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Buprenorphine/Naloxone

STUDY #: NIDA-CTN-0003

SUBOXONE (BUPRENORPHINE/NALOXONE) TAPER: A COMPARISON OF TWO SCHEDULES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ARSW	Adjective Rating Scale for Withdrawal
ASI	Addiction Severity Index
AST	Aspartate Aminotransferase
BC	Blood Chemistry Panel
BUP/NX	Buprenorphine/Naloxone
CAP	American College of Pathologists
CBC	Complete Blood Counts
CCTN	Center for Clinical Trials Network
CLIA	Clinical Laboratory Improvement Amendment of 1988
CM	Concomitant Medication Form
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CTN	NIDA Clinical Trials Network
CTP	Community Treatment Programs
CV	Clinic Visit Form
DL	Dosing Log
DSM-IV	Diagnostic and Statistical Manual -IV
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration
GGT	Gamma Glutamyltranspeptidase
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug
IRB	Institutional Review Board
LFTs	Liver Function Tests
LAAM	Levomethadyl Acetate (L-alpha acetylmethadol)
NIDA	National Institute on Drug Abuse
NTPs	Narcotic Treatment Programs
PG	Pregnancy Test
PHY	Physical Exam Form
RBS	Risk Behavior Survey
SAE	Serious Adverse Event
SQ	Satisfaction Questionnaire
STR	Study Termination Report
TAU	Treatment As Usual
U	Urine Drug Screen for Drugs of Abuse
UA	Urinalysis
VAS	Visual Analog Scales

PROTOCOL SYNOPSIS

Buprenorphine is a mu opiate partial agonist recently approved by the FDA as a pharmacotherapy for opiate dependence. Controlled clinical trials over the past ten years have provided overwhelming support for its therapeutic use. Suboxone, a sublingual combination tablet containing both buprenorphine and naloxone (an opiate antagonist) has been developed to mitigate abuse and diversion. It is anticipated that buprenorphine will attract a large number of patients with opioid dependence into treatment who are currently unwilling or unable to avail themselves of other pharmacological treatments. Buprenorphine treatment may either be long or short term, and many participants will desire to taper from buprenorphine after variable periods of treatment. Currently there is little systematically gathered information available to guide clinicians in the process of tapering patients from buprenorphine treatment. Experience with methadone suggests that tapering from buprenorphine may not be easy. It remains unclear whether the unique pharmacological profile of buprenorphine will make the process less onerous. This study will explore two strategies to discontinue buprenorphine treatment after a period of stabilization, comparing a relatively brief to a more gradual tapering schedule, taking into account the dose on which participants have been stabilized.

Specifically this study aims to compare, in the outpatient setting, the relative advantage of two taper schedules (7 vs. 28 days) of Suboxone (buprenorphine-naloxone) following four weeks of Suboxone stabilization. It is hypothesized that a more gradual taper schedule compared to a shorter one will result in lower rates of illicit opiate use (as reflected by urine toxicology tests) at the end of the taper. However, there may be an interaction between the rate of taper and the stabilization dose. The proportion of participants providing opiate free urines in each group will be compared at the end of the taper, as well as at other time points (i.e. at 1 and 3 months post taper). Safety, as reflected by Adverse Events (AEs) and Severe Adverse Events (SAEs), withdrawal severity, stabilization dose and treatment retention during the study will also be explored.

This is a randomized, open-label, parallel-group design study. Four hundred and eighty (480) participants seeking treatment for opiate dependence will be randomized. Participants will be males and non-pregnant and non-lactating females who are at least 15 years-of-age. Following screening, there will be a 28 day stabilization period on Suboxone. All participants will be inducted onto Suboxone over a period of 3 days with doses not to exceed 8mg on the first day, 12mg on the second day and 16mg on the third day. Until the end of the third week doses may be adjusted in 4 or 8 mg increments to a total dose of 8, 16, or 24 mg, based on clinical need, as judged by the treating physician. During the final stabilization week, participants will receive a constant dose of buprenorphine (either 8, 16, or 24mg). Participants will then be randomized to one of two taper schedules and followed post taper for three months. The duration of study participation for each participant will be a maximum of approximately 5 months, including screening, stabilization, tapering, post-tapering and follow-up. Results from this study will add to the knowledge base of the clinical use of Suboxone and provide clinicians with data to guide the process of tapering from Suboxone treatment after a period of stabilization.

P R O T O C O L S C H E M A

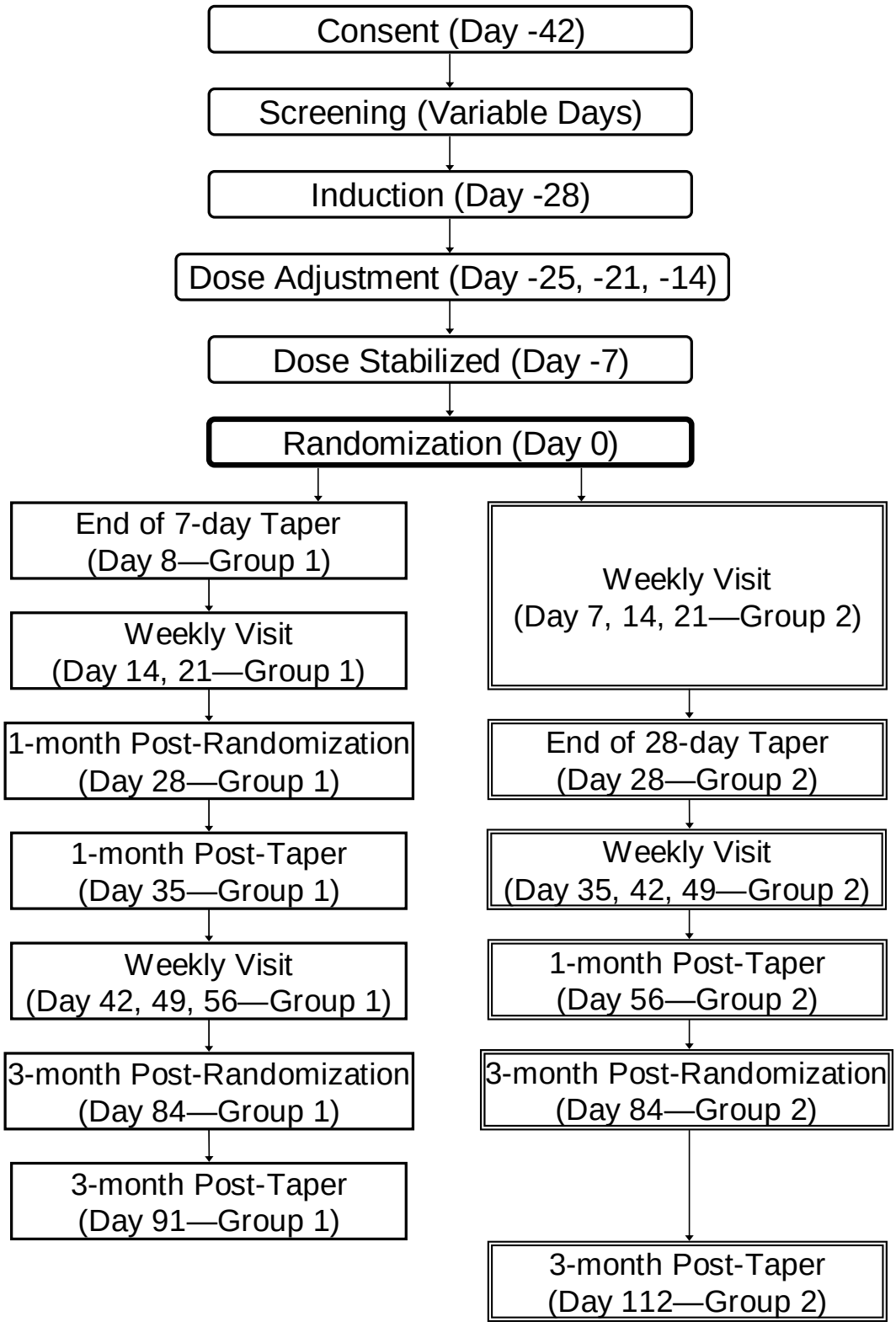

Table 1: Time and Event Schedule

STUDY DAY/MEASURE	-42	-28	-25	-21	-14	-7	0	7	14	21	28	35	42	49	56	84	91	112	TERM
Informed Consent	X																		
Treatment Contract/Suboxone Information Sheet		X																	
Locator Form	X																		
Demographics	X																		
DSM-IV Checklist	X																		
Clinical/Psychiatric Interview	X																		
Inclusion/Exclusion	X																		
Medical History	X																		
Clinic Visit Form (CV)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	1	2	X
Induction Form		X																	
RBS	X											1			2		1	2	X[3]
LFTs	X						X				X								X[3]
Physical Exam (PHY)	X											1			2				X[3]
Hematology/Chemistries/Hepatitis Routine Urinalysis	X											1**			2**				X**[3]
12-lead ECG	X*											1*			2*				X*[3]
Pregnancy Test (PG)	X	X					X				X								X[3]
Adverse Events (AE)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Prior/Concomitant Medications	X[P]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Randomization Form							X												
COWS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	1	2	X
ARSW	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	1	2	X
ASI Lite	X											1			2		1	2	X[3]
VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	1	2	X
STR																	1	2	X
SQ								1			2	1			2		1	2	X
Urine Drug Screen (U)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	1	2	X
Dosing Log (DL)			X	X	X	X	X	X	2	2	2								
Serious Adverse Event (SAE)																	1	2	X

X=All Participants
1=Participants assigned to the 7 day tapering
2=Participants assigned to the 28 day tapering
Term=If a participant terminates from the protocol at any time post induction and prior to the one month post-taper follow-up visit, he/she should complete data collection as indicated
*For Participants over age 40 or with a history of cardiovascular disease.
[P]=Prior Med Form Only ** Hepatitis Tests not repeated (done only at screening)
[3]=Complete only if one month or more has passed since previous assessment

1.0 Background and Rationale

For decades clinicians have been frustrated by the inability to adequately detoxify opiate addicts because opiate-based detoxification, one of the most effective means to achieving that goal, has been unavailable outside the very restrictive confines of narcotic treatment programs (NTPs). This frustration has been more acutely felt over the past several years because of the rise in heroin use and the recent interest in ultra-rapid opiate detoxification, which unfortunately, has often been more a matter of commerce than medicine. Buprenorphine (Subutex), and BUP/NX (Suboxone) in particular, may change all of that.

Buprenorphine is a high affinity, partial μ-opioid agonist recently approved by the FDA as a pharmacotherapy for opioid dependence (Bickel and Amass, 1995; Ling *et al.*, 1994). Treatment with buprenorphine in the United States will emphasize the use of Suboxone, a sublingual combination tablet containing buprenorphine and naloxone in a 4:1 ratio (Chiang and Hawks, 1994; Chiang *et al.*, 1996a, 1996b, Fudala *et al.*, 1998). This combination tablet was developed to help mitigate potential diversion and abuse of buprenorphine. Bioavailability studies with sublingual solution and tablet formulations of buprenorphine indicate that in short term administration the tablets approximate 60-70% of the corresponding sublingual solution dose (Nath et al., 1999; Schuh and Johanson, 1999; Ling *et al*., unpublished). Thus, combination tablet dosages used in clinical practice may need to exceed those shown to be effective in prior controlled studies with the sublingual solution, although with chronic administration, the blood levels of the tablet and liquid formulations appear to approach each other (Ling et al., unpublished). While much of the treatment outcome data on opiate pharmacotherapy suggests that for most participants with chronic addiction, long-term treatment is required, many participants nevertheless desire tapering from opiate maintenance, and there are suggestions that some of these participants, i.e. those who achieve significant clinical improvement, may do well. Difficulties in tapering from methadone, the most widely used agonist for maintenance treatment, have posed a significant challenge to such therapeutic attempts. The unique pharmacological profile of buprenorphine may allow for more successful tapering after stabilization.

Clinical research in the last 10 years has established that buprenorphine (and Suboxone) is a safe and effective alternative to methadone (Bickel *et al*., 1988a; Johnson *et al*., 1992; Strain *et al*., 1994; Ling *et al.*, 1996, 1998; Uehlinger *et al.*, 1988; Amass *et al.*, 2000a) and levomethadyl acetate hydrochloride (LAAM) (Chutuape *et al*., 1999) and produces significant and substantial improvement over time in psychosocial functioning (Strain *et al*., 1996). Buprenorphine also has unique features that permit novel physician office-based uses, which may alter current strategies for maintenance and detoxification (Bickel and Amass, 1995; Amass *et al*., 2000, 2001). In particular, buprenorphine's ceiling on agonist activity decreases the danger of overdose, may limit its abuse liability (Walsh *et al*., l994, 1995) and confers low toxicity even at high doses (Lange *et al.*, 1990; Huestis *et al.*, 1999), increasing the safe dose range. Buprenorphine can also produce sufficient tolerance to block the effects of exogenously administered opioids (Bickel *et al*., l988b; Walsh *et al*., 1995), thus reducing illicit opioid use. Finally, buprenorphine's slow

dissociation from μ-opioid receptors not only results in a long duration of action but also diminishes symptoms and signs of withdrawal upon cessation (Amass *et al*., 1994; Fudala *et al.,* 1990) improving treatment outcomes by permitting accelerated tapering of buprenorphine.

The purpose of this study is to determine the relative ease of two Suboxone tapering schedules (one rapid and one gradual) after stabilization on three predetermined Suboxone dose levels. Although tapering of buprnorphine is likely to be a very common event in clinical practice, little empirical evidence is available to guide rational selection of buprenorphine tapering schedules. The one prior study that has examined this issue (Amass et al., 1994) compared a 36 day buprenorphine taper to a 12 day buprenorphine taper in a very small number of participants, and found advantage for the longer taper schedule. The present study seeks essentially to replicate and confirm that result in a larger, more representative sample. With such a paucity of pilot data, the selection of tapering schedules remains somewhat arbitrary. Taper schedules of 7 and 28 days were chosen to keep approximately the same relative difference between schedules as the Amass et al. study had, but to make the schedules more practical for clinicians and patients by shortening them slightly and making them conform to a precise number of weeks. The diversity of clinics in the CCTN provides an unparalleled opportunity to conduct such a clinical endeavor. The CCTN will benefit directly from the research while at the same time contribute to a gap in the data on buprenorphine. The CCTN leadership had voted studies on Suboxone a top priority.

2.0 Study Objectives

The primary objective of this clinical investigation is:

To compare, in the outpatient setting, the relative advantage of two rates (7 vs. 28 days) of Suboxone tapering following four weeks of flexible dose stabilization, as reflected by the proportion of participants providing opiate free urines at the end of the taper regimen. It is hypothesized that the longer tapering schedule will result in a higher proportion of participants giving opiate free urines on the day following the end of the taper, regardless of the stabilization dose.

Secondary objectives are:

1. To determine the effect of stabilization dose on the relative success of each taper schedule and
2. To determine the effect of treatment on:
    a. Proportion of participants providing opiate free urines at 1 and 3 month follow-ups
    b. Abstinence from other drugs of abuse at the end of the taper and at 1 and 3 month follow-ups;
    c. Concomitant medication use for treating withdrawal symptoms, at the end of taper and at 1 and 3 month follow-ups;

d. Signs and symptoms of withdrawal at the end of taper and at 1 and 3 month follow-ups;
e. Level of craving for opiates at the end of the taper and at 1 and 3 month follow-ups; and,
f. Participant satisfaction with the treatment at the end of the taper and at 1 and 3 month follow-ups.
g. Number (#) and severity of AEs experienced by each group.

Analysis of the data assessing the secondary objectives in combination with the primary objectives will provide a comprehensive overview of the clinical utility of each tapering regimen.

3.0 Study Design

This is a randomized, parallel-group, open-label study. After screening and baseline assessments, participants will receive a three-day Suboxone induction and a 25 day stabilization, (total 28 day stabilization phase). For three weeks (days -28 to -8) the dosing is flexible, but in the final week of the stabilization phase (days -7 to -1 and randomization day 0), participants must be on a stable dose of either 8mg, 16mg, or 24mg of buprenorphine. On day 0 participants will be randomly assigned in a 1:1 ratio to one of two Suboxone tapering regimens. If, for some reason, the participant is unable to attend on day 0, there will be a 3 day window for randomization to occur. Regardless of the actual day on which randomization occurs, it will be named as day 0 (it may occur up to, but no longer than, three days after the actual day 0). Randomization will be stratified, within site, according to the dose being taken on day 0 (8, 16 or 24 mg of buprenorphine). Tapering regimen #1 will be performed over 7 days and regimen #2 will be performed over 28 days. Participants in both groups will be seen weekly for data collection through day 56, followed by a 3 month post randomization visit on Day 84 for both groups and a 3 month post taper follow-up on days 91 and 112 respectively. This design will allow the investigators to analyze the data in either a post taper or a post randomization design. All participants will participate in an equal number of data collection visits throughout the study. Data will be available for 1 and 3 Months Post Taper, as well as 1 and 3 Months Post Randomization.

The maximum length of study participation is expected to be approximately 5 months, including screening, stabilization, tapering, post-tapering and follow-up. All participants will also participate in TAU from the time of consent through at least the end of the taper, at the CTP that manages their study participation. Following the taper, participants may continue in TAU at the CTP or be referred to other available local resources.

3.1 Study Population

A total of 480 persons seeking treatment for opiate dependence will be randomized (see Appendix I for a list of participating sites). Due to variability across sites in start dates and enrollment rates, each of the eleven sites will be expected to randomize between 25

and 75 participants. Participants will be males and non-pregnant, non-lactating females who are at least 15 years-of-age of all racial and ethnic groups. Participants will be recruited by word of mouth, referrals from local narcotic treatment and outreach programs, outpatient and inpatient alcohol and drug abuse clinics, primary care providers, local mental health centers, crisis clinics, public service announcements, newspaper advertisements and hospital emergency rooms. The CTP's local Institutional Review Board (IRB) must approve all recruitment advertisements before use. Participants must meet inclusion and exclusion criteria, as listed below.

3.2 Inclusion Criteria

Participants must:

1. Be 15 years of age, or older as required by state regulations.

2. Meet DSM-IV criteria for opiate dependence.

3. Be in good general health or, in case of a medical/psychiatric condition needing ongoing treatment, be under the care of a physician willing to continue participant's medical management and cooperate with the study physicians. Must be documented in progress note and release of information obtained for physician prior to enrollment.

4. Be agreeable to and capable of signing the informed consent approved by an IRB and, if under the age of 18 (excluding emancipated minors), assent and concurrent consent from a parent or legal guardian.

5. If female with childbearing potential, agree to use of one of the following acceptable methods of birth control:

    a. oral contraceptives/patch
    b. barrier (diaphragm, cervical cap with spermicide, etc) or condom
    c. intrauterine progesterone contraceptive system
    d. levonorgestrel implant
    e. medroxyprogesterone acetate contraceptive injection
    f. complete abstinence

6. Provide a methadone and benzodiazepine negative urine test result immediately preceding Suboxone induction.

3.3 Exclusion criteria

Participants must **not**:

1. Have a medical condition that would, in the opinion of the study physician, make participation medically hazardous (e.g., acute hepatitis, unstable cardiovascular, liver or renal disease).

2. Have a known allergy or sensitivity to buprenorphine or naloxone.

3. Have an acute severe psychiatric condition in need of immediate treatment, or imminent suicide risk.

4. Have dependence on alcohol, other depressants, or stimulants, requiring immediate medical attention.

5. Have a current pattern of benzodiazepine use, as assessed by the study physician, which would preclude safe participation in the study. .

6. Have participated in an investigational drug study, including buprenorphine, within the past 30 days prior to screening.

7. Have had methadone or LAAM maintenance or detoxification within 30 days of enrollment.

8. Have pending legal action that could prohibit or interfere with participation.

9. Be unable to remain in area for the duration of treatment.

10. If female, be pregnant, lactating, or planning to become pregnant.

11. Be seeking long-term (greater than 2 months) opiate maintenance treatment.

3.4 Informed Consent

Prior to the collection of any screening assessments or initiation of any research procedure, study personnel at each site will obtain informed consent for study participation. Adults, or legally emancipated minors will be provided with a consent form describing the study's purpose, general procedures, risks and benefits along with the participant's role in the study. The consent form is valid for a screening assessment period of 15 days (Days –42 to –28).

In cases where local requirements mandate a 24-hour waiting period between the receipt of informed consent and the signing of the informed consent, no research procedures or screening assessments may be performed prior to obtaining a signature.

All minors (15-17 years of age: except for those legally "emancipated" will be required to (a) have parental/guardian consent and (b) provide their assent to participate in the studies.

3.5 Treatment Agreement

All participants will need to self-administer Suboxone, and, therefore, they will be asked to sign an IRB approved Treatment Agreement stipulating acceptable behavior and responsible use of study medication. This agreement is similar to that recommended for use in office based practice (Appendix II).

4.0 Study Procedures

Table 1 summarizes the timing of study procedures and clinical assessments.

4.1 Screening

After obtaining informed consent, participants will complete the following questionnaires: a demographic questionnaire, the Adjective Rating Scale for Withdrawal (ARSW), A Risk Behavior Scale (RBS-measures HIV risk behaviors) and a Visual Analog Scale (VAS measuring craving and withdrawal). Each participant will also meet with qualified medical staff and undergo: the Diagnostic and Statistical Manual-IV (DSM-IV), a Clinical/Psychiatric Interview, a complete medical history, vital signs (on the Clinic Visit Form (CV), and a physical exam (PHY). Appropriately trained medical staff will also obtain blood samples for a Blood Chemistry (BC) panel, Liver Function Tests (LFTs), Complete Blood Count (CBC), serology for Hepatitis B and C, and urine for a standard urinalysis (UA), a drugs of abuse screen (U), and a pregnancy test (PG) for females of child-bearing age. A 12-lead ECG will also be obtained for all participants over 40 and for participants under 40 with a history of cardiovascular disease. Study staff will also administer the Addiction Severity Index (ASI Lite), the Clinical Opiate Withdrawal Scale (COWS) and will obtain information regarding the participant's use of medications in the previous two weeks (Prior Medication Form) and current or ongoing Adverse Events (AEs). On or off-site HIV testing and counseling will be encouraged.

Results from all of these procedures will be used to determine if the participant meets all of the inclusion and none of the exclusion criteria. Participants may not be inducted onto study drug until the results of all baseline assessments, including blood chemistries and ECG, are obtained and eligibility is determined.

Generally participants should only be assessed once to determine if they meet all of the inclusion and none of the exclusion criteria for study participation. However, there may be extenuating circumstances when a participant would become eligible if s/he could be

partially reevaluated on another day. For example, if the only item precluding participation was that the participant provided a methadone positive urine test result, the participant could be brought back on a subsequent day, and another urine screen could be conducted. If that drug screen was negative for methadone, then the participant could participate. Another example would be if the participant were eligible except for his or her reporting having been in methadone treatment within the last 30 days. The participant could be brought back at another time when 30 days would have elapsed. In either of these cases, the reevaluation must be completed within the screening period (Days –42 to –28).

The screening assessment will take approximately 6 to 8 hours, excluding review of returned lab results. Once screening is completed, and eligibility is determined, including review of lab results, participants will be scheduled for induction onto study medication (they do not have to wait the full screening period). The day of induction onto study medication becomes Day –28, no matter how long it has been since the day of consent (but not longer than 15 days). Participants who do not show up for enrollment (induction onto study drug) within 15 days of consent may not be re-consented.

4.2 Visit Schedule

The following schedule is for data collection only. Less frequent visits are not allowed, although more frequent visits may be allowed, as clinically indicated. Each clinic visit will be documented on the Clinic Visit Form (whether it be a data collection visit or a clinically indicated visit for a dose adjustment, or for a prescription).

VISIT DAY	GROUP/PHASE	MAX. PRESCRIPTION
DAY -28	All Participants/Induction	7 DAYS
DAY -25	All Participants/Stabilization (This visit may occur anytime between Days -26 and -22)	8 DAYS
DAY -21	All Participants/Stabilization (This visit may occur anytime between Days -21 and -15)	8 DAYS
DAY -14	All Participants/Stabilization (This visit may occur anytime between Days -14 and -8)	8 DAYS*
DAY -7	All Participants/Stabilization (This visit may occur anytime between Days -7 and -1)	Enough to last through Day 0*

*With Instructions to remain on stable dose from day -7 through day 0.

VISIT DAY	GROUP/PHASE	MAX. PRESCRIPTION
DAY 0	All Participants/RANDOMIZATION (3 day window - post - but becomes Day 0)	7 DAYS
DAY 7* (*G1 Day 8)	Group #1 – END OF TAPER VISIT One visit on Day 8* (3 day window - post)	NONE
	Group #2 - One visit between days 1 and 7	8 DAYS
DAY 14	Group #1 - One visit between days 9 and 14	NONE
	Group #2 - One visit between days 8 and 14	8 DAYS
DAY 21	Group #1 - One visit between days 15 and 21	NONE
	Group #2 - One visit between days 15 and 21	through day 28
DAY 28** (**G2 Day 29)	Group #1 - One visit between days 22 and 28	NONE
	Group #2 – END OF TAPER VISIT One visit on Day 29** (3 day window - post)	NONE
DAY 35	Group #1 - 1 MONTH POST TAPER FOLLOW-UP One visit between days 29 and 35 (7-day window - post)	NONE
	Group #2 - One visit between days 30 and 35	NONE
DAY 42	All Participants - Post Taper Visit One visit between days 36 and 42	NONE
DAY 49	All Participants - Post Taper Visit One visit between days 43 and 49	NONE
DAY 56	Group #1 - One visit between days 50 and 56	NONE
	Group #2 - 1 MONTH POST TAPER FOLLOW-UP One visit between days 50 and 56 (7 day window - post)	NONE
DAY 84	All Participants-3 MONTH POST RANDOMIZATION FOLLOW-UP -One visit between days 78 and 84 (7 day window - post)	NONE
DAY 91	Group #1 only - 3 MONTH POST TAPER FOLLOW-UP One visit between days 85 and 91 (7 day window - post)	NONE
DAY 112	Group #2 only –3 MONTH POST TAPER FOLLOW-UP One visit between days 106-112 (7 day window - post)	NONE

4.3 Induction

To facilitate a comfortable transition onto Suboxone (the BUP/NX combination tablet), participants will be instructed not to use any heroin or other opiates for at least 6 hours prior to the time scheduled to receive their first dose of Suboxone. Study staff at each site will document the time of last drug use and verify any signs and symptoms of withdrawal. On the day of induction, prior to taking the first dose, a urine drug screen will be obtained. Participants providing a screen positive for methadone or benzodiazepines will not be inducted onto Suboxone. Female participants of childbearing potential must also provide a negative pregnancy test on the day of induction. Withdrawal signs and symptoms, vital signs, adverse events, concomitant medications, and craving scores will also be obtained prior to induction. Vital signs will be assessed one hour after first study drug administration to ensure stability before the participant leaves the clinic.

Induction will be defined as the first 3 days of the study (-28, -27, -26) for the purpose of this protocol. The first dose of 2mg or 4mg (expressed as amount of buprenorphine) will be taken sublingually and dispensed in the clinic. Participants will be instructed to hold the tablet(s) under their tongue until the medication has dissolved. Participants will be asked to remain in the clinic for a minimum of one hour to monitor for adverse effects. Participants may receive an additional dose in the clinic at the study physician's discretion. The total dose for day -28 may not exceed 8mg (it may be less than 8mg but no more than 8mg) and may be given entirely in the clinic or part in the clinic and part at home (i.e., 4mg given in clinic and 4mg to take home). Participants should be prescribed and dispensed enough medication to continue dosing until the next scheduled office visit (no more than seven days prescription should be given on induction day). Participants will be asked to make contact with study staff on the following day and will attend the clinic and be seen by study medical staff, at a minimum, one additional day during the first week (between days -26 and -22). Office visits may be scheduled more frequently, at the study physician's discretion. The targeted induction doses, which cannot be exceeded, for days -28, -27 and -26 are as follows: Day -28 (8mg), Day -27 (12mg) and Day -26 (16mg). A daily dose, lower than the target dose, may be allowed if clinically indicated. At the next scheduled visit (between days -26 and -22), participants will be seen for vital signs, evaluation of drug use (self-report and urine screen), craving, signs and symptoms of opiate withdrawal or over medication, any adverse events, and concomitant medication (CM) use. At this visit, the dosage may be adjusted, in 4 or 8mg increments, to between 8mg and 24mg of buprenorphine. A dosing log (DL) will be completed.

All participants will sign and be given a copy of the Suboxone Information Sheet and the Treatment Agreement outlining proper use of medication for take home dosing. A wallet card will be provided to each participant in the research. This card will detail that the person carrying the card is participating in a clinical trial and is taking the drug Suboxone. This wallet card will list both local and national emergency contact numbers for study medical personnel. All participants will return to the CTP at least one additional day during the first week (between days -26 and -22). Individual sites may require more frequent contact with participants than is required for this protocol. Additional visits will

be documented by filling out the Clinic Visit (CV) CRF, but no additional data will be collected during these extra visits (i.e. COWS, ARSW, etc). If a participant's dose is changed or they are dispensed medication during one of these extra visits, this information should be recorded on the Clinic Visit Form. Participants will not be paid for extra visits over and above those scheduled on the time and event schedule.

If a subject complains of withdrawal symptoms while participating in the research study, the provision of ancillary medications, by prescription, will be at the discretion of the study physician at each site. The study physician may choose to provide a prescription to any participant for ancillary medication (other than benzodiazepines) and the participant's use of medications will be recorded on the concomitant medication form at each visit. Study physicians should also note in the clinical chart that such a prescription was provided to the participant.

4.4 Stabilization (with flexible dosing)

Days -25 to -1 comprise the flexible dosing period because prior clinical trials have suggested that individuals vary in their tolerance and treatment response to Suboxone doses. At each scheduled weekly visit during the flexible dosing period, the study physician may adjust the participant's dose in increments of 8mg. The maximum allowable dose is 24mg per day, and the minimum allowable dose is 8mg per day. Dose changes are to be made following participant assessment. At each visit, the study staff will obtain vital signs, evaluation of illicit drug use (self-report and urine), craving, signs and symptoms of opiate withdrawal or over medication, any adverse events, and concomitant medication taken since the last visit. A dosing log will also be completed at each visit. Any additional visits, during this period for clinical indications, will be documented on the Clinic Visit CRF.

All participants are to receive a constant, stable dose of Suboxone on days -7 through 0 of either 8, 16 or 24mg of buprenorphine per day (no dose adjustments may be made by the study physician after day -7).

4.5 Randomization

Participants completing the pre randomization period (-28 to -1) will be randomly assigned, on day 0, to one of two taper schedules. If for some reason, the participant is unable to attend on day 0, there will be a 3 day window following day 0 for randomization to occur. All participants must be randomized by the third day, or they will be dropped from participation. Participants who do not complete the stabilization period, or who are not randomized, may be replaced in order to obtain the appropriate randomized sample size per site. Regardless of the actual day on which participants are randomized, the day of randomization becomes day 0. The first day of either taper schedule begins on Day 1. On Randomization Day 0, participants will be given the medication for the taper, explicit written instructions detailing exactly how to take the medication for the next seven days, and told to begin the taper with the first dose on the following day (Day 1).

Although participant assignment to group will be performed at the site (CTP), the randomization cards will be prepared in advance by the Data Management Group of the Pacific Region Node (Lead Node). We expect some variation in the number of participants stabilized on each of the three doses, and we will provide sites with an adequate supply of randomization envelopes for each dose. Each CTP will receive three sets of randomization cards: one set for participants on the 24 mg dose, one set for participants on the 16 mg dose, and one set for participants on the 8 mg dose. Research assistants will be instructed simply to pull the next consecutive card from the pile corresponding to the participant's dose at the time of randomization. Participants will be assigned to the tapering schedule using a 1:1 ratio of random assignment; that is, regardless of the stabilization dose, each participant will have an equal chance of being assigned to the 7 day or the 28 day taper schedule. Participants will participate in treatment as usual at each site (CTP) during screening, stabilization, tapering and follow-up, or may be referred, following taper, to other appropriate treatment services.

4.6 Tapering

For each tapering group, the dose taper schedule is determined by the dose stratification on Day -1. Taper schedules were designed to maximize participant comfort during the taper phase regardless of group assignment. Schedules are provided for participants starting at 8 mg, 16 mg, and 24 mg doses (expressed as amount of buprenorphine).

Suboxone 7 Day Taper Regimen #1 (Days 1 through 7)

Study Day	Dose of Suboxone (expressed as amount of buprenorphine)		
	Starting dose of buprenorphine = 8 mg	Starting dose of buprenorphine = 16 mg	Starting dose of buprenorphine = 24 mg
1	8	16	24
2	6	12	20
3	6	10	16
4	4	8	12
5	4	4	8
6	2	2	4
7	2	2	2

Suboxone 28 Day Taper Regimen #2 (Days 1 through 28)

Study Day	Dose of Suboxone (expressed as amount of buprenorphine)		
	Starting dose of buprenorphine = 8 mg	Starting dose of buprenorphine = 16 mg	Starting dose of buprenorphine = 24 mg
1-2	8	16	24
3-5	6	12	20
6-8	6	10	16
9-11	6	8	12
12-14	4	8	10
15-16	4	6	8
17-19	4	4	6
20-22	2	4	4
23-25	2	2	2
26-28	2	2	2

4.7 Administrative Withdrawal

Participants in the pre randomization, stabilization phase of the study will be administratively withdrawn if they miss one full week (7 consecutive days) of medication at any time. The reason for this administrative withdrawal is that such participants would not have adequate opportunity to stabilize on the appropriate dosage of buprenorphine. Participants who are administratively withdrawn for this reason will be replaced by new participants to provide the required sample of randomized participants.

Participants in the 28 day taper schedule who miss one full week (7 consecutive days of medication) at any time during the taper will be considered to have completed their taper and will not be restarted on study medication. However, such participants may continue to attend all scheduled study visits and will be considered active participants for the purposes of all other study activities and for data analysis. If these participants choose not to continue to attend study visits they will be withdrawn/terminated. The reasons for not resuming the taper on such participants are as follows: 1) participants who have relapsed to illicit opioid use would require re-induction onto buprenorphine. The re-induction would require several days, and it would be difficult then to reestablish them on their protocol dictated taper schedule; 2) participants who have not relapsed to illicit opioid use would be better served clinically to remain off opioid agonist therapy since the ultimate goal is to reduce the buprenorphine dosage to zero, which they have effectively accomplished.

At any time during the study, if any participant misses three consecutive scheduled visits prior to Day 84 (a period of one month), he/she will be terminated (administratively withdrawn) from the study.

If a participant is hospitalized or imprisoned, he or she will be permanently discontinued from study medication and administratively withdrawn if he or she misses one full week of medication (7 consecutive days). Additionally, at any time during the study, a change in medical status that makes it unsafe for a participant to continue participating will result in study medication discontinuation and withdrawal. The Study Termination Report (STR) will reflect the appropriate reason for withdrawal/termination.

Participants who are administratively withdrawn from the study will be referred, by study personnel, to alternative treatments. This may include remaining in treatment at the study site if clinically appropriate.

4.8 Treatment as Usual (TAU)

Since the CTN protocols are designed to occur in "real-life" clinic settings, psychosocial treatment procedures in existence at each CTP will be followed throughout the study. However, in order to assure that a basic platform of participant education is provided to all participants, all CTPs will be provided with self-help buprenorphine treatment booklets for distribution to research participants. This self-help handbook is attached as Appendix III.

4.9 Post Taper and 1 Month Follow-ups

During this phase the following visits will occur and the measures listed in the time and event schedule should be obtained at the appropriate visit:

Group 1:

Day 8: End of Taper Visit (CV, AE, CM, COWS, ARSW, VAS, SQ, U, DL)
(3 day window - post)
Day 14: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)
Day 21: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)
Day 28: 1 Month Post Randomization Follow-Up
(CV, LFT, PG, AE, CM, COWS, ARSW, VAS, U)
Day 35: 1 Month Post Taper Follow-Up (7 day window - post)
(CV, RBS, PHY, BC, UA, ECG, AE, CM, COWS, ARSW, ASI, VAS, SQ, U)
Day 42: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)
Day 49: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)
Day 56: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)

Group 2:

Day 29: End of Taper Visit and 1 Month Post Randomization Follow-Up
(CV, LFT, PG, AE, CM, COWS, ARSW, VAS, SQ, U, DL)
(3 day window - post)
Day 35: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)
Day 42: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)
Day 49: Weekly Visit (CV, AE, CM, COWS, ARSW, VAS, U)
Day 56: 1 Month Post Taper Follow-Up (7 day window - post)
(CV, RBS, PHY, BC, UA, ECG, AE, CM, COWS, ARSW, ASI, VAS, SQ, U)

It should be noted that the total number of visits during stabilization, taper, post taper and follow-up are the same for both groups (however, they occur in different phases, that is group 2 has more taper visits while group 1 has more post taper visits, but the total is identical).

4.10 Three Month Follow-ups

Each group will attend two separate 3 Month Follow-Up visits, one 3 Month Post Randomization (Day 84) and one 3 Month Post Taper (the end of the taper schedule Days 91 and 112 respectively). The following is the appropriate schedule and measures to be obtained:

Group 1:

Day 84: 3 Month Post Randomization Follow-Up
(CV, AE, CM, COWS, ARSW, VAS, U)
Day 91: 3 Month Post Taper Follow-Up (7 day window - post)
(CV, RBS, COWS, ARSW, ASI, VAS, STR
SQ, U, SAE)

Group 2:

Day 84: 3 Month Post Randomization Follow-Up
(CV, AE, CM, COWS, ARSW, VAS, U)
Day 112: 3 Month Post Taper Follow-Up (7 day window - post)
(CV, RBS, COWS, ARSW, ASI, VAS, STR
SQ, U, SAE)

4.11 Post Study Options/Early Termination

Upon completion of the tapering phase, or in cases of early dropout, participants may continue in TAU at the CTP or may be referred to available local treatment resources. In the event any participant desires additional pharmacological treatment for their opiate

dependence or if the study staff finds that additional treatment is clinically indicated, the site will refer the participant to a local provider of methadone, LAAM, or buprenorphine. Participants enrolled in Treatment As Usual (TAU), usually psychosocial treatment, at the site will be encouraged to continue participation once the taper is complete, if they have not completed this treatment. Any participant who has completed TAU and desires further psychosocial treatment will be given a referral to a local treatment provider. Treatment received after the taper is complete, either pharmacological or psychosocial will not exclude the subject from further participation in this research protocol. Involvement in additional treatment(s) will be noted in the data and participation in this study will continue as outlined. In case of early drop out, a termination visit will be scheduled and all measures as indicated in the "term" column of the Time and Event schedule should be completed.

5.0 Study Medication

Suboxone [BUP/NX-combination tablet]: buprenorphine 2 mg and naloxone 0.5 mg or buprenorphine 8 mg and naloxone 2 mg sublingual tablets are manufactured by Reckitt and Benckiser (Hull, UK) and will be supplied by the approved contractor for the National Institute on Drug Abuse.

5.1 Dispensing Study Medication

Investigational agents will be prescribed, dispensed or administered (furnished) by an individual legally qualified to do so in accordance with state regulations.

Participants receiving Suboxone will be instructed to hold the tablet(s) under their tongue until the tablets have dissolved. Dissolution of tablets will be monitored at each CTP by a nurse, physician or pharmacist, as clinically warranted. Participants will be asked to remain in the clinic, to be observed, for at least one hour on the first day of treatment following the administration of Suboxone. Vital signs will be measured pre and post dose, and participants will be asked not to leave the clinic until vital signs are stable.

5.2 Labeling

Study medication will be distributed to investigational sites in bottles of 30 sublingual tablets. Each site will prepare individual prescriptions for each participant visit. These prescriptions will be provided in child resistant packaging and clearly labeled "Investigational Use Only and "Keep Out Of Reach Of Children." This is an open-label study with no blinding of investigational agents.

5.3 Drug Accountability

Accurate recording of all investigational agents received, dispensed, prescribed or administered, and returned or destroyed will be made.

6.0 Participant Compensation

Participants will be compensated in scrip or cash for their participation in accordance with local IRB requirements. Some sites may be required to compensate participants using scrip. For sites required or electing to use scrip, each CTP can determine what type of scrip is most appropriate (e.g., gift certificates for groceries, department stores, etc.).

Participants will receive $25 in scrip or cash for the following visits; screening, immediately post taper, and for each of the1 month post taper, 3 month post randomization and 3 month post taper visits. Participants completing all post taper visits (end of taper, 1 month and 3 month) will receive an extra $25 in scrip or cash. Participants will receive $10 in scrip or cash for each of the weekly clinic visits during days 1-56 (not including the end of taper and 1 month post taper visits). There are 6 of these visits for each group. The maximum compensation for participation available to participants in scrip or cash will be $210 for either group ($125 for screening and 4 post taper visits, plus $25 bonus, plus $60 weekly visits = $210).

7.0 Measures

7.1 Locator Form

A Basic Locator Questionnaire will be completed at screening and kept confidential and separate from the participant's research records. The Basic Locator Questionnaire will be used to facilitate contact with the participant during the study and follow-up. Participants will be asked to provide locator information including their residential street address and a working telephone number, or an address of a relative if they are homeless, as well as the address and telephone number of a non-drug abusing relative or friend who can reach the participant in emergencies. This information will be updated periodically throughout the study and follow-up.

7.2 Demographic Data

Each participant will complete a Demographic Data Form that records information regarding race and ethnicity, age, education, marital status, and employment status.

7.3 Diagnostic and Statistical Manual-IV (DSM-IV)

The DSM-IV Checklist for Substance Dependence is a clinician-rated questionnaire used to determine the participant's dependence on opiates, benzodiazepines, alcohol, amphetamines, cocaine, cannabis, hallucinogens, inhalants and sedatives. The checklist will be completed at screening. This diagnostic tool will be used to determine that the participant currently meets criteria for opiate dependence. Results of this assessment will aide the physician in assessing the potential participant's benzodiazepine use history in order to help determine eligibility to participate.

7.4 Clinical/Psychiatric Interview

Each participant will be interviewed by the study physician or other appropriately trained medical staff, prior to enrollment, to determine any possible psychiatric or medical exclusion and to obtain a complete psychiatric history. Qualified examiners will document the presence or absence of psychiatric or medical exclusions in the progress notes, on the inclusion/exclusion form and/or on a Medical/Psychiatric Eligibility Assurance Form (a non-data form).

7.5 Inclusion/Exclusion

Inclusion/Exclusion criteria will be assessed at the conclusion of screening in order to determine a potential participant's eligibility. This form may not be completed until all laboratory results and ECG readings (if applicable) are returned and reviewed at the site.

7.6 Medical History

The study physician (or other qualified medical study staff) will conduct a complete medical history covering past and present conditions to help determine eligibility and to provide baseline information regarding medical conditions.

7.7 Clinic Visit Form (CV)

This form is filled out each time the participant is seen at the site, whether for a scheduled visit or for an extra (non-data) visit. Non-data visits may include visits simply to prescribe additional medication or to adjust medication dosage. It will not be filled out for TAU visits, such as psychosocial treatment sessions. At scheduled data visits, this form will be used to collect information regarding amount and type of psychosocial treatment since the last data visit, vital signs (including weight, oral temperature, blood pressure, pulse rate and respiration), pregnancy test results, self-reports and urine drug screen reports of illicit drug use, and prescription and dosing information. At non-data visits, only header information and prescription information (if applicable) will be completed.

7.8 Induction Form

This form documents that inclusion/exclusion criteria have all been satisfied and that the day of induction falls within the appropriate time frame after consent. It is also used to document dropouts prior to induction (i.e. screen fails or no shows for induction). This form will be faxed to the coordinating center at UCLA when a participant is inducted. The coordinating center will fax back to the sites an attendance log, which delineates the appropriate dates for visits up to randomization day (Day 0).

7.9 Risk Behavior Survey (RBS)

This is a brief, 12-item (with multiple sub-items) interviewer administered assessment of HIV risk behaviors including intravenous drug use and sexual risks. This survey will be utilized to assess degree of HIV-infection risk by looking at risk behavior. Measures will include extent and methods of past drug use, sexual preference, sexual history, and extent of unprotected sex; and assessment of travel to international locations of increased HIV-infection rates. This measure takes approximately 20 minutes to administer.

7.10 Liver Function Tests (LFTs)

In addition to collection of liver functions tests (LFTs) at screening, LFTs (including AST, ALT, GGT, ALP, and Bilirubin) will be repeated every 4 weeks for all participants while receiving medication (regardless of Hepatitis B/C status). Specifically, LFTs will be collected, in addition to screening, on Study Day 0 and on study day 28 for all participants (with a 7 day window). Repeat LFTs will also be obtained upon early termination from the study if more than one month has passed since they were last assessed.

Laboratories performing any of the blood tests must either be directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. All sites must provide normal values for their designated lab and proof that the lab is CLIA or CAP certified.

If AST, ALT, GGT, ALP collected at Day 0 or Day 28 are greater than 3 times the normal limit and these results represent an increase of more than 25% from the screening LFT or the total bilirubin is greater than 2.0 mg/dL or the participant has symptoms suggestive of liver toxicity (e.g. fever, extreme fatigue, dark urine, clay colored stools, jaundice), LFTs will be repeated as clinically indicated and at a frequency of not less than every 2 weeks until results are reliably decreasing or stable. If a participant has worsening symptoms or LFTs continue to increase (AST, ALT, or GGT>500 IU or Bilirubin>3.0 mg/dL), physicians should handle the situation as clinically indicated and are strongly encouraged to consult with the study Medical Monitor and/or a hepatologist. All referrals and consultations are to be clearly noted in medical progress notes.

7.11 Physical Exam (PHY)

The study physician (or other qualified medical study staff) will complete a physical exam to help determine eligibility, to ensure that there are no medical concerns regarding participation and to gather baseline information regarding the participant's physical health. The physical exam will be repeated at the 1 Month Post Taper Follow-Up and at early termination if more than one month has passed since last assessed.

7.12 Hematology/Chemistries/Hepatitis

Complete blood counts (CBC) with differentials and platelet count and a standard Blood Chemistry Panel (BC) will be performed to help determine eligibility at screening.

Hematologic tests will also be repeated at the 1 Month Post Taper Follow-Up visit or upon early termination from the study if more than one month has passed since they were last assessed. At screening, Hepatitis B and C serologies will be conducted including Hepatitis B surface antigen (HBs Ag), Hepatitis B core IGM antibody (Anti-HBc) and Hepatitis C virus antibody (HCV Ab).

Laboratories performing any of the blood tests must either be directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. All sites must provide normal values for their designated lab and proof that the lab is CLIA or CAP certified.

7.13 Routine Urinalysis (UA)

Standard urinalysis will be performed to help determine eligibility at screening. Urinalysis will also be repeated at the 1 Month Post Taper Follow-Up visit or upon early termination from the study if more than one month has passed since the last assessment. Each site will be asked to provide normal values from the lab conducting the urinalysis for their site and proof that the lab is certified.

7.14 12-Lead Electrocardiogram (ECG)

Participants over the age of 40, or those under the age of 40 with a history of cardiovascular disease, will be administered 12-lead ECGs at screening and at the1 month post taper follow-up visit. Repeat ECGs should also be obtained on participants (with screening ECGs) who terminate early from the study if more than one month has passed since the last ECG was performed. In order to standardize collection of ECGs across site and ensure ECGs are collected and interpreted in the same manner, the Pacific Node will subcontract with Covance Central Diagnostics for the collection and interpretation of ECGs at each participating CTP throughout the CTN. Covance Central Diagnostics will provide equipment, training, toll free transmission, interpretation and hard copy reports using the MTX-2 telephonic transmission device. The portable MTX-2 permits digital data acquisition, onboard storage, and remote transmission and interpretation and yields high quality ECGs. Reports are received within two hours of ECG collection to facilitate faster inclusion/exclusion decisions and participant care.

7.15 Pregnancy Testing (PG)

Female participants will be required to have a negative pregnancy test (PG) prior to induction and monthly thereafter while receiving Suboxone. Buprenorphine is a Pregnancy Category C Drug. Female participants will also be expected to practice acceptable birth control. Women who become pregnant any time prior to day 7 or 28 (depending on randomization group assignment) will be withdrawn from the study and given immediate access to methadone maintenance services at the CTP or another local treatment provider. Participants refusing methadone maintenance will be referred to another local provider, preferably one providing specialized services for pregnant or post-

partum women. Results of the pregnancy test performed every 4 weeks (Days - 42, -28, 0, 28), will be recorded on the Clinic Visit CRF.

7.16 Adverse Events (AE)

A study physician (or appropriately medically trained designee such as a Physician Assistant or Nurse Practitioner) will meet with the participant once a week to perform an assessment for AEs including any medical or psychiatric side effects. The type of AE, severity of the AE, and the relationship to the study medication will be recorded on an AE CRF. Assessments for serious AEs that may have occurred since the last visit will also be done at the 1 and 3 month follow-ups.

7.17 Prior/Concomitant Medications (CM)

The Prior Medication Form and the Concomitant Medication Form will collect information regarding prescription and over-the-counter drugs used by each participant. At screening, the Prior Medication Form will be used to assess medications taken by the participant for the two-week period prior to the screening. At each scheduled data visit, the Concomitant Medication Form will be used to assess medications taken since the previous visit. Concomitant medications will be recorded at each clinic visit up to and including the visit at Day 84.

7.18 Randomization Form

This form will be used to document the day the subject was randomized, the group assignment and the randomization card number. This form will be faxed to the coordinating center at UCLA when a participant is randomized. The coordinating center will fax back to the sites an attendance log, which delineates the appropriate dates for each additional visit, post randomization. An attendance log will also be provided for the period between Induction and Randomization.

7.19 Clinical Opiate Withdrawal Scale (COWS)

The COWS is an 11-item interviewer administered questionnaire designed to provide a description of signs and symptoms of opiate withdrawal that can be observed directly in the participant (e.g., sweating, runny nose, etc). The COWS will be administered at each clinic visit up to and including the 3 Month Post Taper Follow-Up (Days 91 and 112 respectively). On induction day this measure is to be completed pre dose (screening COWS) and post dose for the induction day COWS.

7.20 Adjective Rating Scale for Withdrawal (ARSW)

The ARSW is comprised of 16 signs and symptoms of opioid withdrawal (Bickel et al., 1988a, 1988b; Amass et al., 2000). Participants rate themselves on a scale ranging from 0 (none) to 9 (severe) (maximum cumulative score = 144) on the following items: muscle

cramps, depressed or sad, painful joints, excessive yawning, hot or cold flashes, trouble getting to sleep, sick to stomach, irritable, runny nose, poor appetite, weak knees, excessive sneezing, tense and jittery, watery eyes, abdominal cramps, and fitful sleep. The ARSW will be completed at each clinic visit up to and including the 3 Month Post Taper Follow-Up (Days 91 and 112 respectively). On induction day this measure is to be completed pre dose (screening ARSW) and post dose for the induction day ARSW.

7.21 Addiction Severity Index Lite (ASI-Lite)

The ASI Lite is a standardized, multidimensional, semi-structured, comprehensive clinical interview, which provides clinical information important for formulating treatment plans as well as problem severity profiles in six domains commonly affected in substance abusers (McLellan et al., 1985). The domains covered are chemical abuse (alcohol and drug), medical, psychiatric, legal, family/social and employment/support. Composite scores for each problem domain are derived mathematically and used as change measures or outcome indicators as a function of treatment intervention. This instrument also provides clinically necessary information on whether the participant is at imminent risk for suicide, thus permitting evaluators to implement any needed immediate and/or early intervention strategies. A revised version of the ASI Fifth Edition, 1997 version (ASI Lite), that includes only those questions used to derive the composite scores along with some demographic information will be administered by a research staff member having at least a Bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. Composite scores will be calculated according to the procedures described by McGahan *et al.* (1982), Carroll *et al.* (1994). The ASI Lite will be administered at screening and at each of the 1 and 3 month Post Taper Follow-Up visits for each group.

7.22 Visual Analog Scales (VAS)

Three VASs will be completed at each clinic visit up to and including the 3 Month Post Taper Follow-Up visit. The scales consist of 100-point lines anchored with "not at all" on one end and "extremely" on the other. Participants will report at each clinic visit the extent to which they felt any craving for opiates, the severity of their withdrawal symptoms, and the extent to which the study medication has helped to ease the cravings (if applicable). On induction day this measure is to be completed pre dose (screening VAS) and post dose for the induction day VAS.

7.23 Study Termination Report (STR)

This form officially tracks the participant's status in the study. It should be completed at the participant's last visit (the 3 Month Post Taper Follow-Up) if the participant completes the study to that point. If the participant drops out of the study prior to completing the 3 Month Post Taper Follow-Up, the STR should be filled out when the participant is officially dropped from participation in the study. This form records reasons for drop out

and whether or not the participant completed the protocol. The date of the last participant contact (prior to drop out) will be recorded on this form.

7.24 Satisfaction Questionnaire (SQ)

The Satisfaction Questionnaire (SQ) is a brief, participant-administered questionnaire asking the participant to rate her or his satisfaction, on a 5 point Likert scale, with their treatment experience. Participants will complete the SQ at the end of taper visit and at 1 and 3 Month Post Taper Follow-Ups.

7.25 Urine Drug Screen (U)

Urine drug screens are always to be collected before dispensing medications. All urine specimens will be collected using temperature controlled urine drug test cups. Urine will be collected at screening, at induction (Day –28) just prior to the first dose of Suboxone, and at each scheduled visit thereafter including each follow-up visit. For this measure, an FDA-approved one-step test will be used. Following collection of the urine sample, staff will immediately perform the test, wait for the results and record the results on the Clinic Visit CRF, following all of the manufacturer's recommended procedures.

Sites that have supplies of Jant's Accutest MultiDrug Screen-10 will use that test kit to screen urine for drugs (until the supply is exhausted). Sites that do not have, or run out of, the Accutest will use ABI's SureStep Drug Screen Card 10A. Both of these kits will test for the presence of the following 10 drugs: amphetamines, barbiturates, benzodiazepines, methadone, tricyclic antidepressants, cocaine, methamphetamine, morphine, phencyclidine, and marijuana. In addition, all sites will test for the presence of oxycodone utilizing ABM's Rapid One Oxycodone single dipstick.

7.26 Dosing Log (DL)

The Dosing Log is an interviewer-administered form where the interviewer collects information from the participant about the amount of Suboxone actually taken each day since the participant's last visit.

7.27 Serious Adverse Event (SAE)

Serious Adverse Events will be recorded at each visit up to and including the 3 Month Post Taper Follow-Up, when applicable, and will be reported in accordance with federal, state and local regulations and guidelines. If any staff becomes aware within one year following study completion of an SAE, for any consented participant, this information will be reported in accordance with all regulatory guidelines.

8.0 Regulatory and Reporting Requirements

8.1 IRB Approval

Prior to initiating the study, the investigator at each study site will obtain written IRB approval to conduct the study. Written IRB approval must be obtained for the study protocol and the associated Informed Consent Form. Should changes to the study protocol and/or Informed Consent Forms become necessary, protocol amendments and/or Informed Consent Forms will be submitted in writing to the IRB, by the investigator, for IRB approval and stamping prior to implementation. In addition, IRBs will approve all advertising materials used for participant recruitment and any educational materials (self-help handbooks) given to the participant.

8.2 Informed Consent

All potential candidates for the study will be given a current copy of the IRB approved Informed Consent Form to read and keep. The investigator, sub-investigators, or study physician at each site will explain all aspects of the study in lay language and answer all questions regarding the study. Candidates who desire to participate in the study will be asked to sign the Informed Consent. Informed Consent will be obtained following all federal regulations and good clinical practice procedures. No study procedure will be performed prior to signing Informed Consent. Participants who opt not to participate or who withdraw from the study will be treated without prejudice. The reason for refusal or withdrawal will be noted on the appropriate CRF.

8.3 Drug Accountability

Upon receipt of the study drug Suboxone, the investigator/pharmacist will be responsible for taking an inventory and providing secure storage. A record of this inventory must be kept and usage must be documented. Any unused or expired Suboxone shall be returned to the provider, unless otherwise instructed. Written instructions and standard operating procedures for drug accountability and return of unused medication will be provided to each site in the operations manual. Training will also be provided, prior to study implementation, on drug accountability, storage, dispensing, use and handling, and return of unused medications.

8.4 Within Study Monitoring

All investigators will allow representatives of their parent Node and/or the Lead Node to audit on a regular basis, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each participant. These monitoring visits provide the parent Node and the Lead Node the opportunity to evaluate the progress of the study at each site and to identify potential problems at the study sites and trends across study sites. The Node level monitors will assure that protocol procedures are being followed, that submitted data are accurate and in agreement with source documentation,

verify that investigational medications are properly stored and accounted for, verify that participants' consent for study participation has been properly obtained and documented, confirm that research participants entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practice guidelines and federal regulations is appropriately filed.

Routine monitoring visits by the Node monitors will be scheduled at appropriate intervals, more frequently at the beginning of the study. All Node level reports will be provided, in a timely manner, to the offices of the Lead Node. Study personnel from the Lead Node will review all Node level monitoring reports and may offer additional training, or provide guidance to the sites in the proper conduct of the study. The Lead Node may, in conjunction with the parent Node and the sponsor (NIDA), take steps to terminate enrollment at any site that, after corrective procedures have been implemented, continues a pattern of serious protocol violations.

The Lead Node monitors will synthesize reports from all sites and will be able to detect any trends or recurring problems during the implementation of the protocol. This will allow the Lead Node to take corrective actions in a timely manner so as to protect the rights of all participants at all sites.

The Quality Assurance procedures to be covered at monitoring visits and a checklist of activities are provided in the operations manual, and training will be provided to all study staff, at all sites, in these procedures.

8.5 Outside Monitoring

Data and Safety Monitoring Board: The conduct of this trial will be monitored by an independent Data and Safety Monitoring Board (DSMB). The Board will examine accumulating data to assure that the risks and benefits of participation remain acceptable and that the results of the trial will be considered scientifically reliable. The conditions under which the Board will examine this data are described below.

Interim analysis of accumulating data by treatment assignment is not planned. Rather, in accordance with the Board's standard operating procedures, presentation of primary and secondary outcome data will be presented for all treatment groups, further broken down by study Node and, if feasible, by CTP. No statistical penalty will be taken for this interim analysis of efficacy data, which will be conducted for the sole purpose of assessing the acceptability of study results.

Adverse event data and other data intended for the monitoring of safety will be presented to the DSMB in an unblinded fashion. Since the trial is not considered to be powered to demonstrate statistically significant differences in adverse events or other safety outcomes, p-values will not be calculated for any differences observed unless specifically requested by members of the Board to assist in the evaluation of a potential safety

concern. No adjustments will be made for the number of interim analyses in the final report.

Although interim analysis of efficacy data is not planned, the Board may feel that such analysis is necessary to permit proper evaluation of study data. For instance, if there are unexpectedly high rates of early dropout from the taper schedules, or toxicity in one group, then interim analysis of efficacy may be needed. Should an unscheduled interim analysis of efficacy be necessary, the Board will specify the question, the analysis required, the critical values for a decision and the statistical procedures necessary to control the overall type 1 error at $p<0.05$. A protocol amendment will be included in the DSMB report of the analysis describing necessary changes in the statistical plan that result from the analysis.

Clinical Monitors: All investigators will allow representatives of the sponsor to audit periodically, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each participant. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to inform the sponsor of potential problems at the study sites. The monitors will assure that protocol procedures are being followed, that submitted data are accurate and in agreement with source documentation; verify that investigational medications are properly stored and accounted for, verify that participants' consent for study participation has been properly obtained and documented, confirm that research participants entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practice guidelines and federal regulations is appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study related documentation exists, assist in training investigators and other site personnel in study procedures and Good Clinical Practice guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals, more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will advise on storage of study records and return of unused study medication. All sites should anticipate visits by NIDA, independent clinical monitors and/or the FDA.

The Quality Assurance procedures to be covered at monitoring visits and a checklist of activities are provided in the operations manual, and training will be provided to all study staff, at all sites, in these procedures.

8.6 Adverse Events Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported according to the specific instructions detailed in this section of the protocol and in the Operations Manual. The occurrence of AEs will be assessed at each clinic visit through the 1 Month Post Taper Follow-up. An assessment for SAEs will also be done at the 3 Month Post Taper Follow-Up visits.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication related or clinically significant. For this study, AEs will include events reported by the participant. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs and should be accounted for in participant's medical history. All AEs must be recorded on the AE Form. The AE Form is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a qualified and trained medical staff member and/or physician must review the AE Form completed for the previous week for any events that were reported as continuing, as well as assess occurrence of any new AEs since the previous visit. Study investigators and/or physicians will follow all AEs regardless of severity, until satisfactory resolution. AEs are to be collected/reported at each visit up to the 3 Month Post Randomization Follow-Up (Day 84).

Withdrawal symptoms are to be reported as AEs on the AE form, but coded as withdrawal symptoms so as to differentiate from other non-withdrawal related, but similar AEs.

8.7 Serious Adverse Events

Each AE will be classified by trained study medical staff as serious or non-serious and appropriate reporting procedures followed. Serious adverse events (SAEs) are defined as any fatal event, immediately life-threatening event, permanent or substantially disabling event, event that requires or prolongs inpatient hospitalization, or congenital anomaly. This category also includes any event that a study investigator or the DSMB judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution. An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure.

Any SAE (including death) due to any cause, which occurs during the course of this investigation, whether or not related to the investigational medication, must be reported within 24 hours by telephone to:

NIDA Medical Safety Monitor
Fax: 301-443-2317
Voice: 301-443-6697

And to:

Walter Ling, M.D., 310-312-0500, ext. 317; or
Jerry Cunningham-Rathner 310 312-0500 ext 353 or
Christie Thomas 310-312-0500 ext 379 and to the study Medical Monitor
Andrew Saxon, M.D. at (206) 277-3770

The telephone report is to be followed by submission of a completed AE and SAE Form with demographic information and a narrative explanation of the event. Attached to the AE and SAE Forms should be photocopies of the Concomitant Medication Forms and the Medical History Form from the participant's CRFs. All SAEs are also to be reported immediately to the Lead Node and the local Institutional Review Board (IRB) according to local regulatory requirements. All participating investigators, at all sites, will be notified of any unexpected SAEs, occurring at other sites, in an IND safety report from the sponsor. The Lead Investigator will report all SAE's to the IRB of record (UCLA M-IRB) according to the rules and regulations of the IRB (i.e. serious/life-threatening SAE's within 48 hours and all other SAE's within 5 days of discovery).

NIDA, as IND holder, is required by FDA regulations to report SAEs to the FDA in a timely fashion. SAEs that are unexpected must be reported to the FDA, in writing, within ten working days from the date the sponsor was notified of the SAE. If the SAE is fatal or life threatening, there is an additional obligation of the sponsor to notify FDA by telephone within 3 working days, with a follow-up written report in 10 working days.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA so that the sponsor can comply with these regulations.

In the event that a study participant either withdraws from the study or an investigator decides to discontinue the participant from the study due to a SAE, the participant must have appropriate follow-up medical monitoring. Monitoring will continue until the SAE resolves, is stabilized with no further change expected, is discovered to be clearly unrelated to study medication, or progresses to death.

9.0 Analytical Plan

9.1 Statistical Hypotheses

The objective of this study is to compare, in the outpatient setting, the relative advantage of two rates (7 vs. 28 days) of Suboxone tapering following four weeks of flexible dose

stabilization, as reflected by the proportion of participants providing opiate free urines at the end of the taper regimen. It is hypothesized that the longer tapering schedule will result in a higher proportion of participants giving opiate free urines on the day following the end of the taper regardless of the stabilization dose.

9.2 Outcome Measures

Primary Outcome Measure

In keeping with this hypothesis, there is one primary outcome, the proportion of participants providing opiate free urines in each group on the day following the end of the taper. This outcome will be evaluated at the end of the taper. It will also be evaluated at 1 and 3 months post completion of tapering.

Secondary Outcome Measure

Several secondary outcomes will be evaluated. These include:

1. Comparison of number of opiate free participants by stabilization dose and taper schedule.
2. Comparison of:
   a. The number of opiate free urine specimens at follow-up
   b. The number of all drug free urine specimens at follow-up
   c. Frequency of concomitant medication used to treat withdrawal symptoms
   d. Severity of withdrawal symptoms as assessed by COWS and ARSW
   e. The mean VAS craving level of each group
   f. The mean SQ score (participant satisfaction) of each group
   g. The number and severity of adverse event

These measures will be analyzed within a time course framework. We will compute change from baseline to follow-up in measures taken only at those timepoints (ASI). For measures collected repeatedly throughout the taper schedule (COWS, ARSW, SQ, concomitant meds, adverse events), we will plot the pattern of responses by group over time.

9.3 Intent-to-Treat and Evaluable Populations

The main intent-to-treat population is defined as the participants who are randomized to a tapering schedule at the end of the 28 day induction and stabilization. The evaluable participant population is defined as participants who are randomized and who complete the tapering schedule without being administratively withdrawn. Parallel analyses will be conducted on these two populations, and their results compared, to assess the impact of completion status on the results.

9.4 Analysis Plan

Each of the primary and secondary outcome measures will be analyzed for the intent-to-treat population and for the evaluable participant population. Major differences in the results, if any, will be further explored. While there is every intention to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency and some adjustments may be required to meet constraints posed by the structure of the data.

Equality of groups at baseline will be established by comparing demographic and drug use information collected on the ASI. A test of proportions will be used for main outcomes evaluated at treatment end. Continuous on-study data will be evaluated using three-factor analysis of covariance with detoxification schedule as one factor (fixed effect), stabilization dose as the second factor (fixed effect), and site as the third factor. Baseline demographic values, where they potentially affect the responses on study or where they are found to be unevenly distributed between groups at baseline despite randomization, may be investigated post hoc. Interaction effects including, but not necessarily limited to, taper schedule X dose, will be investigated post hoc. Repeated measures, survival, and time course analyses will be employed where appropriate.

Statistical tests will be two-sided at a 5% level of alpha. Confidence intervals will be two-sided with a 95% confidence coefficient.

9.5 Descriptive Statistics

Summaries of the characteristics of the participant population in both treatment arms at baseline will be prepared to investigate group equality at baseline as well as provide information necessary for decisions about covariates in post hoc analyses. A summary will be prepared to show dropouts/retention over time in each treatment group. The number of missing observations will be compared between treatments. The compliance of each group at each assessment day will be summarized.

Treatment effects will be summarized by gender, ethnicity, and age group separately. No attempt will be made to assess these factors together in order to maintain power for the main comparisons.

All adverse events will be reported in tabular form indicating the frequency of each type of event by various demographic characteristics such as gender, ethnicity, age, duration of addiction, other medical problems both related to and independent of the addiction.

9.6 Sample Size Estimate

The sample size determination was based on how many opiate users seeking treatment that the sites are capable of recruiting. With 11 sites, each site would be responsible for randomizing approximately 44 participants. It is possible that recruitment may not be

adequate at some sites and therefore enrollment may not be equal across sites. The total N will remain at 480

In a Phase III study for evaluation of the efficacy and safety of the combination product of buprenorphine and naloxone in opiate dependence, Study 1008, the percent of participants with opiate free urine samples after four weeks of treatment was 5.8% in the placebo group, 21% in the buprenorphine group and 18% in the combination group. Assuming that the percent of opiate free urine samples in a control group is 20%, the difference of 12% is considered a clinically significant improvement, and 240 participants per group would provide approximately 82% power for detecting this 12% difference. If 20% of participants dropout in the current study, and dropout occurs at random, then the sample size of 240 participants per group will provide 72% power for detecting a difference of 12%.

In Study 1008A, the mean craving score at Week 4 was 55.1 in the placebo group, 29.8 in the monotherapy group and 33.0 in the combination group. The standard deviation of VAS was estimated from the confidence interval for the difference between treatment groups presented in the 1008 study report. It was estimated to be 40.7. The sample size of 240 per group will provide at least 90% power to detect a difference between the mean craving scores of 33 and 44 at the 0.05 level.

9.7 Post Hoc Analyses

During the course of conducting the primary and secondary analyses, the data may suggest other interesting differences in the treatment groups. Post hoc analyses are anticipated to explore these findings. One potential post hoc analysis would be the exploration of factors found to be significantly different between groups at baseline, as they relate to study outcomes. Another potential post hoc analysis would be the exploration of interaction effects in the Analysis of Covariance (ANCOVA) models of continuous data, including but not necessarily limited to, taper schedule X dose interactions. Still another possible post hoc analysis would be to look at the group differences based on intent-to-treat samples using randomization as the starting point of treatment. Analyses would then be conducted on data from 1 Month Post Randomization and at 3 Months Post Randomization (rather than post taper as in the primary analysis). This is made possible by the design, because participants in both groups are seen for equal contacts following randomization.

10.0 Data Management and Case Report Forms (CRF)

The Pacific Region Node and NIDA will coordinate data management activities and statistical analytical support.

10.1 Data collection

Data will be collected at the study sites and transcribed to either electronic or paper CRFs. The Pacific Region Node will provide other participating nodes with a sample set of CRFs to incorporate in their data management system as appropriate. Each node will prepare identical and numbered CRFs with the data management system at use in the node. The CRFs will be distributed to the node's CTPs by the node data management center. These forms are to be completed on an ongoing basis during the study. The medical chart is the source of verification of data. Forms should be completed according to the instructions provided during training. The investigator is responsible for maintaining accurate, complete and up-to-date records and for tracking receipt and return of CRFs for each participant. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

Paper CRFs must be completed legibly with black ballpoint pen. Corrections should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. Corrections to paper CRFs must be initialed and dated by the person making the correction. Data entered into electronic or paper CRFs must be performed by authorized and trained individuals. Corrections to electronic CRFs shall be tracked electronically with time, date, individual making the change, and what was changed.

During the study, the CRF will be monitored for completeness, accuracy, legibility and attention to detail, both by internal and external monitors. The investigator must retain a copy of all CRFs.

10.2 Data Accrual, Editing and Control

Completed forms/electronic data will be submitted on a regular basis to the node's data management center. When data are received at the node's data management center, they will be reviewed and, if incomplete or inaccurate data are found, a data clarification request will be forwarded to the sites for a response. Sites will resolve data inconsistencies and errors prior to returning data to the node's data management center. All corrections and changes to the data will be reviewed by the Investigator, or his designee, prior to being entered into the study database. Each node will be provided with instructions for the database physical and logical structures including the data dictionary to be developed within their data management system.

10.3 Data Entry, Processing and Analyses

Data will be entered into the database at each node's data management center using the system inherent to the node. Periodically during the investigation (but not less than 4 times per year), data sets will be submitted to the NIDA CCTN central data repository according to procedures provided during training. NIDA CCTN central data repository

will provide the database to the Lead Node for data analysis, both periodically (not less than 4 times per year) and at the completion of the study.

10.4 Study documentation and Records Retention

Study documentation includes all case report forms, data correction forms, electronic data files, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approved consent form and signed participant consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

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. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, participant/patient diaries, ultrasound photographs, participant/patient progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

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.

Federal, state, and institutional regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of clinical trials. Unless otherwise specified, these documents must be kept for a minimum of two years after termination of the IND or 2 years after the approval of a New Drug Application (NDA). When regulations differ, the one that is most stringent must be adopted.

11.0 Confidentiality

11.1 Confidentiality of Data

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

By signing this protocol the investigator affirms to the sponsor that information furnished to the investigator by the sponsor will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethical Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate

understanding of confidentiality with such board or committee, affiliated institution and employees.

11.2 Confidentiality of Participant Records

By signing the protocol the investigator agrees that within local regulatory restrictions and ethical considerations sponsor, sponsor's representative, NIDA or any regulatory agency may consult and/or copy study documents in order to verify case report form data.

11.3 Certificate of Confidentiality

This study will operate under a Confidentiality Certificate, which will be in place before the study begins and protect identifiable research information from forced disclosure. The certificate protects against compulsory legal demands, such as court orders and subpoenas, in any federal state, or local civil, criminal, administrative, legislative, or other proceedings.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (DEA).

Sensitive information protected by the certificate includes (but is not limited to) information relating to sexual attitudes, preferences, or practices; information relating to the use of alcohol, drugs, or other addictive products; information pertaining to illegal conduct; information that, if released, might be damaging to an individual's financial standing, employability, or reputation within the community or might lead to social stigmatization or discrimination; and information pertaining to an individual's psychological well-being or mental health.

However, this protection is not absolute. Personally identifiable information protected by a certificate may be disclosed if participants themselves consent to such action in writing; scenarios involving child abuse, reportable communicable diseases, possible threat to self or others; or voluntary compliance by the researcher with reporting requirements of state laws such as knowledge of communicable disease, provided such intention to report is specified in the informed consent form.

12.0 Signatures

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 8.7 of this protocol.

Typed Name	Signature	Date
_____	_____	_____
Primary Site Investigator		
_____	_____	_____
Sub Investigator		
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