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

10.2.3 Screening Assessments

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

During the screening phase, participants must have at least 2 positive UDS for MA out of a possible 3 tests that must occur within a 10-day period, and at least 2 full days must pass between clinic visits. In addition, participants must self-report MA use on 18 or more days in the 30-day period prior to written consent using the TLFB. These criteria will be used to confirm current MA use and further substantiate a diagnosis of moderate to severe MUD.

In addition, the participant must meet DSM-5 criteria for mild OUD (at least 2 but no more than 3 criteria) or self-report opioid use on at least 2 days in the 30-day period prior to written consent using the TLFB. Additionally, at least once during the screening period and again on the day of expected randomization, the participant must provide a urine sample that is negative for opioids to demonstrate the ability to abstain from using opioids for a short period of time. The urine can be positive for MA. On these visits that the participant provides the required opioid-negative urine samples, the participants must also report a COWS score ≤ 8 to indicate opioid withdrawal symptoms do not present at moderate or severe levels (supporting that the participant has mild opioid use disorder or opioid misuse). If on the day of randomization, the participant instead provides a urine sample that is positive for opioids, they cannot be randomized to the study on that day and must delay study participation for at least one month. After at least one month, they can restart the screening phase. This is allowed only one time per participant in the course of the study.

A physician (MD or DO) who serves in the Site PI or Medical Clinician study role must review and approve safety and eligibility assessments in order to confirm participant eligibility prior to randomization after the participant does the following:

1. Completes all screening assessments,
2. Has 2 MA-positive UDS tests and 1 opioid-negative UDS test per guidelines above,
3. On the day randomization is expected, has a urine sample negative for BUP, methadone, and opioids (but can be positive for MA) and if capable of getting pregnant, has a negative urine pregnancy test, and
4. Is found otherwise eligible for continued participation.

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 screen fails. With Sponsor approval, screen fails may be allowed one additional chance to return at a later date (at least 30 days past initial screen fail date). Demographic data and the reasons for not meeting eligibility criteria will be documented for all screen fails.

After the participant is deemed fully eligible and this is recorded in the Advantage eClinical system, the participant will then complete all assessments required on the day of randomization as detailed in Table 11.1 for Week 1.

10.3 Randomization

Following the collection of the assessments required for screening and eligibility, eligible participants will be randomly assigned to BUP-Inj or PBO-Inj in a 1:1 ratio. The randomization procedure will be conducted electronically by the Advantage eClinical system. The unblinded DSC Statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new participant due to the intent-to-treat nature of the study. All screening assessments must be completed before the participant is randomized and all assessments required on the day of randomization must be completed before the participant is administered any study medication.

10.4 Study Intervention(s) Administration

10.4.1 Induction Phase

Participants will receive sublingual film (BUP) on the day of randomization (Day 0) following randomization and collection of assessments required on the day of randomization. If a participant reports symptoms of withdrawal or side effects, ancillary medications may be used to manage symptoms. This includes management of head and body aches (e.g., ibuprofen), insomnia (e.g., diphenhydramine), diarrhea (e.g., loperamide) and stomach upset (e.g., bismuth subsalicylate). The Medical Clinician will guide the induction onto study medication using a defined dosing strategy to ensure that participants in either condition receive the exact same induction and that participants tolerate the medication before proceeding to the first injection. The induction phase will last between 2 and 3 days. If needed, participants may have subsequent study visits during the induction phase.

10.4.2 Injections

Participants will receive the first subcutaneous injection of study medication (BUP-Inj or PBO-Inj) after determination by Medical Clinician that participants may advance from the induction phase. This will happen in Week 1 of the study. Subsequent subcutaneous injections of study medication should be administered at the beginning of Weeks 5 and 9 and shall be administered following the guidelines in the BUP-Inj package insert. Medical Clinicians will evaluate participants to ensure continued suitability for injectable study medication administration. If a participant reports uncomfortable symptoms or side effects, ancillary medications may be used to manage symptoms. Defined windows for injections will be outlined in the MOP. If a participant misses a window for an injection, they will not receive the injection but will be maintained in the study and

used in the Intent-to-Treat analysis. Given the long-lasting nature of BUP-Inj, these windows will be defined in a way to maximize the possibility for a participant to receive study medication.

10.5 Study Intervention Adherence

The primary study intervention is injectable medication. This prevents a number of adherence issues that come with oral administration. However, continued participation in the study for both those randomized to active medication and randomized to placebo is essential for successful study completion. In order to facilitate adherence to study procedures and to successfully complete the study, a weekly cognitive behavioral therapy (CBT) component modeled on traditional medical management is included in the study procedures.

Participants will meet with trained study staff once weekly for an individual CBT session that utilizes a structured adherence enhancement manual designed for pharmacotherapy trials with participants with substance use disorder[45]. The goal of these CBT sessions is to achieve high quality supportive treatment that reinforces adherence to study procedures and study visits. A session will be approximately 20 minutes and focus on:

1. Setting abstinence from MA as a goal,
2. Learning a skill for instilling abstinence, preventing relapse or returning to abstinence in the setting of lapse or relapse,
3. Participant adherence with study visits and procedures, *and*
4. Current functioning.

Study staff will also review adverse events, and communicate issues to Medical Clinicians (MD or DO) for consideration of potential medication side effects, and discussion of other pertinent issues in keeping with sound medical practice. Medical Clinicians may choose to provide ancillary medications for study medication-related adverse events as clinically indicated or for management of opioid withdrawal symptoms, such as anxiety, nausea, vomiting, diarrhea, muscle pain, and insomnia. At all CBT sessions, the study staff will remind participants about the importance of adhering to the study procedures, including attending scheduled clinic visits. Mutual help support group attendance will be encouraged.

10.6 Premature Withdrawal of Participants

All participants will be followed for the duration of the study unless they withdraw consent, die, or the PI or Sponsor decides to discontinue their enrollment for any reason. Reasons for the PI or Sponsor terminating a participant from the study may include but are not limited to: clinical deterioration, the participant becoming a threat to self or others, or early termination of the study for safety or effectiveness reasons.

10.7 Considerations Regarding Ongoing Opioid Use

The safety of the participants is foremost in the design of this study. There is a chance that participants may experience a worsening of their opioid use. In order to ensure participant safety throughout the trial, the following criterion will be used to trigger an evaluation of the severity of

the participant's opioid use. Participants who provide two weeks of opioid positive UDS (4 consecutive opioid positive UDS), independent of MA result in UDS, will trigger a safety review by the Medical Clinician. If in the Medical Clinician's judgement continuing in the study is not safe for the participant due to worsening of opioid use, independent of status regarding MUD, the Medical Clinician (MD or DO) may elect to discontinue the participant from the medication aspect of the study and refer the participant to a clinic for treatment of OUD. In this instance, the study staff or Medical Clinician will assist the participant with obtaining an appointment with an outpatient MOUD provider. The study staff will follow-up with the participant within 48 hours of the appointment date to assist with transportation or other barriers reaching the appointment. If in the Medical Clinician's judgment continuing in the study is safe for the participant and the opioid use is deemed to not exceed that of mild OUD, the participant will be provided with an additional Naloxone kit with specific instructions for the participant's friends and family on proper usage. Follow-up evaluations of additional opioid positive UDS results by the Medical Clinician will document continued assessment of safety for the participant.

10.8 Rules for Immediate Study Review

The following rules will automatically trigger a review by the DSMB to determine if any action should be taken to adjust conduct of the trial:

- Three or more participants experience severe adverse reactions.
- Four or more participants have four consecutive positive urine toxicology screens for opioid use, and have been reevaluated through any means as having moderate to severe opioid use disorder.
- One or more serious, unexpected and suspected adverse reaction (SUSAR).

10.9 Follow-Up

All enrolled participants will be asked to complete a post-medication phase follow-up visit in Week 16 according to the schedule of assessments (see Table 11.1, Section 11). Given the long-lasting nature of BUP-Inj, there is no tapering possible therefore thorough assessment of side effects and AEs will be completed. Any participant who requests may receive a referral to treatment. 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.

10.10 Discontinuation of Study Intervention

Participants will be withdrawn from further study medication administration if it is clinically determined that continuation may be unsafe or if they become unable to come to clinic for study visits (e.g., they become incarcerated). For example, women who become pregnant during the medication period will be immediately withdrawn from study medication administration. Participants who must start treatment with medications that may interact with BUP 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 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
- Hypersensitivity reaction to the study product
- Requirement for opioid analgesics for general anesthesia for surgery
- Increase in LFT or decrease in platelet test results that may increase participant health risks. This includes any of the following: AST/ALT results >5 times upper limit of normal, total bilirubin >2 times upper limit of normal, or platelets below 75 x 10^3/µL

A physician (MD or DO) who serves in the Site PI or Medical Clinician study role must make the decision to withdraw a participant from study medication. Also, participants may decide at any time that they no longer wish to continue to receive medication or participate in the study.

Given the long-term nature of BUP-Inj, a taper is not possible, even if the Medical Clinician determines medication discontinuation is warranted for medical or psychiatric reasons. In the event a participant becomes pregnant during the medication period, the pregnant participant will be immediately discontinued from further study medication administration, referred for obstetric care, and the pregnancy followed until an outcome is known.

In the event a participant is withdrawn from further administration of study medication, referrals to treatment programs or recommendations for medical care will be provided as appropriate. Unless consent is officially withdrawn, study staff will encourage participants who are withdrawn from study medication or who opt out of study medication to continue completing twice weekly visit assessments and complete all study assessments throughout the duration of the medication phase (Weeks 1-12) and the follow-up phase (Week 16). If a clinically significant finding is identified (including, but not limited to changes from participant's baseline status prior to receiving study medication) after enrollment, the Medical Clinician will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE) if it meets the definition specified in Appendix A of the protocol.

10.11 Blinding

10.11.1 Type of Blinding

This is a double-blind, placebo-controlled study. There are differences in appearance for active and placebo injection products and thus additional procedures, including use of unblinded staff to administer the injections and physical shielding of the injection syringe, will be utilized to maintain the blind for both participants and blinded study staff.

10.11.2 Maintenance of the Blind

Only the DSC staff overseeing the random assignment schedule, a few CCC staff, the central research pharmacy staff preparing the study medication, and a single study staff role (Unblinded Medical Personnel) to administer the injections are unblinded; all other study personnel and participants will remain blinded to treatment arm until the nationwide completion of the trial and the database is formally locked. Detailed information on the study procedures regarding the double-blinding will be contained in a standalone Blinding Management Plan and Study Site Blinding Plan. A DSMB will review study data throughout the course of the trial in a blinded fashion (e.g., masked treatment assignments), however they can request to be unblinded at any time.

10.11.3 Breaking the Blind

In rare cases, it may be necessary to break the blind for a particular study participant before completion of the trial (e.g., emergency surgical procedures or other medical necessity). Any participant who experiences a non-fatal overdose during the study will be unblinded and referred to treatment. The participant will also be withdrawn from all medication aspects of the study. The request to break the study blind for an individual participant will be made by the Medical Clinician after consultation with the Lead Investigator(s). Unblinding the participant should occur only in cases of medical emergency when knowledge of the treatment group/investigational agent may be necessary for clinical management and decision-making. The decision to break the blind for a participant will be made jointly by the Clinical Coordinating Center (CCC) Medical Monitor and at least one of the Lead Investigators.

10.12 Participant Reimbursement

Participants will be reimbursed for their participation in this study. Reimbursement will be in accordance with the IRB of record's policies and procedures, and subject to IRB approval. Study participants will be provided with study medication and cognitive behavioral therapy at no cost. In addition, participants will receive gift cards or cash (based on local site requirements) as reimbursement for time, travel, parking, and other costs borne by the participant. Total reimbursement possible is suggested to be approximately $735, but can be increased based on the local site's standard practice.

11.0 STUDY ASSESSMENTS

11.1 Table of Assessments

Study Phase	Prescreening	Screening	Medication Phase												Follow-up
Study Week		-21 to -1	1	2	3	4	5	6	7	8	9	10	11	12	16
General Measures															
Verbal Consent	X														
Prescreening Interview	X														
Informed Consent		X*													
Demographics		X*													
MINI Modules		X*													
Sexual Risk Behaviors			X					X[2]						X[2]	
Self-Report of HIV Testing (PhenX Tier 1)		X*													
Self-Report of Hepatitis Testing and Treatment (PhenX Tier 1)		X*													
Alcohol and Substance Use (PhenX Tier 1)		X*													
Medical and Psychiatric History		X*													
Safety Measures															
Physical Examination		X*												X[2]	
Electrocardiogram		X*												X[2]	
Medication Side Effects			X[2]												
Buprenorphine-XR/Placebo Injection Site Evaluation				X			X[2]				X[2]			X[2]	
Concise Health Risk Tracking (CHRT) - Participant		X*	X	X	X	X	X	X	X	X	X	X	X	X	X
Concise Health Risk Tracking (CHRT) – Clinician Rated Module[B]		X*						X						X	
Urine Pregnancy Test[B]		X*	2X[A]				X[A]				X[A]			X	X
Pregnancy and Birth Control Assessment		X*	X[2]				X				X			X	X
Vital Signs		X*	2X[A]	X	X	X	X[A]	X	X	X	X[A]	X	X	X	X
Prior and Concomitant Medications		X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Adverse Events, Serious Adverse Events and Medical Review		X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Clinical and Efficacy Measures															
Urine Drug Screen		X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Buprenorphine Urine Drug Screen		X+													

Study Phase	Prescreening	Screening	Medication Phase												Follow-up
Study Week		-21 to -1	1	2	3	4	5	6	7	8	9	10	11	12	16
Timeline Followback		X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Visual Analog Scales for Methamphetamine and Opioid Craving		X+	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Opiate Withdrawal Scale		X[D]	X^				X				X			X	X
Subjective Opiate Withdrawal Scale			X^				X				X			X	X
Inventory of Depressive Symptomology-Self-Report			X	X	X	X	X	X	X	X	X	X	X	X	X
Generalized Anxiety Disorder Scale			X	X	X	X	X	X	X	X	X	X	X	X	X
Concise Associated Symptoms Tracking Irritability			X	X	X	X	X	X	X	X	X	X	X	X	X
Dimensional Anhedonia Rating Scale			X				X				X			X	X
Amphetamine Cessation Symptom Assessment		X*	X	X	X	X	X	X	X	X	X	X	X	X	X
Perceived Stress Scale			X				X				X			X	X
Pain Frequency, Intensity, and Burden Scale			X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive Behavioral Therapy Documentation			X	X	X	X	X	X	X	X	X	X	X	X	
Iowa Gambling Task and Documentation		X*													
Treatment Effectiveness Assessment														X[2]	
Cannabis Use Assessment			X												
Tobacco Use History (PhenX Tier 1)			X											X[2]	
Quality of Life (PhenX Tier 1)			X											X[2]	
Semi-Structured Qualitative Interview			X[E]												
Adherence Measures															
Buprenorphine-XR/Placebo Injection			X[2]				X				X				
BUP-SL Dispensing			X[1]												
Laboratory Evaluations															
Urine Screening for Disease		X*												X	
Complete Blood Count		X*												X	
Blood Chemistry		X*													
Liver Function Tests		X*												X	
Disease Serology		X*												X	
Blood Sample for UTSW Repository		X*												X	
Blood Sample for NIDA Genetic Testing and Family Origin							X[C]								

Study Phase	Prescreening	Screening	Medication Phase												Follow-up
Study Week		-21 to -1	1	2	3	4	5	6	7	8	9	10	11	12	16
Buprenorphine Blood Levels							X[A]				X[A]			X	
Administrative and Other Forms															
Locator Form		X*			X			X			X			X	
Eligibility - Randomization (Enrollment Form)			X												
Visit Documentation Form		X+	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Mental Health Follow-Up Assessment[B]															
End of Medication Form														X[2]	
Protocol Deviation and Review[B]															
Treatment Satisfaction															X
Study Completion															X

NOTES:

X* = once during screening

X+ = at each screening visit

X^ = at each induction visit, including if additional induction visits are required during the medication phase, and on the day of first injection

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

2X = a procedure or assessment performed twice per week

X^1 = on the day of induction only

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

[A] Must be collected prior to administration of any medications at the visit

[B] Completed as applicable

[C] If consent is provided, collect sample on day of 2nd injection if possible. Otherwise, to be collected at any future visit with blood draw.

[D] Collected at screening visit(s) with a UDS negative for opioids and on the day of expected randomization

[E] If verbal consent is provided, interviews can be conducted anytime after the last administration of any medication (sublingual or injectable medication). Note: Participants must have taken at least one dose of sublingual medication to be eligible for the interview.

11.2 General Measures

11.2.1 Prescreening Interview

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

11.2.2 Informed Consent

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

11.2.3 Demographics

The Demographics form will incorporate PhenX Core 1 items and will collect information about demographic characteristics of the participant, including sex, gender, date of birth, ethnicity, race, education, employment status, and marital status.

11.2.4 Mini International Neuropsychiatric Interview (MINI) Modules

The MINI will be used to provide diagnostic information to support the inclusion/exclusion criteria related to both MUD and OUD[46]. Specific modules will be used to assess the presence and history of a major depressive episode (MDE) or major depressive disorder (MDD), suicide behavior, bipolar disorder, alcohol use, and substance use.

11.2.5 Sexual Risk Behaviors

The Sexual Risk Behaviors assessment will 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, drug paraphernalia, and alcohol during sex.

11.2.6 PhenX Tier 1

The Substance Abuse and Addiction Collection of the PhenX Toolkit (http://www.phenxtoolkit.org) includes measures that are being adopted across NIDA-funded research. The Core Tier 1 collection includes measures for demographics (age, ethnicity, gender, race, educational attainment, employment status, and marital status), body mass index, quality of life, and HIV risk and status; substance use measures include age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco and other substances. Where possible, answers to Core Tier 1 questions are populated from the answers to questions from other assessments, but some additional questions may be incorporated to accommodate this requirement. Quality of Life and Tobacco Use History are 2 such additions. In addition, although not considered a part of the PhenX toolkit, self-report of hepatitis testing and treatment will be collected in conjunction with the PhenX self-report of HIV status assessment.

11.2.7 Alcohol and Substance Use

The Alcohol and Substance Use form will be completed at screening to incorporate PhenX Core Tier 1 items[47]. The participant will be asked whether they have ever used alcohol and/or various substances as well as the 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.

11.2.8 Medical and Psychiatric History

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

11.3 Safety Measures

11.3.1 Physical Examination

A physical examination will be completed to collect baseline information regarding the participant's physical health and to ensure there are no exclusionary medical conditions. The exam will include an examination of the participant's abdominal area and the planned injection site(s) to assess appropriateness for subcutaneous injections. The exam will be completed again at study exit to confirm the health of the participant.

11.3.2 Electrocardiogram (ECG)

A 12-lead ECG will be administered to assist in determination of participant eligibility and again to assess safety. The ECG tracings will be reviewed by a 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 Medical Clinician.

11.3.3 Medication Side Effects

At the visit after the participant receives sublingual buprenorphine (Week 1, 2nd Visit), participants will be asked to report any expected adverse reactions experienced after taking SL-BUP using the Medication Side Effects form. The self-administered form lists different expected adverse reactions, and participants will rate each possible reaction according to the severity of their perceived reaction. Events that are documented on the Study Medication Side Effect form will not be duplicate-reported as AEs unless one or more SAE criteria are met.

11.3.4 Buprenorphine-XR/Placebo Injection Site Evaluation

Unblinded medical personnel will examine the injection site during the study visit following each subcutaneous injection. These examinations will usually occur at visits immediately following injections but should occur at the next attended visit if any of the aforementioned visits are missed. Additional monitoring may also be required. Participants will be asked to immediately report any injection site reactions to allow evaluation, monitoring, and possible referral, as needed. In the event an injection site reaction is reported by a participant or an abnormality is identified during an injection site evaluation, it will be captured on this form. All injection site reactions should be documented on the Buprenorphine-XR/Placebo Injection Site Evaluation form throughout study participation (from first injection through Week 16 Follow-up). If the abnormality results in a

Serious Adverse Event (SAE), the Adverse Event forms must also be completed. Well-developed precautionary procedures will be followed to avoid adverse events associated with injectable study medication administration. For example, abdominal area will be assessed during the physical exam at screening to assure that subcutaneous depot administration is feasible. Individuals whose abdominal area is unsuitable for subcutaneous depot injection will be excluded from the study.

11.3.5 Concise Health Risk Tracking (CHRT) —Participant (CHRT-SR)

The CHRT-SR is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors[48]. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA)[49]. The CHRT-SR will assess high risk suicidal ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of, thoughts of how and/or a specific plan to commit suicide). A positive response will prompt completion of the Concise Health Risk Tracking (CHRT) – Clinician Rated Module before the participant leaves the clinic, and completion of the Mental Health Follow-up Assessment form.

11.3.6 Concise Health Risk Tracking (CHRT) —Clinician Rated Module (CHRT-CR)

The CHRT-CR is a brief clinician-rated assessment of suicidal thoughts, actions, or related behaviors. The assessment will be completed once during Screening, Week 6, and Week 12 during the same visit as the CHRT-SR. Additionally, the Medical Clinician should complete the assessment during any visit for which it is clinically indicated and must complete the CHRT-CR when a participant indicates high-risk suicidal ideation on the CHRT-SR (see assessment detail for specific criteria).

11.3.7 Urine Pregnancy Test, Pregnancy and Birth Control Assessment

For biologically female participants, who are of childbearing potential as defined in the MOP, urine pregnancy test (UPT) administration, test results, and self-reports of birth control method(s) will be documented during screening. A UPT will be performed at the first screening visit to confirm that a woman is not pregnant before proceeding with screening. A UPT will be performed to confirm that a woman is not pregnant before receiving any study medication at randomization, before receiving an injection at each subsequent visit, at the end of the medication phase, and at Week 16. A UPT may also 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 medication, given an appropriate referral, and followed until resolution of the pregnancy. Self-reports of birth control method(s) will be documented if applicable at each injection visit during the medication phase, at the end of the medication phase, and at Week 16.

11.3.8 Vital Signs

Vital signs (e.g., body temperature, blood pressure, pulse, respiration rate) will be collected at least once during screening. During study medication injection clinic visits, vitals will be collected

before participants receive the study medication. On non-injection clinic visits, vitals should be collected weekly. Following the first administration of sublingual BUP and following the first BUP-Inj, additional vital signs will be collected after medication administration to monitor for participant medication tolerance and safety. Vital signs can be repeated to confirm the reading or on more frequent intervals, as clinically indicated.

11.3.9 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. Participants may be excluded based on medications reported during screening. At subsequent visits, the form will document medications taken since the previous data collection visit. Participants will be instructed to contact the Medical Clinician before taking any non-study medications, including prescription medications, over-the-counter preparations, and herbal supplements, during the course of the study.

11.3.10 Adverse Events, Serious Adverse Events, and Medical Review

Medical or psychiatric adverse events (AEs) will be collected by inquiring of participants, for example: “How have you been feeling since your last visit?”, and both elicited or spontaneously reported AEs should be recorded at each visit after consent, according to the adverse event reporting definitions and procedures. After randomization, for participants who report opioid use on Timeline Followback or who have a positive urine drug screen for opioids the Medical Clinician will offer facilitated linkage to MOUD. If interested, participants would be withdrawn from the medication aspect of the study. In the event that participants decline MOUD, this will be recorded in the participant’s study record. If an AE or abnormality suggests medical or psychological deterioration, it will be brought to the attention of the Medical Clinician (MD or DO) for further evaluation. All AEs and SAEs will be medically managed, reported, and followed in accordance with applicable regulatory requirements, including any required reporting to the DSMB. Adverse event (medical and/or psychiatric) assessment will initiate with participant written consent and follow-up of ongoing adverse events will continue through resolution or 30 days post last study visit.

11.4 Clinical and Efficacy Assessments

11.4.1 Urine Drug Screen (UDS)

Urine samples will be collected at every clinic visit. Urine drug screen (UDS) testing will be performed on site using a Federal Drug Administration (FDA)-cleared for use one-step urine drug dip card and/or dipsticks following the manufacturer's recommended procedures. Fentanyl dipsticks are not FDA cleared; therefore, results cannot be used for clinical care. Results can only be used to add to the research database to characterize a study population.

The UDS will test for the presence of fentanyl, opiates (including heroin, morphine, codeine), oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamine, marijuana (THC), methadone, phencyclidine (PCP) 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. If the only out of range value from the first sample is a high specific gravity on the adulterant test strip and there are no visible precipitants, this sample may be considered unadulterated and can be drug tested. If the specimen is considered adulterated, the first urine sample will be discarded, and the participant will be asked to provide another sample following oral hydration. Similar to the first, 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 unadulterated 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.

During screening and on the day of randomization, urine will also be tested to evaluate urine BUP levels to confirm inclusion/exclusion criteria. 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.

11.4.2 Timeline Followback (TLFB)

The Timeline Followback procedure[50] will be used to elicit the participant's self-reported use of substances, including MA, opioids, and MA/opioid co-use during the screening phase and throughout study participation. During the screening phase, this form will be used to assess substance use for the 30-day period prior to written consent. During the trial, TLFB will be administered to document the participant's self-reported use of substances for each day since the previous TLFB assessment. For participants who report opioid use or who have a positive urine drug screen for opioids during the trial, Medical Clinicians will offer them the opportunity to withdraw from the medication aspects of the trial and to initiate MOUD through a referral to appropriate care. In the event that participants decline this offer, this will be recorded in the participant's study record.

11.4.3 Visual Analog Scales for Methamphetamine and Opioid Craving

Participants' craving for methamphetamine and opioids will be documented on visual analog scales (VAS) that ranges from 0 (no craving) to 100 (most intense craving possible)[51].

11.4.4 Clinical Opiate Withdrawal Scale (COWS)

Participants' signs and symptoms of opiate withdrawal will be documented with the Clinical Opiate Withdrawal Scale (COWS), which is an 11-item scale administered by a Medical Clinician that can determine the stage or severity of opiate withdrawal and assess the level of physical dependence on opioids[52].

11.4.5 Subjective Opiate Withdrawal Scale (SOWS)

Participants will self-assess their symptoms of opioid withdrawal through the Subjective Opiate Withdrawal Scale (SOWS), which contains 16 symptoms whose intensity are rated on a scale of 0 (not at all) to 4 (extremely)[53].

11.4.6 Inventory of Depressive Symptomology - Self-Report (IDS-SR)

Participants' depressive symptoms will be assessed through the Inventory of Depressive Symptomology - Self-Report (IDS-SR), which is a 30-item questionnaire measuring depressive symptoms on a four-point scale from 0 to 3[54]. Responses of *2* or *3* on question 18 (Thoughts of Death or Suicide), will prompt a clinician assessment for suicide risk before the participant leaves the clinic, and completion of the Mental Health Follow-up Assessment form.

11.4.7 Generalized Anxiety Disorder Scale (GAD-7)

Participants' anxiety symptoms will be assessed through the Generalized Anxiety Disorder Scale (GAD-7), which is a 7-item scale that can be summed to produce a score that relates to mild, moderate, or severe anxiety[55].

11.4.8 Concise Associated Symptoms Tracking Irritability Scale (CAST-IRR)

Participants' associated mood symptoms will be assessed using a version of the Concise Associated Symptom Tracking Scale (CAST-IRR), a 10-item self-report scale that assesses irritability[56,57].

11.4.9 Dimensional Anhedonia Rating Scale (DARS)

Participants' anhedonia will be assessed using the Dimensional Anhedonia Rating Scale (DARS), a 17-item scale that measures desire, motivation, effort and pleasure[58].

11.4.10 Amphetamine Cessation Symptom Assessment (ACSA)

Participants' symptoms of amphetamine withdrawal will be assessed through the Amphetamine Cessation Symptom Assessment (ACSA), a 16-item scale that assesses severity of withdrawal from amphetamines[59].

11.4.11 Perceived Stress Scale (PSS)

Participants' perceived level of stress will be assessed with the Perceived Stress Scale (PSS), a 10-item self-administered scale that is used to measure an individual's level of perceived stress in the past month[60].

11.4.12 Pain Frequency, Intensity, and Burden Scale (P-FIBS)

Participants' pain will be assessed through the Pain Frequency, Intensity, and Burden Scale (P-FIBS), a 4-item scale that measures pain symptoms related to frequency, intensity, and burden[61].

11.4.13 Cognitive Behavioral Therapy Documentation

This form will note the completion of cognitive behavioral therapy sessions and if the participant is attending any mutual help support groups.

11.4.14 Iowa Gambling Task (IGT) and Documentation

The Iowa Gambling Task is a computer task of impulse inhibition. Psychology Experiment Building Language (PEBL) 0.14 computerized version of the IGT will be used[62]. It consists of four virtual decks of cards, A, B, C, and D, each associated with a unique combination of short-term fixed rewards and probabilistic losses, in addition to an associated long-term net payout. Riskier decks (A and B) present short-term high-reward and high-loss contingencies, with consistent choices of such decks yielding low cumulative totals. In contrast, optimal decks (C and D) are linked to short-term low-reward and low-loss contingencies, yielding moderately high cumulative totals. The objective of the IGT is to maximize long-term cumulative payout earned on the task by learning to shift or avoid selection of riskier, disadvantageous decks A and B and favor safer, more advantageous decks C and D within 100 trials. Results from this task will be added to an eClinical documentation form.

11.4.15 Treatment Effectiveness Assessment

The Treatment Effectiveness Assessment is a 4-item self-administered assessment that uses a Likert scale (1-10) to document changes in four life domains: substance use, health, lifestyle, and community[63].

11.4.16 Cannabis Use Assessment

This form assesses participants' recreational and medical cannabis/marijuana use frequency over the past 12 months, including reasons for use (e.g., to address medical/psychological concerns, to replace other substances or medications), method of administration, and perceived harm or benefit associated with use.

11.4.17 Tobacco Use History

The Tobacco Use History assessment will incorporate PhenX Core Tier 1 items[47]. Tobacco use items assessed include lifetime use, 30-day quantity and frequency, and age of first tobacco use.

11.4.18 Quality of Life

Quality of Life will be assessed using items from the PhenX Core Tier 1[47]. Participants will be asked to provide ratings of general health, physical health, and mental health during the past week.

11.4.19 Semi-Structured Qualitative Interview

Participants who have taken at least one dose of sublingual medication are eligible for a qualitative interview, which allows for an open conversation about the participant’s experiences taking the sublingual and injectable medications. The goal is to understand processes and experiences taking the medication and whether these experiences may influence their responses to methamphetanie and their decision to seek treatment in the future. Qualitative interviews will be

conducted using a interview guide, by site and/or LN staff, and recorded via a video and audio-conferencing platform (e.g., Zoom).

11.5 Adherence Measures

11.5.1 Buprenorphine-XR/Placebo Injection

This form will document the in-clinic administration of injectable study medication and will be completed at each visit when injectable medications are administered throughout the study. All required REMS procedures will be fully detailed in the MOP and will be explicitly followed.

11.5.2 BUP-SL Dispensing

This form will document the dispensing of sublingual buprenorphine and will be completed at each visit when sublingual medications are administered throughout the study. All required REMS procedures will be fully detailed in the MOP and will be explicitly followed.

11.6 Laboratory Evaluations

Specific instructions detailing the preparation, handling, and storage of specimens will be detailed in the Manual of Operations (MOP).

11.6.1 Urine Screening for Disease

Urine samples will be collected and submitted to screen for the sexually transmitted infections chlamydia and gonorrhea. An accredited local laboratory (College of American Pathologists or equivalent) that meets Clinical Laboratory Improvement Amendments (CLIA) guidelines will perform testing, provide normal values, and provide proof of lab certifications.

11.6.2 Complete Blood Count, Blood Chemistry, and Liver Function Tests

Complete blood counts (CBC), blood chemistry (BUN and creatinine), and liver function tests (AST, ALT, ALP, and bilirubin) will be performed to help determine eligibility at screening. A CBC and LFTs will be repeated for safety monitoring in the final week of the medication phase. 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.

11.6.3 Disease Serology

Serology for HIV and Hepatitis C will be performed at screening and will be repeated ideally during the final week of the medication phase. 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.

11.6.4 Blood Sample for UTSW Repository

Participants will have approximately 27 mL (2 tablespoons) of blood collected during screening and in Week 12 to be stored at the UTSW Central Repository for later evaluation of blood-based factors that may affect treatment outcomes. Participants may consent to allow these samples to be used in future genetic research.

11.6.5 Blood Sample for NIDA Genetic Testing and Family Origin

NIDA CCTN has requested that samples for genetic analysis be collected for all new CTN pharmacotherapy trials. Randomized participants who provide consent for genetic testing will have approximately 27 mL (2 tablespoons) of blood drawn for genetic analyses and will complete a Family Origin form. This sample will ideally be collected on the day of the second injection. If the sample cannot be collected on the day of the second injection, the sample may be collected at any other future visit with a blood draw. The blood sample will be sent to the NIDA Genetics Consortium Repository for storage and future analysis. The blood sample will be coded and only the local investigators will know the true identity of the participant providing the blood sample.

The Family Origin Form is designed to be interviewer administered. It collects information about the participant and her/his biological family members' race/ethnicity, place of birth, and ancestry. If a participant does not know the information requested, the participant may answer *unknown*.

11.6.6 Buprenorphine Blood Levels

Existing data suggests that metabolism of BUP may differ between Caucasian and minority populations. BUP is heavily metabolized by cytochrome P450 (CYP) hemoenzymes, specifically subfamily CYP3A4. This is the primary enzyme that is noted as a key drug-drug interaction site for the use of BUP and specifically the injectable version, Sublocade™, which will be used in this study. Polymorphisms of CYP3A4 have been shown to affect the metabolism of BUP[64], and may play more of a role for African-Americans due to the enrichment of the CYP3A4*1B variant, which is present in 66% of African-Americans in contrast to 4% of Europeans and 0% of Asian populations[65]. An accelerated metabolism of OUD treatments, including BUP, has been shown in patients with CYP3A4*1B compared to the wild-type CYP3A4*1A variant, and those patients reported requiring higher doses of BUP to obtain full clinical effects[66]. The majority of these patients were African-American and those that were classified as ultra-metabolizers based on CYP3A4 phenotype also reported withdrawal symptoms more frequently than those classified as intermediate or extensive metabolizers.

The evidence for key pharmacogenomic interactions affecting treatments used for opioid use disorder are extensive and growing[67]. Investigation of the contribution of this CYP3A4*1B variant in the metabolism of BUP has to date been limited. Evidence for this polymorphism to affect drug response is found in other pharmacogenomic interactions[68] and an effect is detected in Caucasian populations with lesser variant prevalence. Thus, obtaining data further supporting understanding of this pharmacogenomic effect of BUP in African-Americans is timely and necessary. Given the pilot nature of this study and the preliminary examination of these differences in metabolism, this study will only compare blood levels of BUP between racial/ethnicity groups and not directly examine genetic information. In order to explore how differences in metabolism may affect the outcomes of the study, blood samples will be collected to test for buprenorphine and metabolites levels.

11.7 Administrative and Other Forms

11.7.1 Locator Form

A locator form obtains information to assist in finding participants during screening, treatment and at follow-up. This form collects the participant's current address, email address, phone numbers, etc. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends who may know how to reach the participant are collected, as well as additional participant information such as social security number, driver's license number, and other information to aid in searches of public records. This information will be collected at screening and should be updated when changes occur in addition to the required timeframes to confirm information noted on the Table of Assessments. No information from this form is used in data analyses, nor is this information captured in the data capture system.

11.7.2 Eligibility-Randomization (Enrollment Form)

This 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 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. The Enrollment form is to be completed in the electronic data capture system after all screening procedures are complete. Final eligibility will be confirmed on expected day of randomization. Eligible participants will be randomized; ineligible participants will be excluded and deemed screen failures.

11.7.3 Visit Documentation

This form documents visit attendance, non-visit attendance, and missed visits. This assessment has been developed to document visits that could occur out of window, off-site, or missed due to COVID-19. This is a visit-based form expected at all visits in which we would typically have a regular missed visit form. If a visit did not occur for any reason, this form will capture the reason for the missed visit. Completing this and indicating that the visit did not occur will remove the requirement for all assessments scheduled for that visit. Active tracking and follow-up should be performed for all missed visits. The form also captures specific data collection settings if applicable, such as in clinic, off-site, or remote.

11.7.4 Mental Health Follow-up Assessment

This assessment must be completed if the participant endorses high risk suicidal ideation on either the Concise Health Risk Tracking (CHRT)—Participant (CHRT-SR) Suicidal Behavior Evaluation or on the Inventory of Depressive Symptomology - Self-Report (IDS-SR). Any response of *agree* or *strongly agree* on question 14, 15, and/or 16 of the CHRT-SR, and/or any response of *2* or *3* on question 18 of the IDS-SR will be considered as a high risk suicidal ideation and will require the completion of the Mental Health Follow-up Assessment form. The completion of the Mental Health Follow-up Assessment form documents that a physician (MD or DO) who serves in the Site PI or Medical Clinician study role has been notified. Evaluation of the participant by a physician (MD or DO) who serves in the Site PI or Medical Clinician study role will be conducted according to the site-specific SOP. Only one Mental Health Follow-up Assessment form will be completed per study visit. If a physician (MD or DO) who serves in the Site PI or

Medical Clinician study role is unavailable, a non-study physician (MD or DO) may complete the assessment. If a non-study physician is unavailable, the site should refer to their site-specific SOP for additional instructions.

11.7.5 End of Medication

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 final Medication Phase visit.

11.7.6 Protocol Deviation and Review

These forms should be entered into the electronic data capture system whenever a protocol deviation occurs. These forms 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. This form will also capture if protocol deviations were a result of COVID-19 specific restrictions.

11.7.7 Treatment Satisfaction

Satisfaction with medication and other study procedures will be recorded on the Treatment Satisfaction form completed at the Week 16 visit. This form will be used to evaluate the acceptability of the medication.

11.7.8 Study Completion

This form tracks the participant's status in the study. 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. It is expected to be completed at the Week 16 visit or once the Week 16 follow-up visit window lapses for participants who do not complete this final follow-up. This form is used in data analyses to address variables such as treatment retention and completion. This form also provides a location for the Site PI attestation of review of all study data.

12.0 MEDICATION PACKAGING / HANDLING / STORAGE / ACCOUNTABILITY

12.1.1 Study Medication Management

Each research site is required to observe local, state, and federal regulations regarding receipt, custody, dispensing, and disposition of all study medications. Each site will maintain an adequate supply of unexpired study medications on site.

Appropriately qualified and trained study personnel maintain accurate and current accounting of all study medication by utilizing drug accountability records which are made available for review by study monitors and other appropriate research personnel.

Accurate drug accountability records:

- Demonstrate that the study medication was dispensed according to the protocol.
- Document receipt of the study medication, date, lot # and expiration date (if provided), quantity and dosage.
- Account for unopened, un-dispensed, unused, returned, wasted or broken medication.
- Dosing logs will record participant ID #, date dispensed, drug name, lot # and amount dispensed.
- Indicate who dispensed or handled the study medication.
- Temperature logs should show a daily record of medication storage temperature.

12.1.2 Dispensing of Study Medication

All injectable study medications shall be prepared by unblinded research site staff members or pharmacist appropriately trained and authorized to prepare and administered only by an unblinded licensed/certified medical practitioner (RN, LVN, MA, or other healthcare provider) appropriately trained and authorized to inject these study medications per local and federal regulations.

12.1.3 Study Medication Storage

Study medication should be stored in compliance with federal, state, and local laws and institutional policy. Study medication is stored in a secured location under the conditions specified by the package insert(s)/product guide.

12.1.4 Used/Unused Medication

Unused study medication will be logged into a perpetual inventory of study medication. Damaged, expired, or unused study medication will be accounted for by the NIDA contract monitor and sent to the study central pharmacy which will arrange with a reverse distributor for eventual destruction due to the sublingual buprenorphine and BUP-Inj being scheduled medications. Expired sublingual buprenorphine and Sublocade™ (BUP-Inj) must be returned to the central pharmacy after a full drug accountability is conducted with the NIDA contract monitors/CRAs.

Other ancillary medications will not be required to be returned by a participant. If any is returned by choice of the participant, these ancillary medications will be destroyed on site or sent for destruction per local institutional policies.

12.1.5 Lost Medication

The sublingual buprenorphine used during the induction period will be the only medication that will be dispensed to participants. At the discretion of the site study treatment team, very limited replacement of study medications is permitted.

12.1.6 Medication Packaging

The study medication and placebo will be obtained from the study medication manufacturer and sent to the central pharmacy managed by the CCC. Details of the blinding techniques, procedures, and medication packaging will be described in detail in the Manual of Procedures (MOP).

13.0 GENETIC SAMPLING

Participants may provide consent to optional genetic testing. If this consent is provided, the blood samples stored at the UTSW Repository may be used for genetic testing. Additionally, this consent would permit the collection of an additional blood sample to be provided to the NIDA CCTN for genetic testing.

14.0 TRAINING REQUIREMENTS

14.1 Overall

A comprehensive Training Plan will be developed to incorporate general training, study-specific training, mechanisms for competency assessment as well as a detailed description of training, supervision, and fidelity monitoring procedures. The Investigative Team is responsible for the development of a comprehensive Training Plan, instructional material, and delivery of the training, with the team comprised of the Lead Node, CCC, DSC, as well as other participating nodes and subject matter experts, as applicable.

The CTN-0110 study staff will be trained as specified in the study Training Plan. Training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP) as well as protocol-specific training on assessments, medication management for pharmacological studies, study interventions, safety and safety event reporting, study visits and procedures, data management, quality assurance, laboratory procedures, etc. The Lead Node is primarily responsible for development and delivery of study-specific training related to the study intervention(s) and procedures. The CCC is responsible for the development and delivery of non-intervention training, including regulatory and laboratory procedures, safety and safety event reporting, quality assurance and monitoring, etc. The DSC is responsible for training related to data management (DM), the electronic data capture system, and good DM practices. Other parties will contribute as needed based on the subject matter and material to be covered. The various sub-teams will collaborate to deliver quality instructional material designed to prepare research staff to fully perform study procedures based on the assigned research roles and responsibilities.

In addition to general and study-specific training, the Training Plan will include a description of the delivery methods to be used for each training module (e.g., via self-study, online, webcast, or teleconference). Study staff is required to complete institutionally required training per their research site, Institutional Review Board(s), and authorities with regulatory oversight. Tracking of training completion for individual staff as prescribed for assigned study role(s) and responsibilities will be documented. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

15.0 CONCOMITANT THERAPIES OR INTERVENTIONS

There are no concomitant therapies or interventions intended to treat substance use disorders allowed during participation in this trial.

15.1 General

During the trial, participants will be withdrawn from the study medication if they begin ongoing treatment with medications that are clinically relevant, such as CYP3A4 or CYP2C8 inducers or inhibitors (e.g., rifampicin, azole antifungals, macrolide antibiotics), Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone) or medications that put them at significant risk for development of serotonin syndrome while possibly taking BUP-Inj.

In addition, participants who have an intercurrent illness that requires treatment with opioid-containing medications (e.g., to manage postoperative pain) for more than three days will be withdrawn from the study medication but remain in the study.

15.1.1 Medications and Interventions Allowed During Trial

Ongoing medications that the participant is taking at the day of randomization will be allowed, unless specifically listed as exclusionary criteria. Medications additionally prescribed during the conduct of the trial or over-the-counter medications to manage conditions are also allowed, unless the Medical Clinician is concerned that the medications would then qualify as exclusionary criteria. All medications will be reported on the Prior and Concomitant Medications form (during all study visits) to provide a clear record that is available for analysis to ensure the integrity of the study outcomes. The only medications believed to affect the outcomes of this study are listed as exclusionary criteria. Participants are also allowed to attend mutual support groups, such as Narcotics Anonymous, during the trial but not engage in any other groups or treatments that are designed to treat substance use disorders.

16.0 STATISTICAL DESIGN AND ANALYSES

A formal Statistical Analysis Plan (SAP) will be written for this study but the general design and statistical strategies are described below.

16.1 General Design

16.1.1 Study Hypothesis

Administration of BUP-Inj will produce a significantly greater number of MA-negative UDS tests obtained during Weeks 9-12 of the 12-week long medication phase, relative to the PBO-Inj.

16.1.2 Primary and Secondary Outcomes (Endpoints)

The full descriptions of outcomes and the measures from which they are obtained are described in Section 7.0. The primary outcome measure is the number of MA-negative UDS results obtained during Weeks 9 through 12 of the medication phase as measured for the BUP-Inj and PBO-Inj conditions.

16.1.3 Randomization and Factors for Stratification

Participants will be randomized in a 1:1 ratio to BUP-Inj or PBO-Inj, using a permuted block design with random block sizes and stratified by enrolling site. A separate randomization plan will be developed with additional details regarding treatment allocation. Given that the study is double-blind, only certain staff at the DSC and CCC will be able to access individual treatment assignments and detailed information contained in a separate Blinding Management Plan.

16.2 Rationale for Sample Size and Statistical Power

A sample size of 246 was chosen for this study to provide 90% power to detect a statistically significant difference between the two treatments. Power was based on an effect size derived from the proportion of MA-negative urines during the last 4 weeks of Phase I of the ADAPT-2 study (CTN-0068) comparing the active treatment arm to the placebo arm. Imputing all missing data as positive, the relevant proportions in ADAPT-2 were 0.17 and 0.07) in the treated (AMC) and control (PBO) arms respectively, so we take the treatment effect of interest for MURB to be a risk difference of 0.10 corresponding to an odds ratio of 2.72. This outcome from the ADAPT-2 study was chosen because it was believed to be the most comparable available result using this substance-using population to the BUP-Inj outcome for this study.

To simulate data for CTN-0110, we first imputed all missing ADAPT-2 visits as UDS-positive for MA, then bootstrapped the ADAPT-2 participants, keeping the participant's site and visits together, thus respecting whatever temporal and site-dependent correlations might exist in the data. We assumed equal treatment allocation. To draw bootstrap samples of size N, we bootstrapped differently under null and alternative hypotheses as follows:

- Null: We treated the two simulated treatments the same way: for each of the N/2 simulated participants receiving that treatment, we flipped a fair coin to decide which ADAPT-2 arm (109 AMC and 294 PBO) to draw it from, and then drew it randomly with replacement from that arm.

- Alternative: For AMC, we drew N/2 observations randomly with replacement from the 109 AMC patients. For PBO, we drew N/2 observations randomly with replacement from the 294 PBO patients.

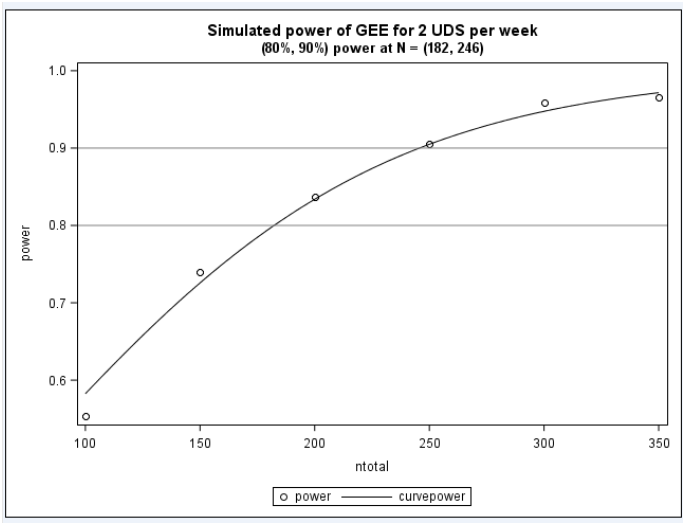
To simulate 2 UDS per week we used all 8 visits of a participant in order. The model under which we performed the power analysis is the same as that to be used for the primary analysis, discussed in Section 16.3.

Simulated power for the generalized estimating equation[69] is shown as a function of total N (N/2 in each arm) in Table 16.1 and in Figure 16.1, in which the total sample size required for power (0.8, 0.9) is interpolated from the simulated data using a logistic function, and estimated to be (182, 246).

Table 16.1: Simulated power for the GEE as a function of total N (N/2 in each arm)

Total N	Power
100	0.55
150	0.74
200	0.84
250	0.91
300	0.96
350	0.97

Figure 16.1: Logistic function fitted to simulated power for the GEE as a function of total N (N/2 in each arm)



16.2.1 Projected Number of Sites

A total of 4-8 sites will participate in the trial.

16.2.2 Projected Number of Participants per Site

It is anticipated that each site will randomize approximately 31-61 participants over the recruitment period. The enrollment for all sites will be competitive.

16.3 Statistical Methods for Primary and Secondary Outcomes

16.3.1 Primary Outcome

UDS will be collected twice a week during Weeks 9 through 12, or 8 assessments. For each assessment, the outcome will be 1 if the UDS is MA negative and 0 if the UDS is MA positive or missing. The probability of an MA negative UDS during Weeks 9-12 will be computed via a GEE approach postulating a binomial distribution with a logit link, an AR(1) correlation for the repeated observations of a single participant, and utilizing the robust (sandwich) estimator for the covariance of the regression betas. Despite other possible sources of variance such as random site effects, the regression coefficients will be asymptotically unbiased with consistent standard errors using this estimation strategy. The model will have a term for treatment group (BUP-Inj and PBO-Inj) as the between-subjects factor. The model will be used to compute an average probability of MA-negative UDS across Weeks 9 through 12 in each group. Letting y_{it} be an indicator of whether the UDS for participant *i* (*i*=1, …, *n*) at timepoint *t* during this evaluation period (*t*=1, …, 8), and z_i is an indicator of participant *i* being assigned to the BUP-Inj arm, the logistic model is given by

$$logit\ P(y_{it} = 1) = \alpha + \beta\, z_i.$$

The hypothesis will be tested by the statistical significance of the odds ratio using a two-sided test (i.e., $H_0: e^{\beta} = 1;\ H_1: e^{\beta} \neq 1$). An *a priori* alpha (i.e., type I error) of 0.05 will be used for this analysis.

SAS code to estimate the primary outcome follows:

```
proc genmod data = dat;
     class patid treat;
     model metneg(event = "1") = treat / dist = bin link = logit;
     repeated subject = patid / type = ar(1);
     run;
```

Where **patid** is the participant's unique identifier, **treat** is an indicator of being assigned to the BUP-Inj treatment arm, and **metneg** is an indicator of whether the UDS is negative for MA.

16.3.2 Secondary Outcomes (medication phase, Weeks 1-12):

1. *Alternate measures of methamphetamine use*: both

    a. MA Treatment Effectiveness Score (TES), as measured by number of UDS results negative for MA by condition, during Weeks 1-12 (score range 0-24) will be analyzed as count data, which typically follows a Poisson distribution.

However, we expect there will be more subjects with 24 negative UDS than would be expected based on the Poisson distribution (ceiling effect). Also, there may be more subjects with 0 negative UDS than determined by the Poisson distribution (floor effect). Given the presence of ceiling and floor effects a more flexible model is needed than the hurdle model or zero-inflated Poisson model that would typically be used with count data with floor effects. Therefore, a beta-binomial regression model is anticipated[70]. In this approach, the number of negative UDS is modeled as the number of 'successes' in 24 trials where each trial can result in a success or failure (UDS negative or positive) outcome. The probability of success across subjects is modeled with the beta distribution which is flexible enough to allow for a 'U' shaped distribution with both ceiling and floor effects or only ceiling effects depending on which parameters of the beta distribution are selected. The model will have terms for time, treatment group, treatment group by time interaction, baseline measure of the outcome, and any covariates. The primary hypothesis will be tested by significance of the main effect or interaction effect[71].

b. Self-reported days of MA use during Weeks 1-12 (score range 0-84) will be analyzed using TLFB data that will be collected in Weeks 1-12 with days of use counted over that period. Count data typically follow a Poisson or Negative Binomial distribution. However, we expect that there will be more participants with zero positive UDS than expected under these distributions (floor effect). We do not expect ceiling effects for this outcome. We will deal with the excess zeros using a hurdle model in which it is assumed that all participants have the potential to use drugs but "resistance" to drug use, or a hurdle, must be overcome before drugs are used. The existence of the hurdle results in an excess of participants with zero positive UDS[72]. The hurdle model will contain a random participant effect, treatment group (buprenorphine vs control), baseline number of use days (in the 30 days before written consent) and any other covariates needed to improve balance between the intervention and control groups. If the data are not zero-inflated, Poisson regression will be used.

2. *Measures of opioid use:* both

a. Opioid Treatment Effectiveness Score (TES), as measured by number UDS results negative for opioids by condition, during Weeks 1-12. Results from radio-immune assay strips will be used to measure opiates (OPI-300), oxycodone / synthetic opioids, fentanyl for each UDS and

b. Self-reported frequency of opioid use during Weeks 1-12. Reports of any opioid used will be combined into one measure that includes opiates, oxycodone and synthetic opioids, fentanyl and analogues for each report, will be analyzed using a hurdle model (ceiling effects are not expected) similarly as described for the secondary outcome 1b.

3. *Measures of MA and opioid co-use:* both

    a. MA and Opioid Treatment Effectiveness Score (TES), as measured by number of same-day UDS results negative for MA and opioids by condition, during Weeks 1-12 and

    b. Self-reported days of both MA and opioid use during Weeks 1-12. All data related to opioid use will be compiled as detailed in secondary outcome 2 and will be analyzed using a hurdle model (ceiling effects are not expected) similarly as described for the secondary outcome 1b.

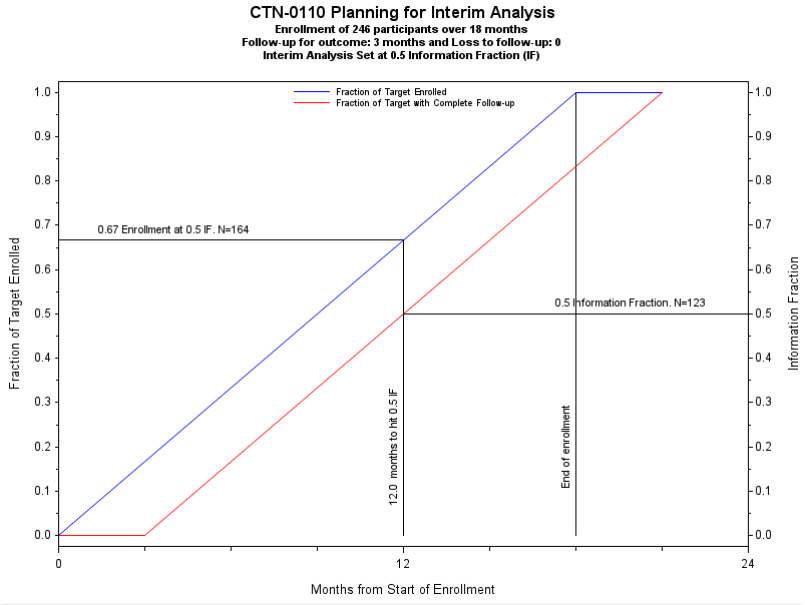
16.4 Significance Testing

The primary outcome will be evaluated using a two-sided test with a type I error rate of 5%. There are numerous secondary outcomes; however, multiple comparisons will not be adjusted for since these are not part of the study's primary objective.

16.5 Interim Analysis

When at least 50% of the final sample has attained endpoint assessment (i.e., Week 12), a sample-size re-estimation will be performed. Figure 16.2 shows sample sizes expected at the time of sample-size re-estimation, assuming recruitment is constant over time. The blue line in Figure 16.2 depicts recruitment, while the red line depicts attainment of primary endpoint. As noted previously, recruitment is anticipated to take 18 months to attain a sample size of 246. Primary endpoint data accumulates starting at month 3 and will terminate at month 21. Since missing UDS data will be assumed as MA-positive, the primary endpoint is always observed. Half of the 246 primary endpoints (i.e., 123 endpoints) will be attained at month 12, at which time a sample size re-estimation will be conducted. We expect at that time to have recruited 67% of our final sample size, or 164 of 246 participants.

Figure 16.2: Sample sizes during sample-size re-estimation.



The objective of sample size re-estimation is not to re-calculate the sample size using a treatment effect different from that posited during trial design, but rather to discover whether nuisance parameters, such as the site effect or the within-subject autocorrelation, were mis-specified, thus rendering invalid the original sample size calculation. Given that the study is double-blinded, only data from participants in the control (i.e., PBO-Inj) arm will be used in the re-estimation to preclude the need to break the blind during the conduct of the study. Modified bootstrapping will also be used for the sample size re-estimation as was done for the original sample size calculation. The unit of bootstrapping with be the entire participant history, together with the participant's site. Missing observations will be imputed to be MA-positive. Only control participants completed will be used in the sample size re-estimation bootstrap. There will be many bootstrap iterations. After each one, there will be a simulated test of the null hypothesis. The proportion of iterations in which the simulated two-sided test is significant at level 0.05 will be taken as the prediction of final power under the design alternative.

Participants with the endpoint assessment in the control arm will be randomly chosen with replacement to attain the desired sample size in the simulated control arm. In each bootstrap iteration, the entire simulated control arm will be recreated *de novo*. That is, the already-enrolled control participants will not be maintained together as a group within the simulated set of control participants.

To choose participants for the simulated treated arm, we will perform biased bootstrap sampling of the already-completed patients in the control arm. The method for performing biased bootstrap sampling will be discussed in the standalone Statistical Analysis Plan, but basically, some control patients will be preferentially chosen to allow Pr(success) in the simulated treated arm to be as desired. Biased bootstrap sampling will allow us to calculate power under the design alternative. More specifically, computer code will (1) estimate $\hat{p} = \Pr(success)$ in the control arm, (2) use biased bootstrap sampling of the participants in the control arm to force their mean simulated probability of success to be $\hat{p} + \Delta$, where Δ is the design treatment effect, namely 0.10. This can be done without explicitly calculating the observed treatment effect or revealing it to trial personnel.

The results of the sample size re-estimation will be presented to the DSMB, who will make recommendations to the Sponsor who will then decide what action, if any, should be taken. We anticipate re-estimation will be used only to increase trial recruitment, not to curtail it.

16.6 Exploratory Analysis

Exploratory analyses include:

1. *Measures of MA subjective effects*: both (a) MA withdrawal, as measured by scores on the Amphetamine Cessation Symptom Assessment during Weeks 1-12 and (b) self-reported MA craving as measured by the Visual Analog Craving Scales (VAS) during Weeks 1-12 will be analyzed by repeated-measures mixed-effects model. The model will have terms for time, treatment group, treatment group by time interaction, baseline measure of the outcome, and any covariates. Person effects will be random and all other effects fixed.

2. *Measures of opioid subjective effects*: All measures, (a) Observer rating of opioid withdrawal as measured by the Clinical Opiate Withdrawal Scale (COWS) on the day of randomization; each subsequent visit during induction in Week 1, if needed; prior to each injection in Weeks 1, 5, and 9; and at Week 12 ; (b) Self-reported rating of opioid withdrawal as measured by the Subjective Opiate Withdrawal Scale (SOWS) on the day of randomization; each subsequent visit during induction in Week 1, if needed; prior to each injection in Weeks 1, 5, and 9; and at Week 12; (c) Self-reported opioid craving, as measured by Visual Analog Craving Scales (VAS), during Weeks 1-12 will each be analyzed using repeated-measures mixed-effects models, with terms for time, treatment group, treatment group by time interaction, baseline measure of the outcome, and any covariates. Person effects will be random and all other effects fixed.
3. *Self-reported craving for MA and opioid co-use*: As measured by Visual Analog Craving Scales (VAS), during Weeks 1-12 will each be analyzed using repeated-measures mixed-effects models, with terms for time, treatment group, treatment group by time interaction, baseline measure of the outcome, and any covariates. Person effects will be random and all other effects fixed.
4. *Measures of mood, pain and stress*: All measures, (a) Changes in self-reported depressive symptoms as measured by the IDS-SR during Weeks 1-12, (b) Changes in self-reported anxiety symptoms as measured by the GAD-7 during Weeks 1-12, (c) Changes in self-reported mood symptoms as measured by the CAST-IRR during Weeks 1-12, (d) Changes in self-reported anhedonia as measured by the DARS during Weeks 1, 5, 9, and 12, (e) Changes in self-reported pain as measured by the P-FIBS during Weeks 1-12, and (f) Changes in self-reported stress as measured by the PSS during the Weeks 1, 5, 9, and 12 will each be analyzed using repeated-measures mixed-effects models, with terms for time, treatment group, treatment group by time interaction, baseline measure of the outcome, and any covariates. Person effects will be random and all other effects fixed.
5. *Retention*, defined as the number of visits (0-24) present and providing urine drug samples during Weeks 1-12 will be analyzed similarly as described for the secondary outcome.
6. *Measures of Infectious disease control, incidence, and risk*:
    a. Defined as the biomarkers measured at Week 12, remaining HIV-negative for those that started the trial HIV-Negative and remaining HCV-negative for those that started the trial HCV-Negative, will be analyzed using logistic regression with HIV status and HCV status as the outcomes, respectively, and treatment group and other covariates as predictors.
    b. Self-Reported HIV transmission risk behaviors measured at Weeks 1, 6 and 12, defined as (a) Self-reported number of new sexual partners, (b) Self-reported number of sexual partners with condomless sex who are serodiscordant or unknown serostatus, (c) Self-reported number of sexual partners with condomless sex with partners who are serodiscordant or unknown serostatus with whom illicit substance were used (chemsex), (d) For men, self-reported

number of male sexual partners, (f) Self-reported number of episodes sharing needles, and (g) Self-reported number of episodes sharing injection equipment and paraphernalia will each be analyzed using a repeated measures mixed effects model for count data outcomes. If zero-inflation is observed a zero-inflated poisson, negative binamial, or hurdle model will be used depending on which model best fits the data. However, if an outcome has low counts, we may collapse it into a binary (presence/absence) outcome. If the data are very sparse, we may collapse across weeks and use a logistic regression model.

7. *Measures of functioning*:
    a. Changes in self-reported assessment of Quality of Life (QoL) at Week 1 and Week 12 will be analyzed using repeated-measures mixed-effects model, with terms for time, treatment group, treatment group by time interaction, baseline measure of the outcome, and any covariates. Person effects will be random and all other effects fixed.
    b. Self-reported overall functioning as measured by the Treatment Effectiveness Assessment (TEA) at Week 12 will be analyzed using analysis of covariance.
8. *Measures of adverse events*: both (a) Number and severity of adverse events reported during Weeks 1-12 and (b) Number and outcomes (non-fatal, fatal) of overdose events during Weeks 1-12 will be analyzed using Chi-square tests for each measure of AEs.
9. Self-reported measures of alcohol, tobacco and other drug use on TLFB at Weeks 1, 5, 9, and 12, and UDS results of other substance use not quantified for primary or secondary outcomes will be analyzed using a repeated-measures mixed-effects model for continuous outcome (amount of use) or binary outcome (presence/absence of use). The models will have terms for time, treatment group, treatment group by time interaction, baseline measure of the outcome, and any covariates. Person effects will be random and all other effects fixed.
10. Urinalysis results indicating a new chlamydia or gonorrhea diagnosis at Week 12 will be analyzed using a logistic regression with the presence of a Week 12 diagnosis as the outcome and treatment group and other covariates and predictors.
11. IGT at screening as a predictor of treatment response will be analyzed using the primary outcome analysis being repeated with the addition of terms for baseline IGT performance and IGT by time interaction.

16.7 Missing Data and Dropouts

In the primary analysis, missing and drop-out urine drug testing data will be imputed as MA use. On trial completion we will consider sensitivity analyses to investigate the extent to which the results of the main analysis of the primary outcome depend on the assumptions made about missing values. An extremely simple approach imputes missing as non-use and re-analyzes the outcome. If the conclusions are the same, there is little else necessary to do, but this is unlikely. Multiple imputation (MI) is one way to explore more complex possibilities. In MI, non-missing data are used to impute missing data under a missing-at-random (MAR) assumption. MAR seems an

unlikely hypothesis in a substance use trial, but the missing-not-at-random (MNAR) hypotheses may be introduced to explore sensitivity as detailed below.

To explore MNAR alternatives, we shift the values of the imputations by a chosen shift value. We choose the shift value for the two arms of the trial separately. A p-value for the primary outcome can then be calculated for every shift pair via multiple imputation. The pair can be plotted on two axes: one axis for the control shift, and one for the treated shift. This generates a p-value surface showing regions in which the trial is significant or not as a function of the MNAR assumptions. The primary outcome is a single point on this surface. If the primary outcome is surrounded by a large region of MNAR assumptions that agree with the primary concerning the significance of the outcome, this will lend credence to the primary outcome. But if the primary outcome is close to points that disagree, this will cast doubt on the primary analysis' conclusion.

Sensitivity analyses will be done for secondary analyses where appropriate to determine the possible effects of missing data on the final results.

16.8 Demographic and Baseline Characteristics

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

16.8.1 Subgroup Analyses

Per NIH policy, subgroup analyses will be implemented to assess whether sex, race and/or ethnicity are effect modifiers. For each demographic, a model will be fit including an interaction with treatment assignment and the subgroup effect will be reflected by a two-sided test of whether the interaction regression coefficient is different from zero. Additionally, the treatment effect will be presented for each category of the demographic factor from these interaction models.

16.9 Safety Analysis

Treatment emergent adverse events (AEs), including treatment emergent serious adverse events (SAEs), will be summarized by presenting the number of events, number of participants experiencing AEs, and the severity and relatedness of adverse events by treatment arm. All adverse events will be coded using MedDRA® (The Medical Dictionary for Regulatory Activities). The number and proportion of participants experiencing each treatment emergent AE will be provided overall and by treatment arm. Treatment emergent adverse events will be summarized by System Organ Class (SOC) and Preferred Term (PT). If a participant experiences multiple episodes of an event, then the event is only counted once. Detailed listings of treatment emergent adverse events and non-treatment emergent events in the safety population by treatment arm will be provided and include severity, relationship to study medication(s), and action taken, as available. The criteria for an immediate study review by the DSMB will be monitored closely. These criteria are either (1) three or more participants experience severe adverse reactions; (2) four or more participants have four consecutive positive urine toxicology screens for opioid use,

and have been reevaluated through any means as having moderate to severe opioid use disorder; or (3) one or more SUSAR.

17.0 REGULATORY COMPLIANCE, REPORTING AND MONITORING

17.1 Statement of Compliance

This trial will be conducted in accordance with the current version of the IRB-approved protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonisation Good Clinical Practice (GCP) Guidelines, applicable US Code of Federal Regulations (CFR), the NIDA Terms and Conditions of Award, and all other applicable state, local, and federal regulatory requirements. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a reference guide and study quality assurance tool.

17.2 Institutional Review Board Approval

Prior to initiating the study, participating site PIs will obtain written approval from the Ethics Review Committee (ERC) or Institutional Review Board (IRB) to conduct the study at their respective site, which will include approval of the study protocol. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the PIs for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials given to the participant, and any changes made to these documents throughout study implementation. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator is responsible for maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the PI prior to the initiation of research activities at the site and must be available at any time for audit. Unanticipated problems (UP) involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

UT Southwestern will serve as the single IRB (sIRB) of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating sites/institutions will agree to rely on the sIRB and will enter into reliance/authorization agreements for Protocol CTN-0110. The sIRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution. Some sites may meet Exception Criteria to the National Institutes of Health (NIH) sIRB Policy and may not utilize the IRB of Record.

17.3 Research Advisory Panel of California (California sites only)

Prior to initiating the study at a California site, the Sponsor or designee will obtain written approval from the Research Advisory Panel of California (RAP-C) for applicable research. 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 medication, as well as research for the treatment of controlled substance addiction or abuse utilizing any drug, scheduled or not (Substance Abuse Treatment studies), must be submitted to RAP-C for review and approval prior to study start-up.

Study approval is based on review of the study protocol, consent form, and other pertinent study documents. Yearly reports will be provided to the RAP-C by the Sponsor or designee in order to obtain continuing study approval. Protocol amendments will also be submitted, and it is required that the Panel be notified of any significant study medication related adverse events that may emerge during conduct of the study at the California sites only. The Panel must also be notified of study conclusion.

17.4 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. Informed consent continues throughout the individual's study participation. The informed consent form(s) will include all of the required elements of informed consent and may contain additional relevant consent elements and NIDA CCTN specific additional elements. Each study site must have the study informed consent(s) approved by the IRB of record. Prior to initial submission to the IRB and with each subsequent consent revision, the consent form(s) must be sent to the CCC and the LN to confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(b), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(c) and any applicable CCTN requirements. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with all applicable IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form. Additionally, participants at California sites should be provided with a copy of the California Research Participant's Bill of Rights.

During the informed consent process, research staff will explain the study to the potential participant and provide the potential participant with a copy of the consent form to read and keep for reference. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family and close friends or think about it prior to agreeing to participate. If the participant is interested in participating in the study, a qualified staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose. The participant, or participant's legally authorized representative, will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the IRB of record, will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the PI to obtain informed consent must be listed on the Delegation of Responsibility and Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate GCP and Human Subjects Protection training, as mandated by NIDA standard operating procedures.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

17.5 Quality Assurance Monitoring

In accordance with federal regulations, the study Sponsor is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. Qualified monitors will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation auditing, monitoring of drug disposition, and ensuring the informed consent process is being correctly followed and documented. Non-conformity with protocol and federal regulations will be reported as a protocol deviation and submitted to the study Sponsor and study IRB of record, (as applicable), for further review.

17.6 Participant and Data Confidentiality

Participant confidentiality and privacy are strictly held in trust by the participating PIs, their staff, the safety and oversight monitor(s), and the Sponsor(s) and funding agency, and will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the Lead investigator, Sponsor, the funding agency (NIDA), and the participant.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Participant records will be held confidential by the use of study codes for identifying participants on Case Report Forms (CRFs), secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in Section 17.12, Records Retention and Requirements.

By signing the protocol signature page, the PI affirms that information furnished to the PI by the Sponsor will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, 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.

17.6.1 Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). This protects participants from disclosure of sensitive information (e.g., drug use). It is the NIH policy that PIs and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects PIs to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

17.6.2 Health Insurance Portability and Accountability Act (HIPAA)

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

17.7 Investigator Assurances

Each site must have on file an active Federalwide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects in alignment with 45 CFR 46, Subpart A, with documentation sent to the Sponsor and NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to Sponsor and NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page and investigator agreement, providing assurances that the study will be performed according to the standards stipulated therein.

17.7.1 Financial Disclosure/Conflict of Interest

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the Sponsor annually that they have met their institutional financial disclosure requirements.

17.7.2 DEA Registration

All Drug Enforcement Administration (DEA) requirements must be met, including registration, inspection if required, and certification, as applicable. In order to receive shipments of study drug, sites must have a DEA registration (facility research registration or a practitioner registration) that has the address where study drug will be shipped on the registration. Additionally, dispensing any controlled substance requires a DEA registration unless exempt by federal or state law or pursuant to CFR Sections 1301.22-1301.26.

17.7.3 IND Requirements

An IND application will be submitted to the FDA for this study. Any subsequent amendments to this clinical trial submitted to the FDA will reflect awareness of and compliance with U.S Code of Federal Regulations 45 CFR 46 and its subparts, as well as the International Council for Harmonization Good Clinical Practice Guidelines (ICH E6 R2). This IND study will also be conducted in accordance with all applicable FDA regulations and will comply with all applicable laws and regulations at clinical research sites.

17.8 Clinical Monitoring

PIs will host periodic visits by NIDA contract monitors who will examine whether study procedures are conducted appropriately 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), informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and principal investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the Lead Investigator, Sponsor, and NIDA CCTN.

Qualified node personnel (Node QA monitors) or other designated party(ies) will provide site management for each site during the trial. Node QA staff or other designated party(ies) will audit source documentation, including informed consent forms and any other separate regulatory forms, including HIPAA or state-specific forms. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the node personnel's review of study documentation indicates that additional training of site study personnel is needed, node QA personnel will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

17.9 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population, with additional focus on enrolling a minimum of 25% women of total study enrollment. In addition, specific attention should be given to enrolling the representative minorities who are reported to have MA and co-use of opioids by population health studies. Minority enrollment at each study site should reflect the relevant local population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or group-to-group individual meetings. Sites will be encouraged to implement strategies such as linkages with medical sites, treatment programs, or community organizations that serve a large number of women and/or minorities, using targeted advertisement in media with a high female and/or minority audience, and partnerships with community organizations who work with these groups. In compliance with NIH policy, subgroup analyses will be performed to evaluate the interaction with treatment assignment for sex, race and ethnicity.

17.10 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. In order to meet these additional protections, the institution's IRB will obtain certification from the Office of Human Research Protections (OHRP) to enroll prisoners and follow-up with participants who become prisoners during the course of the study, as necessary.

17.11 Regulatory Files

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

17.12 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, audio and video recordings, and regulatory files) are to be maintained by the PI 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, Lead Investigator, and NIDA must be notified in writing and acknowledgment from these parties must be received by the site prior to the destruction or relocation of research records.

17.13 Reporting to Sponsor

The site principal investigator agrees to submit accurate, complete, legible and timely reports to the Lead Investigator, and 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. Safety reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor and NIDA.

17.14 Audits

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

17.15 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, Sponsor-Investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence and approved consent form and signed participant consent forms. As part of participating in a NIDA-funded study, each site will permit authorized representatives from NIDA, the Sponsor and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

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. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document, and that it is marked to indicate it is a photocopy.

17.16 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the PI, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor

protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the IRB of record as needed. All 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.

All protocol deviations should be recorded in the EDC system via the Protocol Deviation CRF. The CCC, DSC and the LI must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

Additionally, each site is responsible for reviewing the IRB of record's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

17.17 Safety Monitoring

A physician (MD or DO) who serves in the Site PI or Medical Clinician study role will review or provide consultation for each Adverse Event (AE) and Serious Adverse Event (SAE), as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The physician (MD or DO) who serves in the Site PI or Medical Clinician study role will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, the Sponsor will assign a Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary. The Medical Monitor will determine which safety events require expedited reporting to the Sponsor, NIDA, Indivior, the DSMB and regulatory authorities. This will include events that are serious, related and unexpected. The study staff will be trained to monitor for and report AEs and SAEs.

Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. 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.

17.17.1 Data and Safety Monitoring Board (DSMB)

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

17.17.2 Safety Monitor / Medical Monitor

The CCC Safety Monitor/Medical Monitor is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed within one business day of being reported in the eClinical. The Safety Monitor/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 are reviewed on a regular basis to observe trends or unusual events.

The CCC Safety Monitor/Medical Monitor will summarize each SAE and will provide a report to the Lead Investigator, Sponsor, and NIDA. If the event meets the criteria for FDA-defined expedited reporting, the CCC safety team and regulatory team will work together to submit an expedited safety report to the FDA. A copy of the expedited report will be submitted to the DSMB through the DSC. A copy of the expedited report will be submitted to Indivior and all participating sites. Other safety reports will be generated and presented at the scheduled Data Safety Monitoring Board (DSMB) meetings.

17.17.3 Adverse Events (AEs)

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

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

Events that are temporally associated with SL-BUP use, but that are not recorded using either the Medication Side Effects form, or a different study-specific CRF (e.g., withdrawal on the COWS/SOWS, Buprenorphine-XR/Placebo Injection Site Evaluation), will be recorded as an AE.

Events related to the injection of the study medication are recorded on the Injection Site Examination form and will not be duplicate reported on an AE form, unless they meet the SAE definition.

Events related to withdrawal symptoms are captured on the COWS and SOWS forms and will not be duplicate reported on an AE form, unless the event meets the definition of an SAE. Withdrawal symptoms not captured by scheduled COWS and SOWS form should be reported as an AE. Any spontaneous reporting of withdrawal symptoms by the participant will be captured using the AE form in the following situations: withdrawal symptoms reported at visits without scheduled specific structured questionnaires (COWS and SOWS CRFs) and withdrawal symptoms not listed in the specific structured questionnaires (COWS and SOWS CRFs) reported at any visit.

Any of these events that meet the definition of an SAE are reported on the AE/SAE form set.

17.17.4 Serious Adverse Events

For the purpose of this study, all SAEs will require reporting in the electronic data capture system. Reporting of AEs and SAEs is described in Appendix A. The study sites are responsible for reporting all AEs and SAEs to the IRB of record (and local IRB, as applicable) per IRB guidelines.

17.17.5 Known Potential Toxicities of Study Medication

Specific known potential toxicities of the study medication include risk of overdose. Buprenorphine, as Sublocade™ in this study, is a Schedule III controlled substance. An IND will be on file with the FDA to provide safety monitoring. The medication will be handled and administered using the required REMS procedures. All other clinical considerations regarding risk for use of this medication, such as possible drug interactions or hepatic impairment, have been integrated in the exclusion criteria and safety monitoring procedures utilized in this study.

Refer to the package insert for Sublocade™ for complete list of adverse reactions and toxicities.

18.0 DATA MANAGEMENT

18.1 Design and Development

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

18.2 Qualitative Data Management

Qualitative data will be collected and analyzed by the study investigators. The study investigators will be responsible for developing the qualitative interview guide, obtaining IRB approval, training staff, as well as the collection and analysis of qualitative data.

18.3 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in the Advantage eClinical User's Guide and CRF Manual.

18.4 Data Center Responsibilities

The DSC will 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide final Case Report Forms (CRFs) and electronic CRFs (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for use of Advantage eClinical and for completion of CRFs/eCRFs, 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.

18.5 Data Collection and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with CRF paper source documents and completion instructions. Data entry into Advantage eClinical should be completed according to the instructions provided, project specific training and guidelines established by DSC. Data entry into eCRFs shall be performed by authorized individuals. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant. Selected eCRFs may also require the investigator's electronic signature. In some situations, data collected on source documents will

not be entered into Advantage eClinical, but when it is entered, it will follow the guidelines stated above.

18.6 Data Editing

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

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

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

18.7 Data Transfer/Lock

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

The DSC will conduct final data cleaning activities and "lock" the study database from further modification. The final raw analysis datasets will be transferred to the Lead Investigator, Sponsor or designee and to NIDA, as requested, for storage and archive. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated party for storage and archiving. These datasets may be posted on the NIDA Data Share website.

18.8 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

18.9 Data Quality Assurance

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

19.0 DATA SHARING, PUBLIC ACCESS AND PUBLICATIONS

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) and the HEAL Public Access and Data Sharing Policy (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/research/heal-public-access-data-sharing-policy). Investigators will also register and report results of the trial in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration (https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm).

Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. For more details on data sharing please visit https://datashare.nida.nih.gov/.

The primary outcome(s) publication will be included along with study underlying primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

Every attempt will be made to publish results in peer-reviewed journals. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN. Considerations for ensuring confidentiality of any shared data are described in Section 17.6.

20.0 PROTOCOL SIGNATURE PAGE

SPONSOR/SPONSOR'S REPRESENTATIVE

Printed Name	**Signature**	**Date**

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 8.0 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 (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	**Signature**	**Date**

Clinical Site Name _____

Node Affiliation _____

21.0 PROTOCOL AMENDMENT HISTORY

The table below is intended to briefly capture changes of IRB-approved versions of the protocol, including a description of the major change(s) and rationale (only the most meaningful, substantial changes to the protocol should be documented here). Use of this table is recommended, but not required.

Version	Date	Description of Change	Brief Rationale

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23.0 APPENDIX A: ADVERSE EVENT REPORTING 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 medication related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status, ECGs, lab results, x-rays, physical examinations, etc., that is considered clinically significant by the Medical Clinician are considered AEs.

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

Adverse reaction is any adverse event caused by the study medication.

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 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 medication(s), 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) Is an 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 while a participant is enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Women who become pregnant during the active treatment period will be discontinued from further medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

Medical and Psychiatric History

A thorough medical and psychiatric history during the screening phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site’s Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up of ongoing adverse events will continue through resolution or 30 days post last study visit. Study personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult with the Safety Monitor/Medical Monitor as warranted.

Standard reporting, within seven days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of the site’s becoming aware of the event) is required for reportable SAEs (including death and life-threatening events). Sites are responsible for reporting SAEs to the IRB of record, per the IRB of record’s guidelines.

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

Reportable 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's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A physician (MD or DO) who serves in the Site PI or Medical Clinician study role will review reportable AEs for seriousness, severity, and causality within the established reporting timeline.

Guidelines for Assessing Severity

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

Grade 1	**Mild**	Transient or mild discomfort (typically < 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 unlikely
Grade 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.

Guidelines for Determining Causality

A physician (MD or DO) who serves in the Site PI or Medical Clinician study role will use the following question when assessing causality of an adverse event to study medication/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study medication caused the event?

Site's Role in Monitoring Adverse Events

Local quality assurance monitors will review study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

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

A Sponsor-assigned Safety Monitor/Medical Monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Safety Monitor/Medical Monitor, Lead Investigator, and designees. All SAEs will be reviewed by the Safety Monitor/Medical Monitor in Advantage eClinical and, if needed, additional information will

be requested. The Safety Monitor/Medical Monitor will also report events to the Sponsor, NIDA, and the DSMB. The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the Sponsor-assigned Safety Monitor/Medical Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the Safety Monitor/Medical Monitor in writing for review by the Lead Investigator, Sponsor, and the DSMB. Subsequent review by the Safety Monitor/Medical Monitor, DSMB, FDA and ethics review committee or IRB, the Sponsor, NIDA, or relevant local regulatory authorities may also suspend further trial treatment at a site. The Sponsor, NIDA, the DSMB, and FDA retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Regulatory Reporting for an IND study

All serious and unexpected suspected adverse reactions are reported by the Medical Monitor on behalf of the Sponsor to the FDA in writing within 15 calendar days of notification. Suspected adverse reactions that are unexpected and meet the criteria for death or immediately life-threatening also require notification of the FDA as soon as possible but no later than 7 calendar days of notification of the event, with a follow-up written report within 15 calendar days of notification of the event. The Medical Monitor will prepare an expedited report (MedWatch Form 3500A or similar) for the FDA and other regulatory authorities, the Sponsor, NIDA, the DSMB, Indivior and copies will be distributed to all sites. Expedited reports will be placed in the site regulatory files upon receipt. A copy of all expedited reports will be forwarded to the site's local IRB, if required.

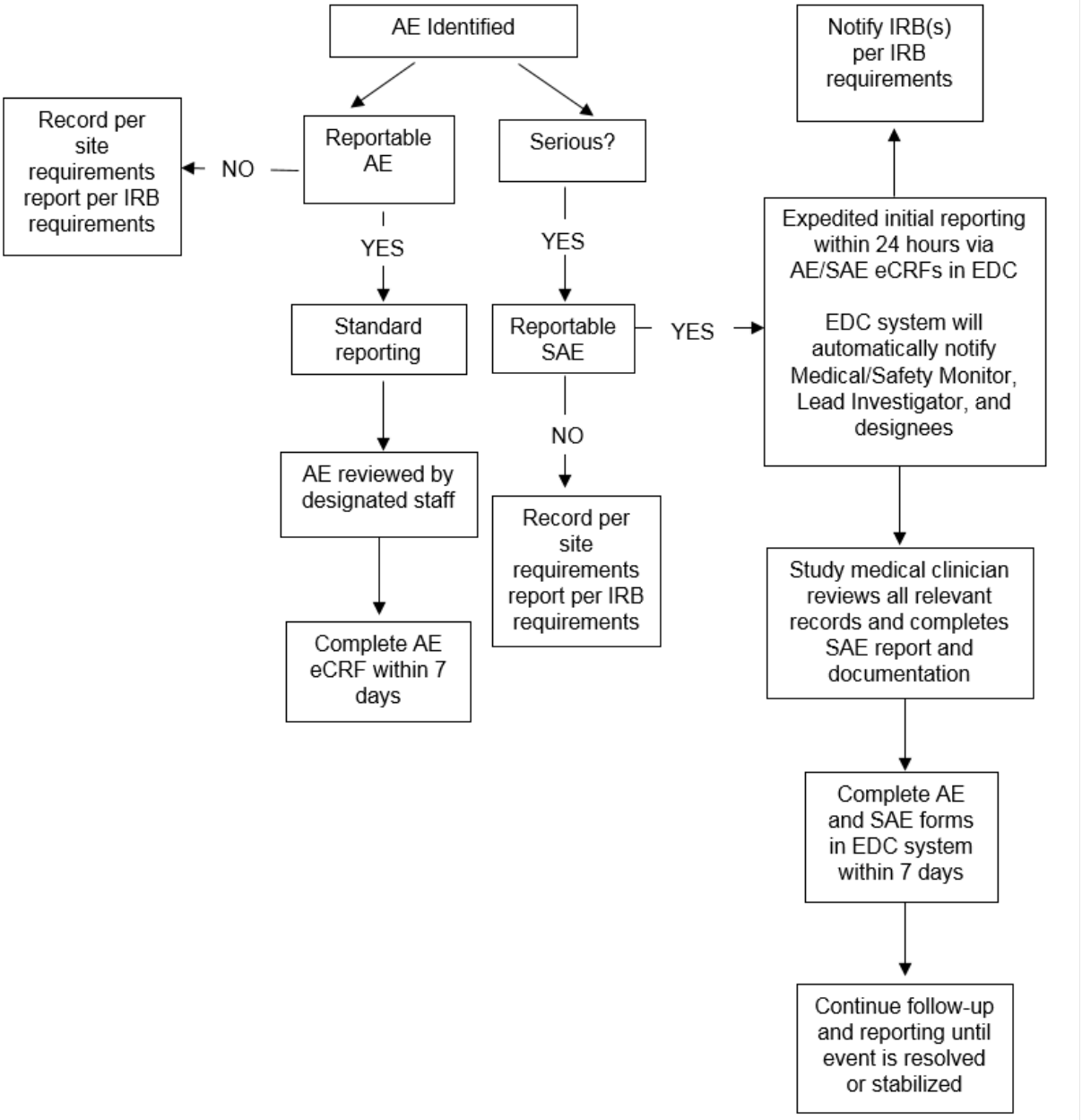
Reporting to the Data and Safety Monitoring Board

The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Participant Withdrawal

The 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 be withdrawn from further study medication administration/study intervention. A physician (MD or DO) who serves in the Site PI or Medical Clinician study role must make the decision to withdraw a participant from study medication. If necessary, a Medical Clinician (MD or DO) 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.

23.1 Adverse Event Reporting (Chart)



24.0 APPENDIX B: DATA AND SAFETY MONITORING PLAN (DSMP)

24.1 BRIEF STUDY OVERVIEW

This study will randomize approximately 246 individuals to 12 weeks of outpatient BUP-Inj or to 12-weeks of outpatient PBO-Inj to test if BUP-Inj reduces urine-verified MA use in Weeks 9-12 of the study. Eligibility will be determined during a maximum 21-day screening period and participants must have at least 2 positive UDS for MA of a possible 3 tests to occur at clinic visits within a 10-day period, with at least 2 days between visits, must self-report MA use on 18 or more days in the 30-day period prior to written consent using the Timeline Followback (TLFB) and meet diagnostic criteria for moderate or severe MUD per DSM-5 (4 or more criteria) at screening. Participants must also have at least one negative UDS for opioids during the screening period and on the day of expected randomization, and must meet diagnostic criteria for mild opioid use disorder per DSM-5 (at least 2 but no more than 3 criteria) or opioid misuse demonstrated by self-report of opioid use of at least 2 days in the 30-day period prior to written consent using the TLFB 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 receive either 1) BUP-Inj or 2) PBO-Inj. Injections will be provided in weeks 1, 5, and 9. Participants will be required to submit twice weekly urine samples, and complete once-weekly cognitive behavioral therapy based on a treatment manual adapted for stimulant use disorder specifically for this study. The primary outcome measure is the number of MA-negative UDS results obtained during Weeks 9 through 12 of the medication phase as measured for the BUP-Inj and PBO-Inj conditions.

24.2 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) 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.

All adverse events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported according to the Protocol.

The occurrence of AEs and serious adverse events (SAEs) will be assessed at each clinic visit during the study. Serious adverse events will be followed until considered resolved or stable.

Reportable AEs are required to be entered into the data system within 7 days of the site staff becoming aware of the event. Reportable SAEs (including death and life-threatening events) are required to be entered into the data system within 24 hours of site's knowledge of the event.

B. CCC Medical Monitor

The NIDA CTN Clinical Coordinating Center's (CCC) Medical Monitor or designee is responsible for reviewing all adverse events and serious adverse events reported. The CCC Medical Monitor is alerted via email each time an SAE is reported in Advantage eClinical. All SAEs will be reviewed at the time they are reported in the EDC. The Medical Monitor or designee will also indicate concurrence or not with the details of the report provided by the site. Where further information is

needed, the Medical Monitor or designee will discuss the event with the site staff. Reviews of SAEs by the CCC Medical Monitor or designee will be documented in the Advantage eClinical data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

Mandatory Regulatory Reporting in IND Trials:

For trials conducted under IND, the CCC Safety Monitor/Medical Monitor or designee will report events to the regulatory authorities if the event meets the definition of an expedited event (21CFR312.32). All SAEs that meet expedited reporting will be reported to the FDA/Regulatory Authorities in writing within 15 calendar days of notification of the CCC. If the SAE also meets the criteria for death or immediately life-threatening, the CCC will notify the FDA/Regulatory Authorities electronically, by phone or by fax as soon as possible but no later than 7 calendar days of notification of the CCC pharmacovigilance team, with a follow-up written report within 15 calendar days of notification of the CCC. The CCC pharmacovigilance team will prepare an expedited report (MedWatch Form 3500A or similar) for the FDA/Regulatory authorities and copies will be distributed to all participating site investigators.

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. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of AEs and narratives of all SAEs at a frequency requested by the DSMB and CCTN, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence 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). This includes the rules for triggering immediate DSMB review, defined as three or more participants experiencing severe adverse reactions; four or more participants have four consecutive positive urine toxicology screens for opioid use, and have been reevaluated through any means as having moderate to severe opioid use disorder; or one or more serious, unexpected and suspected adverse reactions.

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication summarizing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site(s) will be conducted on a regular basis using a combination of NIDA CCTN CCC monitors (if applicable) and the local Node QA Monitors (if applicable). Investigators will host periodic visits for the monitors. The purpose of these visits is to assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as to document the integrity of the trial progress. The investigative site will provide direct access to all trial related sites (e.g., pharmacy, research office), source data/documentation, and reports for the purpose of monitoring and auditing by the monitors, as well as for inspection by

local and regulatory authorities. 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 as needed to enhance research quality.

Site Visit Reports will be prepared by the NIDA CCC Clinical Research Associates (CRAs) following each site visit. These reports will be sent to the site Principal Investigator, the study Lead Investigator and NIDA CCTN.

Local Node QA site visit reports will be prepared following each site visit, as applicable. These reports are sent to those entities required of them by the Lead Investigative team, generally including the Lead Investigator, site Principal Investigator, Node PI and a CCC representative, usually the Clinical Study Manager for the study.

E. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, and secure storage of any documents that have participant identifiers on site, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant on site will be kept locked/securely stored separately from the study files and the medical records. No identifying information will be disclosed in reports, publications or presentations.

Information That Meets Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and 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 site's study Medical Clinician or other designated and qualified individual will evaluate all pertinent screening and eligibility assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. This will further be confirmed by a physician (MD or DO) who serves in the Site PI or Medical Clinician study role in order to proceed formally to randomization. AEs and concomitant medications will be assessed and documented at each study visit. Individuals who experience an AE that compromises safe participation in a study 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

Participants may not be currently pregnant, breastfeeding, or planning on conception in order to be included in the study. In order to support this exclusion criterion, urine pregnancy tests will be completed to confirm a negative result before randomization and at each study visit before administration of the next study medication injection. A positive pregnancy test post-randomization will result in the cessation of study medication and, if necessary, referral to appropriate obstetric care. The site staff will follow the participant until an outcome of the pregnancy is known and reported.

Study Specific Risks

There is a risk to untreated MUD, especially in the setting of opioid co-use, particularly ongoing risks for opioid overdose which will be reduced due to the partial agonist properties of BUP. Naloxone overdose reversal kits will be provided to participants in both conditions with instructions to participants and their friends/family members on their use in the setting of overdose in order to address opioid overdose risks. There are serious risks for overdose and death should BUP-Inj be injected intravenously. A chain of custody will be maintained and documented detailing transfer from the manufacturer to the study pharmacy to the study staff who will administer the BUP-Inj product to participants assigned to the BUP-Inj condition. No take home injectable medications will be provided – all study products will be prepared and administered to study participants at the research clinic. To document safety and drug accountability, the Risk Evaluation and Mitigation Strategy (REMS) procedures will be followed.

There are expected adverse events to the BUP-Inj medication. Medication-related adverse events that occur in more than 5% of subjects when using BUP-Inj include constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain. These are minor, will be treated with ancillary medications, and tolerable in comparison to protection from opioid overdose and potential for treating MUD[32]. Concerns for hepatic impairment is managed through exclusion criteria justified by LFTs to assess liver function during screening. BUP-Inj medication is habit forming. The risks to PBO-Inj are mild, including injection site reactions and tolerable withdrawal symptoms. To avoid risks for iatrogenic illness, all participants must meet criteria for moderate to severe MUD and mild OUD or demonstrate opioid misuse. Throughout the study, management of complaints of opioid withdrawal symptoms for all participants will include provision of over-the-counter medications for head and body aches (e.g., ibuprofen), insomnia (e.g., diphenhydramine), diarrhea (e.g., loperamide) and stomach upset (e.g., bismuth subsalicylate) and ongoing opioid use will be monitored to ensure that any escalation of opioid use that suggests moderate or greater OUD is evaluated by the Medical Clinician.

Overdose Risks: Death or serious harm can happen if you take benzodiazepines, sleeping pills, tranquilizers, muscle relaxants, sedatives, or if you drink alcohol in excess. For safety, participants with excess use of other substances deemed unsafe by the Medical Clinician will not be allowed to participate. Substance use will also be recorded and monitored at each visit throughout the study using TLFB and Prior and Concomitant Medications (PCM) forms, which will be used to monitor safety related to other substance use.

24.3 DATA MANAGEMENT PROCEDURES

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

24.3.1 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 final Case Report Forms (CRFs) and electronic Case Report Forms (eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of CRFs/eCRFs, 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 the final study database lock.

24.3.2 Data Collection and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical, or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with CRF paper source documents and completion instructions. Data entry into Advantage eClinical should be completed in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC. Data entry into the eCRFs is performed by authorized individuals. Selected source documents and eCRFs may also require the investigator's signature (wet or electronic). In some situations, data collected on source documents will not be entered into Advantage eClinical, but when it is entered, it will follow the guidelines stated above.

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

24.3.3 Data Monitoring, Cleaning and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and missing 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 eCRFs and between eCRFs and post queries in Advantage eClinical on a scheduled basis. Sites will resolve data queries by entering all corrections and changes directly into Advantage eClinical or verifying the data are correct as is.

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

Trial progress and data status reports, which provide information on items such as recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits,

regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site staff, local Node staff, the Lead Investigators, the coordinating centers, and NIDA CCTN, to monitor each site's progress on the study.

24.3.4 Database Lock and Transfer

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. Individual participants and their research data will be identified by a unique study identification number; further, some identifiable data may be collected in eClinical. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

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 raw analysis datasets will be transferred to the Lead Investigator, Sponsor or designee and to NIDA upon request. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated party for storage and archiving. These datasets will be posted on the NIDA Data Share website.

Reference: http://grants.nih.gov/grants/guide/notice-files/not98-084.html