NIDA CTN Protocol 0027

Starting Treatment with Agonist Replacement Therapies (START)

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CONTACT INFORMATION

CTN Co-Chairmen:

Walter Ling, MD
Director, Integrated Substance Abuse Programs
University of California, Los Angeles
11075 Santa Monica Boulevard, Suite 200
Los Angeles, CA 90025
Phone: (310) 267-5888
Fax: (310) 312-0552
E-mail: lwalter@ix.netcom.com

Andrew Saxon, MD
Director, Addiction Treatment Center
Veterans Affairs Puget Sound Health Care System
1660 South Columbian Way, (116 ATC) Box 358280
Seattle, WA 98108
Phone: (206) 764-2782
Fax: (206) 764-2293
E-mail: Andrew.saxon@med.va.gov

John Rotrosen, MD
Department of Psychiatry
New York University School of Medicine/VA NYHHS
423 East 23rd Street, VET-17W
New York, NY 10010
Phone: (212) 263-6802
Fax: (212) 951-6891
E-mail: john.rotrosen@med.nyu.edu

Ron Jackson, MSW
Executive Director, Evergreen Treatment Services
1700 Airport Way South
Seattle, WA 98134-1618
Phone: (206) 223-3644
Fax: (206) 223-1482
E-mail: ronjack@u.washington.edu

NIDA Project Director:

Frank Vocci, PhD
Director, Division of Pharmacotherapies &
Medical Consequences of Drug Abuse
National Institute on Drug Abuse
National Institutes of Health
6001 Executive Boulevard, Room 4123
Bethesda, MD 20892-9551
Phone: (301) 443-2711
Fax: (301) 443-2599
E-mail: fv6k@nih.gov

CONTACT INFORMATION - *continued*

Mary Ellen Michel, PhD
Deputy Director, Center for Clinical Trials Network
National Institute on Drug Abuse
National Institutes of Health
6001 Executive Boulevard
Bethesda, MD 20892-9551
Phone: (301) 435-0883
Fax: (301) 443-2317
E-mail: mm108w@nih.gov

National Project Director:

Albert Hasson, MSW
Integrated Substance Abuse Programs.
University of California, Los Angeles
11075 Santa Monica Boulevard, Suite 200
Los Angeles, CA 90025
Phone: (310) 267-5224
Fax: (310)312-0552
E-mail: alberthasson@earthlink.net

NIDA Medical Monitor:

Roberta Kahn, MD
Div. of Pharmacotherapies & Medical
Consequences of Drug Abuse
National Institute on Drug Abuse (NIDA)
National Institutes of Health
6001 Executive Boulevard, Room 4123
Bethesda, MD 20892-9551
E-mail: rkan@nida.nih.gov

NIDA Regulatory Affairs Manager:

Robert Walsh
Chief, Regulatory Affairs Branch
Div. of Pharmacotherapies & Medical
Consequences of Drug Abuse
National Institute on Drug Abuse (NIDA)
National Institutes of Health
6001 Executive Boulevard, Room 4123
Bethesda, MD 20892-9551
E-mail: rwalsh@nida.nih.gov

NIDA CCTN Protocol Coordinator:

Petra Jacobs, MD
National Institute on Drug Abuse
National Institutes of Health
6001 Executive Boulevard, Room 3105, MSC 9557
Bethesda, MD 20892-9551
Phone: (301) 443-6697
Fax: (301) 443-2317
E-mail: pjacobs@nida.nih.gov

IND Holder:

National Institute on Drug Abuse (NIDA)
Division of Pharmacotherapies & Medical Consequences of Drug Abuse

CONTACT INFORMATION - *continued*

NDA holder:

Rolley E. Johnson, PharmD
Vice-President, Clinical, Scientific and Regulatory Affairs
Reckitt-Benckiser Pharmaceuticals, Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235
Phone: (804) 379-1090
Fax: (804) 379-1215
E-mail: ed.Johnson@reckittbenckiser.com

Data Coordinating Center:

Carl Pieper, Dr.P.H.
Box 3003
Center on Aging
DUMCDurham, NC 27710
Phone 919-660-7525
Fax: 919-684-8569
E-mail: cfp@geri.duke.edu

Clinical Coordinating Center:

Jack Chally
Project Liaison
The EMMES Corporation
401 N. Washington St, Suite 700
Rockville, MD 20850
Phone: (301) 251-1161 Ext. 238
Fax: (301) 576-3924
E-mail: jchally@emmes.com

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APPENDIX D: medications* known to have a risk of QT interval prolongation 81

1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP, alk phos	alkaline phosphatase
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
BUN	blood urea nitrogen
BUP	buprenorphine
BUP/NX	buprenorphine/naloxone
CAB	Clinical Trials Network Common Assessment Battery
CAP	College of American Pathologists
CBC	complete blood count
CCC	CTN Clinical Coordinating Center
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DSC	Data and Statistical Center
DSMB	Data and Safety Monitoring Board
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders: 4th Ed.-Text Revision
EDC	Electronic Data Capture
EMMES	The EMMES Corporation
FDA	Food and Drug Administration
FTND	Fagerstrom Test for Nicotine Dependence
FWA	Federal Wide Assurance
GCPs	Good Clinical Practices
GGT	gamma glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
LT	liver test
MELD	Model End Stage Liver Disease
MET	methadone
Mg	milligram
NIDA	National Institute on Drug Abuse
NDA	New Drug Application
NX	naloxone
OTP	opioid treatment program
PI	Principal Investigator
PT	Prothrombin Time

LIST OF ABBREVIATIONS continued

PV	Protocol Violation
SAE	serious adverse event
Suboxone®	buprenorphine/naloxone
SOP	standard operating procedure
TLFB	Time Line Follow Back
ULN	upper limit of normal

2.0 STUDY SCHEMA*

TOTAL N = 600 Evaluable Participants [completed]

↓

Sign Informed Consent

Perform Eligibility Assessments

↓

History and physical examination, psychiatric evaluation including a checklist for opioid and other substance dependence from the DSM-IV checklist, HIV risk assessment, and clinical laboratory tests (blood chemistry, hematology, liver function and injury, pregnancy test [if female] and urinalysis)

↓

Meet Study Inclusion Criteria

↓

Randomize Participants using 2:1 allocation ratio (BUP/NX:MET)
stratified by site based on liver enzyme status
[normal vs. abnormal transaminases]

↓

BUPRENORPHINE/NALOXONE	**OR**	**METHADONE**
n=300 Evaluable		**n=300 Evaluable**

↓

Active Phase (Weeks 1-24): routine blood (chemistry, hematology, liver function, HIV, Hepatitis A, B, and C serologies) & urine samples (urinalysis, urine pregnancy, and urine toxicology), and other clinical assessments.

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Follow-up Phase (Weeks 28 & 32): routine blood (liver function) & urine samples (urine pregnancy, and urine toxicology), and other clinical assessments.

*SEE Table 1, Schedule of Events, for frequency of evaluations and assessments.

3.0 PROTOCOL SYNOPSIS

3.1 Study Objectives

The Food and Drug Administration (FDA) has requested a study comparing buprenorphine/naloxone (BUP/NX) and methadone (MET) on indices of hepatic safety. The primary objective of the current study is to compare changes in liver enzymes related to treatment with BUP/NX to changes in liver enzymes related to treatment with MET in the outpatient setting during 24 weeks of treatment in participants meeting DSM-IV criteria for opioid dependence.

Secondary objectives will attempt to

1. identify risk factors at baseline and during treatment that could contribute to interactions with BUP/NX or MET causing liver dysfunction,
2. assess abstinence from illicit opiates, amphetamines, cocaine, cannabinoids, and benzodiazepines, as determined by self-report and urine drug screen measured at baseline, during the active study period (weekly for urine drug screen and at 4-week intervals for self-report), and at follow-up, and
3. assess abstinence from alcohol as determined by self-report and Breathalyzer.

3.2 Study Design

This is a randomized, open-label, multi-center, Phase 4 study to assess the changes in liver enzymes related to treatment with buprenorphine/naloxone (BUP/NX) and methadone (MET) in participants entering opioid agonist treatment. Randomization will be stratified, within site, according to normal versus abnormal eligibility assessment phase liver tests (LT) and participants will receive either BUP/NX or MET using a 2:1 allocation ratio. Participants meeting entry criteria will be dosed for 24 weeks during the active phase of the study with assessment of liver function and injury at weeks 1, 2, 4, 8, 12, 16, 20, 24 and with follow-up assessments at week 32. Clinicians will be encouraged to treat with adequate doses of BUP/NX and MET. A central laboratory will be used for liver tests.

3.3 Study Population

Eligible participants include males and females seeking opioid agonist treatment. The goal is for 600 (300 per group) evaluable participants to complete at least 24 weeks of maintenance therapy and provide a minimum of four LT samples between the eligibility assessment phase and week 24. It is estimated that 1000 participants may need to be enrolled to have 600 participants complete 24 weeks of treatment. Enrollment will continue until the goal of 600 evaluable participants is reached.

3.4 Eligibility Criteria

3.4.1 Inclusion

Treatment seeking males and females, at least 18 years of age, who meet Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV-TR) criteria for opioid dependence determined by semi-structured clinical interview (DSM IV checklist), and who have the ability to understand, and provide written informed consent will be included in this study. Women will be required to use an acceptable method of birth control.

3.4.2 Exclusion

Participants will be excluded if they have any medical condition that would make participation medically hazardous, have known allergy or sensitivity to buprenorphine (BUP), naloxone (NX) or methadone (MET), or have acute psychosis, severe depression, or immediate suicide risk. Participants with a DSM IV diagnosis of current alcohol, benzodiazepine, or other sedative-hypnotic dependence will be clinically assessed for study appropriateness (e.g., need for immediate medical attention or likelihood of intravenous misuse [as determined by prior history of intravenous use] in the case of benzodiazepines). Participants who are dependent upon other depressants or stimulants, requiring immediate medical attention or who have participated in another investigational study within the last 30 days will be excluded. Participants with ALT or AST liver enzyme levels > 5 times the upper limit of normal, ALP liver enzyme level > 3 times the upper limit of normal, for total bilirubin greater than 2.0 mg/dl, albumin less than 2.5 g/dl or prothrombin time more than 3 seconds will be excluded. Participants with cardiac risk factors as confirmed by abnormal ECGs will be excluded. Pregnant females and lactating females will be excluded. HIV positive participants will *not* be excluded. Participants, who have pending legal actions or who, for any reason, are unable to remain in the local area for the duration of the study will be excluded.

3.5 Dosing

3.5.1 BUP/NX Group

For the BUP/NX group, all participants will receive up to 16 mg BUP/4 mg NX on day 1 and up to 32 mg BUP/8 mg NX on day 2. It is recommended that dose changes be made in 2 to 8 mg buprenorphine increments, with the range of allowable daily doses between 2 mg and 32 mg starting on day 3 and thereafter according to clinical impression and depending upon the participant's clinical need. Investigators are encouraged to dose adequately to decrease craving and to obtain negative urine toxicology specimens.

3.5.2 MET Group

For the MET group, all participants will receive a maximum of 30 mg for the first dose and a maximum of 40 mg on Day 1. It is recommended that participants receive a dose on day 2 that is 10 mg higher than their total day 1 dose, and a dose on day 3 that is 10 mg higher than their total day 2 dose, unless, in the clinical judgment of the physician, a slower induction is needed. Doses will be adjusted on Day 4 and thereafter according to clinical impression and depending

upon the participant's clinical need with no specific upper limit. Investigators are encouraged to dose adequately to decrease craving and to obtain negative urine toxicology specimens.

3.5.3 Dose Adjustments

To help determine appropriate adequate doses for both medications, participants should receive careful clinical evaluation checking for signs and symptoms of opioid withdrawal or opioid intoxication. Signs and/or symptoms of opioid withdrawal would indicate possible need for a dose increase. The Clinical Opiate Withdrawal Scale (COWS) will be utilized for this purpose. Even if no such signs and symptoms are present, but participants continue to express a desire to use additional opioids (i.e. craving), an increase in dose may be indicated. Conversely, signs and/or symptoms of opioid intoxication would indicate possible need for a dose decrease unless the intoxication is deemed related to illicit opioid use. Urine toxicology testing for illicit drugs will provide objective evidence of illicit opioid use. If such use is ongoing, it generally indicates the need for an increase in medication dose to help suppress the illicit use.

3.6 Duration of the Study

The total duration of study participation for each participant will be 32 weeks with ≥24 weeks of medication and a follow-up visit at week 32. To be considered evaluable, a participant must remain on his/her assigned medication for at least 24 weeks with no single interruption in study medication lasting longer than 14 days and must provide a minimum of 4 LT samples between the eligibility assessment phase and week 24. Participants with liver abnormalities will be followed as clinically appropriate through week 32 or until the participant terminates participation, whichever is the longest. AEs/SAEs will be followed until resolution or stabilization even beyond the end of the study.

3.7 Safety Assessments

Both BUP/NX and MET have been shown to have a favorable safety profile among adults in treatment for opioid dependence. The known risks of taking BUP/NX or MET are small when compared to the risks of untreated opioid dependence. Close monitoring should provide adequate safeguards to quickly identify and respond to adverse events if they occur.

3.7.1 Side Effects

Known potential side effects of BUP/NX include sedation; physical dependence; precipitation of withdrawal; and overdose that may be fatal if combined inappropriately with high doses of benzodiazepines, sedatives, or other CNS depressants. BUP/NX may also be abused and an opioid withdrawal syndrome may be precipitated if a person, who is physically dependent on opioids, injects the medication. Known potential side effects of MET include respiratory depression, dizziness, sedation, nausea, vomiting and sweating). Methadone may also be abused and there is the potential for fatal overdose if methadone is combined inappropriately with high doses of benzodiazepines, sedatives, or other CNS depressants, or if non-tolerant individuals take high doses.

Each of these potential problems will be explained in the informed consent and reviewed orally and in writing with the participant. Symptomatic relief of withdrawal using non-opioid medications will be provided as clinically indicated during the time it takes to explain the study, obtain informed consent, and complete eligibility assessment phase measures. Additional

medication may be administered for short-term symptomatic relief during and following treatment, as is normally done in the collaborating CTPs. All medication use will be recorded as concomitant medications.

3.7.2 Eligibility Assessments

This study allows for an extensive eligibility evaluation before participants are randomized to either study medication. Informed consent procedures will be initiated before any eligibility assessment activities and will outline both the eligibility assessment process and the treatment phase of the study. During the eligibility assessment phase, all potential participants will have a physical examination including: vital signs, weight, medical history, vaccination history, history of prior medications use and current medications use. Clinical laboratory tests (blood chemistry, hematology, liver function and injury, and urinalysis) will also be performed during the eligibility assessment phase. Additionally, an evaluation will be performed during the eligibility assessment phase, which includes: a checklist for opioid and other substance dependence from the DSM IV checklist and an HIV Risk Survey.

Females will be given a urine pregnancy test initially during the eligibility assessment phase and again within 48 hours prior to starting study medication. Neither pregnant females nor lactating females will be included in the study.

3.7.3 Ongoing Monitoring

Study participants will be required to undergo HIV testing and Hepatitis A, B, and C serologies during the week 1 visit and those participants who test negative will be required to have the test(s) repeated at week 24. Individuals who test positive for active hepatitis A, B or C will be referred for appropriate medical care as established by the participating clinic's policies and procedures, but will not be excluded from participation. HIV disease can directly cause liver injury and/or interact with Hepatitis C to exacerbate the liver injury caused by that disease. In order to understand the potential medication induced changes in liver tests observed in this study, it will be essential to know the HIV status of study participants. Confidential pre and post test counseling will be provided. Participants who test positive for HIV will be referred for appropriate medical care as established by the participating clinic's policies and procedures, but will not be excluded from participation.

Total and direct bilirubin, ALT, AST, ALP, GGT, serum total protein, and albumin will be performed during the eligibility assessment phase and repeated 1 week (-/+ 2 days), 2 weeks (-/+ 2 days), and 4 weeks (-/+ 7 days) after randomization, and every 4 weeks (-/+ 7 days) thereafter through week 24, then again at week 32 (-/+ 14 days). The prothrombin time will be performed on the eligibility assessment phase and repeated at week 8 (-/+ 7 days), week 16(-/+ 7 days), week 24(-/+ 7 days) and then again at week 32 (-/+ 14 days). The eligibility assessment phase medical evaluation will be repeated at week 24 or as soon thereafter as possible if the participant does not attend the week 24 visit. Study staff will perform urine drug screens and Breathalyzers at screening, at every study visit from week 1 through week 24 and at week 32. Study staff will also evaluate all participants weekly and then at the same 4-week intervals as blood samples are collected to record self-reported drug and alcohol use. Adverse Events (AEs) will be assessed on an ongoing basis during study participation. AEs and SAEs will be reviewed and evaluated by the site physician, reported to the Clinical Trials Network (CTN) local node Principal Investigator (PI), the local IRB, Study Chair and IRB as applicable, NIDA as study sponsor and the CTN DSMB as per FDA and local requirements, FDA, and Reckitt Benckiser (holder of the NDA for BUP/NX).

Women who are not pregnant but wish to participate in the study will be required to use an acceptable method of birth control for the duration of the study (see Inclusion Criteria, Section 9.1. for complete listing of acceptable methods). Women will be given a urine pregnancy test during the eligibility assessment phase and again within 48 hours prior to starting study medication, at study week 4 and every four weeks thereafter through study week 24, and then at study weeks 28 and 32. Women in the BUP/NX group who become pregnant during the study will be given immediate access to MET maintenance services at the CTP or another local treatment provider. MET is currently considered the optimal treatment for pregnant opioid-dependent women. Pregnant women who refuse MET may continue in the study on BUP (buprenorphine [Subutex®]) after reviewing the risks/benefits with the study physician. Such pregnant women will be allowed to continue in the study and included in the evaluable sample N=600. Pregnant women who switch from BUP/NX to MET will be allowed to continue in the study, but will not be included in the evaluable sample N=600. Women who become pregnant during the study will be asked to sign a release of information in order for the study staff to access the necessary medical records for the outcome of the pregnancy.

3.8 Outcome Assessments

3.8.1 Hepatic Safety

A comparison of liver test results measured during the eligibility assessment phase, at study weeks 1 (-/+ 2 days), 2 (-/+ 2 days), and 4 (-/+ 7 days), and at 4-week intervals (-/+ 7 days) thereafter through 24 weeks will be made during this study. A final measurement of liver tests will be conducted at week 32 (-/+ 14 days) or at the termination visit if the termination visit occurs prior to week 32. Liver tests for this study will refer to the battery of screening tests routinely conducted in most clinical laboratories which include: serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALP), serum total protein, serum albumin, serum gamma glutamyl transferase (GGT), serum total and direct bilirubin.. Prothrombin time is also included as a liver test but the assessment schedule for this test includes the eligibility assessment and is repeated at week 8 (-/+ 7 days), week 16(-/+ 7 days), week 24(-/+ 7 days) and then again at week 32 (-/+ 14 days). These values, over time, will be examined to determine whether or not chronic dosing with BUP/NX and/or MET has an effect on liver function or injury.

3.8.2 Risk Factors

The study will also attempt to identify any risk factors during the eligibility assessment phase and during treatment (e.g., viral hepatitis status, concomitant drug use, or other contributing factors) that could contribute to liver dysfunction.

3.8.3 Abstinence

Use of opiates, amphetamines, cocaine, cannabinoids, and benzodiazepines will be assessed by urine drug screen measured during the eligibility assessment phase, weekly through week 24 and again at week 32. Self-report of drug use will be collected during the eligibility assessment phase and at weeks 4, 8, 12, 16, 20, 24, and 32. Alcohol use will also be assessed by Breathalyzer readings during the eligibility assessment phase, weekly through week 24 and at

week 32, and by self-report during the eligibility assessment phase and weeks 4, 8, 12, 16, 20, 24, and 32.

4.0 BACKGROUND AND RATIONALE

4.1 Trial History and Current Status

BUP is a high affinity, partial μ-opioid agonist. NX is an antagonist at the μ-opioid receptor. In 2002, Subutex® (buprenorphine hydrochloride) and Suboxone® (buprenorphine hydrochloride and naloxone hydrochloride dihydrate) were approved by the FDA for the treatment of opioid dependence. The FDA has requested a study comparing BUP and MET on indices of hepatic safety. This Phase 4 clinical study plans to obtain hepatic safety data in men and women enrolling in opioid agonist treatment while also identifying risk factors for hepatic dysfunction such as baseline viral hepatitis, concomitant drug use, or other contributing factors. The study will determine the effects of BUP/NX and MET on liver enzymes among participants who have underlying viral hepatitis and also among participants who do not have viral hepatitis.

4.2 Introduction

Clinical research has demonstrated that treatment with an opioid agonist is effective in treating many opioid dependent participants. Opioid agonists have been administered both for medical withdrawal (i.e., detoxification) and as maintenance treatment. MET is a synthetic opioid agonist, acting primarily at the μ-receptor. It imitates the action of other opioids without producing euphoria in tolerant individuals and reduces symptoms of opioid withdrawal. Since the mid-1960s, MET has been widely established as an effective treatment for opioid dependence.

BUP is a μ-opioid partial agonist that has recently been approved by the FDA for the treatment of opioid dependence. Its tight binding and slow dissociation from opioid receptors permit a long duration of action and are thought to explain the relatively mild withdrawal syndrome noted with BUP discontinuation (Lewis, 1978; Jasinski et al, 1978), making it useful for opioid medical withdrawal (i.e., detoxification) and maintenance. Early investigations showed that it could substitute for morphine, suppress withdrawal, and decrease heroin self-administration (Jasinski, 1978; Mello and Mendelson, 1980; Mello et al., 1982). Extensive clinical research in the U.S., including large-scale controlled trials involving more than 1000 patients, have shown that BUP is safe and effective for treating opioid dependence in adults (Johnson et al., 1992, Schottenfeld et al., 1994, Kosten et al., 1994, Strain et al, 1994,1996, Ling et al., 1998, Johnson et al, 2000, Fudala et al, 2003).

Most of the controlled studies of BUP have used the liquid preparation, but in late 2002, a sublingual tablet formulation of BUP and BUP/NX (4:1) were approved and marketed (Subutex® and Suboxone®, respectively). Studies of these tablet formulations have shown that buprenorphine bioavailability approaches 70% or more of the liquid (Ling et al., unpublished data, 2001; Strain et al., 2004), with potential higher bioavailability from the Suboxone® as compared to the Subutex® formulation. Most importantly, the available evidence indicates that the incorporation of naloxone should deter intravenous use so that it can be safely dispensed to adults outside the opioid treatment program (OTP) setting (Mendelson et al., 1996, Fudala et al., 1998).

In controlled clinical trials, BUP compares favorably to MET in the maintenance and medical withdrawal (i.e., detoxification) of opioid-dependent individuals. BUP and BUP/NX have also been considered as safe and effective alternatives to MET (Johnson et al., 1992, Ling et al., 1996, Mattick et al., 2003).

Concern that possible hepatotoxicity might only be recognized after a medication is marketed in the U.S. has led to the placement of significant limitations on various medications (e.g., dose restrictions and/or warnings); potential withdrawal of the medication from the market. FDA has requested a Phase 4 study to compare BUP and MET to determine if there is any evidence that these medications are associated with changes in liver tests in people seeking treatment for opioid dependence.

The liver is the body's largest single internal organ and performs many functions that are essential to life. While there is no one specific test to evaluate liver function and/or injury, the routine panel of laboratory tests that is used in screening for liver disease includes serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum alkaline phosphatase (ALP), serum total protein, serum albumin, serum gamma glutamyl transferase (GGT), serum total and direct bilirubin, and prothrombin time. The aminotransferase levels provide a day-by-day record of the amount of hepatic cell injury when elevated. Elevated ALP levels reflect an obstruction to the flow of bile. Serum albumin and prothrombin time are indicators of hepatic protein synthesis (Scheig, 1996). Moseley (1996) explains that while laboratory assays that reflect liver disease are generally termed liver function tests, they are actually only markers of liver injury.

Liver damage that can lead to serious clinical outcomes is usually associated with impaired synthetic function (prolonged prothrombin time and reduced albumin), encephalopathy and, in some cases, renal or other organ failure (J. Lewis, personal communication, April 2003). Liver enzyme monitoring is performed to identify possible liver injury during the course of some types of medication treatment, such as with the statin class of medications. Elevations in AST or ALT values associated with rises in bilirubin ("Hy's Law") have been used by some researchers to try to predict serious or fatal liver injury in clinical trials. This "law" resulted from observations that the combination of aminotransferase and bilirubin elevation often predicted the occurrence of severe liver injury in some patients.

Chronic liver disease is a complication of parenteral narcotic abuse. Novick et al. (1981) cites that long-term MET therapy has been well tolerated by patients with mild or moderate liver function impairments and has no hepatotoxic effects. Neither MET and NX have known adverse effects on the liver. While studies in rat hepatic microsomes and mitochondria showed that the hepatotoxicity of high doses of BUP is related to its impairment of mitochondrial respiration (Berson et al., 2001a), the literature has few reports of BUP treatment and hepatic injury or dysfunction in opioid-dependent individuals. Lange et al. (1990), in their study on BUP safety and side effects, reported that some participants showed an increase in serum aminotransferase levels. However, the increase could not be directly attributed to BUP. Berson et al. (2001b) described hepatitis after intravenous BUP misuse in heroin dependent individuals. While four cases of BUP-induced hepatitis were reported in heroin addicts, the authors admit that this is a "Most uncommon complication even after intravenous misuse, considering the large number of patients (about 65,000) placed on BUP treatment, and the likelihood that a certain number may misuse and inject it intravenously" (Berson et al., 2001b). Petry et al. (2000) reported that opioid-dependent patients without hepatitis did not show any change in liver enzyme levels after BUP treatment. However, some individuals with hepatitis B or C who were placed on BUP did experience increases in liver enzymes: AST and ALT (Petry et al.,

2000). The increases were small, and it was unclear if they resulted from BUP or hepatitis, since most patients had hepatitis C.

This clinical study will compare changes in liver enzymes related to treatment with BUP/NX and MET in men and women meeting DSM-IV-TR criteria for opioid dependence.

5.0 STUDY OBJECTIVES

The primary objective of this clinical investigation is to compare the changes in liver enzymes related to treatment with BUP/NX to the changes in liver enzymes related to treatment with MET during chronic outpatient treatment for 24 weeks in men and women seeking treatment for opioid dependence. The study is purely descriptive with no *a priori* hypothesis. Elevation of LTs in this patient population is common (e.g. due to hepatitis C virus, continued illicit drug use, dirty needles, etc.). The FDA advised during their initial review of the protocol that the study should have at least 300 evaluable participants (i.e., complete 24 weeks of treatment) in each study arm.

The secondary objectives will attempt to:

1. Identify risk factors at baseline and during treatment that could independently, or in interaction with BUP/NX or methadone, contribute to liver injury or dysfunction;
2. Assess abstinence from illicit opioids, amphetamines, cocaine, cannabinoids, and benzodiazepines, as determined by self-report and urine drug screen measured during the eligibility assessment phases, at weekly (urine drug screen) and at 4 week intervals (self-report) during the active study period, and at follow-up;
3. Assess abstinence from alcohol as determined by self-report and Breathalyzer during the eligibility assessment phase, at weekly (Breathalyzer) and at 4 week intervals (self-report) during the active study period, and at follow-up.

6.0 STUDY SPONSOR

The National Institute on Drug Abuse is the Sponsor.

The study will be conducted under NIDA's IND 35,877. Reckitt Benckiser will have access to all data for the purpose of reporting to the FDA. Reports will be filed to Reckitt Benckiser NDA # 20-733.

7.0 STUDY SITES

This study will be conducted at approximately 10 community treatment program (CTP) sites that have a licensed opioid treatment program. If needed, additional CTPs will be added.

8.0 STUDY DESIGN

This is a randomized, open-label, parallel-group, multi-centered, Phase 4 study to assess hepatic function over a ≥24-week maintenance period of BUP/NX and MET administered to 600 opioid–dependent participants seeking opioid agonist treatment with continued medication and follow-up through week 32. After eligibility assessments are performed, participants will be randomized to receive either BUP/NX or MET using a 2:1 allocation ratio stratified by clinical site according to liver enzyme status (normal or abnormal).

Participants who miss 3 or more consecutive days of medication dosing will need to be re-inducted on medication. Medication can be restarted if the participant returns within 14 days of the participant's last medication dose. For BUP and MET treated participants, the re-induction can use the identical dosing schedule as the initial dosing or an alternate schedule deemed clinically appropriate by the study physician. Participants who miss 14 or more consecutive days of study medication will not have it restarted but will be encouraged to continue with non-research medical and/or psychosocial treatment. These participants will be terminated from the study and an attempt will be made to contact these participants to complete a termination assessment and liver tests.

9.0 PARTICIPANT SELECTION

A total of 600 treatment-seeking males and females, at least 18 years of age, who meet Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV, American Psychiatric Association 2000) criteria for opioid dependence determined by structured clinical interview (DSM-IV checklist), will complete the 24-week study. Each CTP will enroll approximately 125 participants to reach a combined total of 600 completed participants.

Participants will be recruited by word of mouth, Internet, referrals from local narcotic treatment and outreach programs, outpatient and inpatient drug abuse clinics, local mental health centers, newspaper advertisements and hospital emergency rooms. There will be specific outreach programs for recruiting women and minorities as participants such as targeting women's shelters, women's health centers, and minority newspapers. Sites with significant numbers of women and minorities will be approached to be involved with the study. Each site's Institutional Review Board (IRB) will approve recruitment advertisements.

9.1 Inclusion Criteria

Treatment-seeking males and non-lactating/non-pregnant treatment-seeking females who are:

1. Age 18 years or older
2. Meet DSM-IV-TR criteria for opioid dependence
3. In good general health, or, in case of a medical/psychiatric condition requiring ongoing treatment, are under the care of a physician willing to continue participant's medical management and cooperate with study physicians
4. For female participants, use one of the following acceptable methods of birth control:
    a. oral contraceptives
    b. barrier (diaphragm or condom) with spermicide
    c. IUD
    d. intrauterine progesterone contraceptive system
    e. levonorgestrel implant
    f. medroxyprogesterone acetate contraceptive injection
    g. contraceptive transdermal patch
    h. hormonal vaginal contraceptive ring
    i. surgical sterilization
    j. complete abstinence from sexual intercourse
5. Able to read and verbalize understanding and voluntarily sign the approved informed consent form prior to performance of any study-specific procedures.

9.2 Exclusion Criteria

Potential participants will not be allowed to enter the study if they have:

1. ALT or AST values > 5 times the upper limit of normal as per the criteria of the laboratory

2. ALP values >3 times the upper limit of normal per the criteria of the laboratory

3. Any documented past or present history of ascites, presence of esophageal or gastric varices, hepatic encephalopathy or other signs of significant liver disease as indicated by a Model for Endstage Liver Disease score (Kamath et al., 2001) of ≥11.

4. Total bilirubin > 2.0 mg/dl (participants with documented Gilbert's syndrome will be included)

5. Prothrombin time more than 3 seconds prolonged

6. Albumin level less than 2.5 g/dl

7. Any cardiopathy or risk factor listed below without evidence of a normal ECG* with report performed within 6 months prior to first study medication dose

   a. Congestive heart failure
   b. Left ventricular hypertrophy
   c. Bradycardia
   d. Hereditary QT prolongation
   e. Uncorrected electrolyte imbalance
   f. Concomitant medications that are known to have a risk of QT interval prolongation; refer to Appendix D for a list of medications. *Note: The list is not intended to be all-inclusive.*

*An abnormal ECG is defined as the presence of one or more of the following:

Significant ST segment abnormalities:

- ST segment elevations in two or more continuous leads of > 0.1 mV
- ST segment depression of greater than 1 mm that are flat or down-sloping at 80 msec after the J point

ST segment abnormalities that are identified as "non-specific" are acceptable. If a potential participant's ECG indicates ST segment elevations or depression consistent with ischemia, a medical history of cardiac symptoms should be obtained, and the participant should be referred for evaluation.

Conduction abnormalities:

- Mobitz II 2nd degree or 3rd degree heart block
- Atrial fibrillation, atrial flutter, or any non-sinus tachyarrhythmia
- Three or more consecutive ectopic ventricular complexes at a rate of > 100 per minute.

Repolarization abnormalities:

- QTc greater than 450 msec in men and 480 msec in women

8. Acute medical condition that would make participation, in the opinion of the study physician, medically hazardous (e.g., unstable pancreatic, cardiovascular or renal disease, significant anemia)

9. Known allergy or sensitivity to BUP, naloxone or MET or to any of the inactive ingredients in the study medications (including lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, Acesulfame K sweetener)

10. Known diagnosis of acute psychosis, severe depression or imminent suicide risk as determined via clinical interview by study physician or surrogates

11. DSM-IV diagnosis of dependence on alcohol requiring immediate medical attention.

12. DSM-IV diagnosis of dependence on benzodiazepines requiring immediate medical attention

13. DSM-IV diagnosis of dependence on other depressants, or stimulants requiring immediate medical attention

14. Participation in an investigational drug study within the past 30 days

15. Treatment with MET, BUP/NX, or BUP for more than 15 of the past 30 days (illicit use of these medications is allowed)

16. Pending legal action that could prohibit study participation

17. Unable or unwilling to comply with study requirements

18. Unable or unwilling to remain in the local area for duration of treatment

19. Poor venous access such that venipuncture could not be accomplished from a vein in an extremity during eligibility

20. Pregnant or lactating (females only)

10.0 INVESTIGATIONAL AGENTS

BUP/NX is a combination sublingual tablet, manufactured by Reckitt Benckiser Healthcare (UK) Ltd. (Hull, United Kingdom), and will be supplied to the National Institute on Drug Abuse (NIDA).

MET will be purchased and obtained directly by each clinical site. Both medications are approved by the FDA and are commercially available.

Written approval of the protocol by the appropriate IRB(s) and a current DEA license by the treatment program or medical staff who are responsible for dispensing controlled substances are required prior to shipping BUP/NX. BUP/NX supplies will be coordinated by the CTN Clinical Coordinating Center (CCC). Medication will be prescribed, dispensed and administered by legally qualified persons in accordance with federal and state regulations.

BUP/NX dosing is discussed in Section 11.6.1 and MET dosing is discussed in Section 11.6.2.

10.1 Dispensing Study Medications

BUP/NX may either be dispensed daily (clinic schedule permitting) by a nurse, physician or pharmacist OR dispensed three times weekly with take home doses for days medication is not administered in clinic. Participants in the MET group will be dispensed MET (in liquid or tablet formulation) daily (clinic schedule permitting) by a nurse, physician or pharmacist. Access to take-home study medication, by the participant, will be determined in accordance with all pertinent federal, state and local rules and in keeping with each CTP's SOPs. Medication dispensing practices at each CTP must be standardized with all participants in a treatment arm. Take-home study medication will be provided in properly labeled, child-resistant containers. There will be no replacement of any lost or stolen take home medication.

10.2 Labeling

BUP/NX and MET will be provided to the study sites as U.S. commercially available products and will not be re-labeled by the Sponsor. Take-home medication will be labeled according to institutional, state, and federal regulations.

10.3 Ancillary Medications

Ancillary medications may be used for relief of withdrawal symptoms including insomnia, muscle aches, nausea, diarrhea or anxiety as clinically indicated and according to standard practices at the clinical sites. Any use of all such medications will be documented regarding indication (if known), dose, frequency, method of administration, adverse events, etc. by study staff on the concomitant medications case report form. Ancillary medications will neither be provided by nor paid for by the study.

10.4 Medication Accountability

Accurate recording of all study medication use will be recorded at each transaction and each participant's clinic and research visit. The research pharmacy and site physician will maintain accurate and current records of all dispensed and returned medication. Returned medication will be disposed of at the site and witnessed by at least two staff members. Returned medication will not be re-used.

11.0 STUDY PROCEDURES

11.1 Informed Consent

Program staff at each CTP will be trained in the protocol procedures at their site, with emphasis on inclusion (Section 9.1) and exclusion (Section 9.2) criteria. Potential participants identified by program staff as possibly appropriate for the study will be provided with information about the research protocol and, if interested, will be given an appointment with research staff to provide informed consent and enroll in the study. The informed consent form must be reviewed and signed by potential study participants before any study related procedures, including eligibility assessment procedures, take place.

Participants considered ineligible for the research study during the initial eligibility assessments will be referred to standard treatment services within the CTP or at another local treatment facility. Any participant who is found ineligible during the eligibility assessment phase may be re-evaluated for eligibility at a later time, if deemed appropriate; however, informed consent procedures must be repeated and a new consent form signed.

The informed consent will outline all study procedures and must be signed by the participant before any procedure associated with this research study is performed. Each CTP must provide the sponsor with a copy of the informed consent approved by that site's IRB. Original signed consent forms will be retained in the participants' study records, duplicates will be filed in participants' clinical medical records, and a copy will be provided to each participant. Individual IRBs may have further requirements for informed consent documentation. Each CTP investigator will assure that each informed consent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outline the basic elements of informed consent. A consent form template will be provided to each site to be used as a guide in preparing the site specific informed consent form. The template is found in Appendix A.

The informed consent form documents the information the investigator provides to the individual and the individual's agreement to participate in the study. The investigator (or trained designee) will fully explain to the participant the nature of the study, methods, anticipated benefits and potential risks and discomforts that participation might entail. Further, participants will be asked to answer questions about the study to ensure they understand the purpose, duration and risks.

Since participants may self-administer BUP/NX or MET, they will be asked to sign an IRB-approved treatment contract, specifying agreements between the participant and the provider regarding acceptable behavior and responsible use of medications. This contract is found in Appendix B.

Participants will be asked to provide locator information to assist staff in maintaining contact during the study for the purposes of safety and participant retention.

11.2 Eligibility Assessments

Eligibility assessments and randomization must be completed within 30 days of signing the informed consent form. The purpose of the eligibility assessment phase is to ensure that the study candidates satisfy all study eligibility criteria. The history, physical examination, presence of opioid withdrawal signs and symptoms, and an opioid-positive urine test will all help confirm opioid dependence with physiologic features, although an opioid-positive urine test is not required for diagnosis. Prior to dosing with study medication, participants will be instructed not to use any heroin or other short acting opioid drugs for at least 6 hours, not to use any methadone for at least 24 hours, and to be in mild to moderate opioid withdrawal prior to receiving their first dose of BUP/NX or MET. Study staff at each site will take a history from the participant prior to administering the first dose of BUP/NX or MET and record the time and date of last opioid use and verify participant withdrawal status.

11.2.1 Biopsychosocial Assessments

Research staff at the CTPs will conduct a comprehensive assessment with all participants. This interview will:

1. Confirm data required for determining participant eligibility
2. Provide the CTP providers with clinical data required for a routine patient assessment
3. Provide comprehensive characterization of the study sample.

Data gathered consist of the Common Assessment Battery of the CTN and will include: demographic information, drug abuse (type, route, frequency, duration, and severity), multidimensional substance use consequences, HIV risk, DSM-IV substance use disorders diagnosis, and prior treatment history. The interview incorporates:

11.2.1.1. Demographics

Demographic information collected will include information about participants' age, gender, marital status, race, ethnicity, years of education, occupation, and drug use history.

11.2.1.2. Clinical Opiate Withdrawal Scale (COWS)

The Clinical Opiate Withdrawal Scale (COWS) is an independent observer scored assessment of 11 signs of clinical withdrawal, each of which is rated from 0 (not present) to 4 or 5. The summed score of the eleven items can be used to assess a participant's level of opiate withdrawal and to make inferences about the participant's level of physical dependence on opioids. Signs or symptoms will be rated on just the apparent relationship to opiate withdrawal. For example, if heart rate were increased because the participant was jogging just prior to assessment, the increased pulse rate would not add to the score. The degree of clinical opiate withdrawal corresponds to the sum of all 11 items in the following manner: a score rating of 5-12=mild withdrawal; 13-24=moderate; 25-36=moderately severe; more than 36=severe withdrawal. The maximum achievable score is 48.

11.2.1.3 DSM-IV Checklist

The DSM-IV Checklist is a semi-structured interviewer administered instrument that provides current diagnoses for substance use disorders based on DSM-IV diagnostic criteria. It asks

about past 30-day substance use symptoms. It has also been shown to be an efficient method for screening and diagnosis for major psychiatric disorders. The DSM-IV Checklist will be used to determine whether potential participants meet DSM-IV criteria for Axis I substance abuse or dependence prior to main study enrollment.

11.2.1.3. Risk Behavior Survey (RBS)

The RBS is an abbreviated version of the Risk Behavior Assessment developed for a NIDA Cooperative Agreement assessing involvement in HIV and HCV risk behaviors of injection drug use and sexual behavior. Most of the questions assess involvement in risk behaviors for the prior 30 days. Reliability and validity assessments of the RBS support its adequacy as a research tool for populations of drug users (Needle et al., 1995; Weatherby et al., 1994). The RBS will be repeated at study weeks 12 (-/+ 1 week) and 24 (-/+ 1 week).

11.2.1.4. Medical Outcomes Study Short Form 36-item Health Survey (SF-36)

The SF-36 is a self-report instrument that assesses health status over a 4-week-period and measures each of eight health concepts: physical functioning, physical role limitations, bodily pain, social functioning, emotional role limitations, general mental health, vitality, and general health perceptions (Ware & Sherbourne, 1992). The SF-36 has become the most frequently used measure for assessment of health-related quality of life in medical conditions (Ware & Sherbourne, 1992; Kazis et al., 1998) and is commonly the basis for computing quality-adjusted life years used in cost-effectiveness analyses. Quality of life measures have been shown to change in response to opioid agonist treatment within 30 days of initiating treatment (Torrens et al., 1999). The SF-36 will be completed during the eligibility assessment phase, study week 4, and study week 24 (or termination).

11.2.1.5. Fagerstrom Test for Nicotine Dependence (FTND)

The FTND is a 6-item self-report questionnaire that assesses dependence on nicotine (Heatherton et al., 1991; Kozlowski et al., 1994). This instrument has acceptable internal consistency (.61) and its items form a homogeneous set in factor analysis. The scale correlates significantly with biological measures of smoking consumption. One of its items provides a measure of number of cigarettes smoked per day. It is important to have some assessment of cigarette smoking behavior in this study because there is evidence that cigarette smoking is independently associated with elevated ALT levels in individuals with Hepatitis C (Wang et al, 2002). The FTND will be completed during the eligibility assessment phase, at study week 12, and at study week 24.

11.2.1.6. Time Line Follow Back (TLFB)

The time line follow back (TLFB) method obtains retrospective reports of daily drug use by using a calendar and other memory prompts to stimulate recall. It gathers daily information on specific drugs used and amount of use (number of drinks, hits, rocks, etc.). The TLFB yields consistently high test-retest correlations over periods of up to 1 year (Carey, 1997; Mason et al., 1994), and has been shown to correlate with other self-reports as well as with collateral reports (Sobell & Sobell, 1992). During the eligibility assessment phase and every 4 weeks through study week 24, and again at week 32, research staff will obtain self-reports of daily substance use including alcohol use for the period since the last assessment using the TLFB method.

Additional questionnaires will also be completed to provide information about any concomitant medications received either over the counter or by prescription.

11.2.2 Medical Assessments

Medical and psychiatric status will be determined by medical history and physical examination including: vital signs, weight, medical history and history of prior medications use. The examination will include an interview by the study physician or other appropriately trained medical staff, prior to randomization, to determine any possible psychiatric or medical exclusion and to obtain a complete history of psychiatric illness. 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).

This evaluation will include clinical laboratory tests (blood chemistry, hematology, liver function and injury, and urinalysis), alcohol Breathalyzer, and urine screen for drugs of abuse. Participants who have any single liver enzyme that is more than five times the upper limit of normal (as defined by the laboratory performing the testing), or who have abnormal values for total bilirubin, albumin or prothrombin time will be excluded. These criteria are also noted in section 9.2. To be certain that an objective measure is used for excluding potential participants with pre-existing end stage liver disease, the Model for Endstage Liver Disease scores (Kamath et al., 2001) will be used, and potential participants who score 11 or greater will be excluded from participation in the study. The Model for Endstage Liver Disease score is calculated using a mathematical formula based upon an individual's serum creatinine level, serum bilirubin, and INR (Refer to Appendix C for an explanation of the methods for calculating the Model Endstage Liver Disease score). Participants with a DSM-IV diagnosis of current alcohol dependence requiring *immediate* medical attention will be excluded due to potential alcohol induced hepatotoxicity. Participants with a DSM-IV diagnosis of benzodiazepine dependence requiring *immediate* medical attention will be excluded. If immediate medical attention is not needed, they will be clinically assessed for study appropriateness.

Medical assessments will also include a HIV Blood Test, Hepatitis A, B, C serologies. These tests will be performed at study week 1. Study participants who test positive for hepatitis A, B or C will be referred as clinically indicated for acute problems but will not be excluded from participation. Local site clinicians should refer any individuals for Hepatitis A or B vaccine if indicated based on test results.

Female participants will be required to have a negative urine pregnancy test prior to receiving their first dose of BUP/NX or MET. All female participants will be given a urine pregnancy test during the eligibility assessment phase and again within 48 hours prior to starting study medication, at study week 4 and every four weeks thereafter through study week 24, and then at study weeks 28 and 32. Women will also be required to practice acceptable birth control, as detailed in Section 9.1. The birth control method will be recorded on the CRF. Those who become pregnant and are on BUP/NX will be offered MET treatment, currently considered the optimal treatment for pregnant opioid-dependent women. If treatment with MET is refused, the female participant may continue in the study on BUP (Buprenorphine mono [Subutex]; study drug without Naloxone) only if the participant agrees to sign a release relating to medical information concerning the pregnancy. The study physician will review the risks/benefits of continuing with BUP (buprenorphine mono [Subutex]) with the participant.

11.3 Routine Laboratory Tests

The following blood and urine samples will be collected for routine laboratory testing, analysis of liver function and injury, and drug screening during the eligibility assessment phase and throughout the study period:

Blood Chemistry:	Alanine aminotransferase (ALT, SGPT) Albumin Aspartate aminotransferase (AST, SGOT) Alkaline phosphatase (ALP) Bilirubin (total and direct) BUN Calcium Chloride Creatinine Gamma Glutamyl Transferase (GGT) Glucose Lactic dehydrogenase (LDH) Phosphorus Potassium Protein (total) Sodium Uric acid
Immunology:	Hepatitis A (HAV-IgM) Hepatitis B (HBsAg, anti-HBs, anti-HBc HbcIgM; HBV-DNA for Hepatitis B carriers) Hepatitis C (+antiHCV, HCV-RNA if Hepatitis C positive) HIV (antibody and confirm if indicated)
Hematology:	Complete blood count with differentials Hematocrit Hemoglobin Platelet count Red blood cell count (RBC) White blood cell count (WBC) Prothrombin time
Urinalysis:	Specific gravity pH Bilirubin Blood Glucose Ketones Protein White blood cells Red blood cells Epithelial cells

Pregnancy:	Urine pregnancy
Drug Screen:	Breath Alcohol Urine: Amphetamine Benzodiazepine Cocaine metabolite (benzoylecognine) Methadone Methamphetamine Opiate 300 (codeine, morphine, heroin, hydrocodone, and hydromorphone) Oxycodone Propoxyphene THC

11.4 Enrollment

Following completion of the eligibility assessment phase, participants must meet all inclusion/exclusion criteria to enroll in this study. A study investigator will verify that the inclusion criteria are met and that no exclusion criteria are present.

11.5 Randomization

A stratified random 2:1 allocation of subjects to study groups will be developed by the DSC to balance groups with respect to intervention group within site and prognostic factors. The treatment groups will be balanced with respect to clinical site and liver enzyme status (normal vs. abnormal) as defined by eligibility assessment transaminases (abnormal means both ALT and AST are > ULN, based on values of central lab).

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be randomized into the study. Both randomization and study medication induction will occur within 24 hours. Confirmation of treatment assignment will be provided to the study staff after randomization for inclusion into the participant's study record.

11.6 Medication Dosing

11.6.1 Buprenorphine/Naloxone Dosing

First 3 days of dose induction

- BUP/NX will be administered under direct observation, and the first dose will be from 2 mg BUP/0.5 mg NX to 8 mg BUP/2 mg NX. The study staff will observe participants within 2 hours after dosing. It is recommended that a second dose be given if clinically appropriate (i.e., symptoms of withdrawal are present following first dose as evidenced by a COWS score of 5 or greater) as long as the total amount of BUP/NX administered on the first day does not exceed 16 mg.

- Participants will return on day 2, and the dose will be adjusted upward to double the first day's dose or to a maximum of 32 mg BUP/8 mg NX, according to the physician's clinical judgment, as a single dose. Participants may be observed for 2 hours, if needed.

- On day 3 the participant will be given the same dose as on day 2, if it was well tolerated, or the dose may be increased or decreased in 2-8 mg increments as indicated and according to clinical judgment. Participants who reached a daily dose of 32mg BUP/8mg NX may not exceed that dose.

- To summarize each induction day's dosing:
    - On day 1, the participant can receive up to 16 mg BUP/4 mg NX.
    - On day 2, the participant can receive double the day 1 dose or a maximum total dose of 32 mg BUP/8 mg NX.
    - Dosing on day 3 can remain at the day 2 dose, or be adjusted upward or downward in 2-8 mg increments as needed. Participants who reached a daily dose of 32mg BUP/8mg NX may not exceed that dose.

Dosing after first 3 days until week 4

Data from prior clinical trials with BUP have suggested that people vary in their response to treatment but can generally be maintained at BUP doses between 2 and 24 mg/day. Therefore, a flexible dosing schema should be employed during the stabilization period. Participants experiencing bothersome side effects will have their dosage adjusted until stabilization is achieved. Investigators are encouraged to dose adequately so that sedation and residual withdrawal symptoms are minimized, craving is decreased and negative urine toxicology specimens are obtained. It is recommended that dose changes be made in 2 to 8 mg buprenorphine increments, with the range of allowable doses between a minimum of 2 mg and a maximum of 32 mg (dependent on physician's clinical judgment). Dose changes are to be made following participant's request and/or upon physician discretion. Stabilization will have been achieved when the study physician judges that the participant has few or no signs and symptoms of sedation or withdrawal during the 24-hour dosing interval. Study physicians are encouraged to adjust BUP/NX doses so that participants are generally on a stable dose of BUP/NX within 4 weeks of the initial dose.

Dosing from week 4 until termination

It is recommended (though not required) that BUP/NX doses not be changed more than 4 mg within any discrete 7 day period unless the participant is being placed on an administrative taper or the participant has missed 3 or more consecutive days of medication.

11.6.2 Methadone Dosing

First 3 days of dose induction

- MET will be administered under direct observation, and the first dose will be a maximum of 30 mg. The study staff will observe the participants within 2 hours after dosing. If, a need for additional MET is evidenced by a COWS score of 5 or greater, a second dose

of MET may be administered. The total amount of MET administered on the first day should not exceed 40 mg.

- On day 2, it is recommended that participants receive a MET dose 10 mg higher than their total MET dose on day 1. For example, if they received a total MET dose of 30 mg on day 1, they should receive a MET dose of 40 mg on day 2. If they received a total MET dose of 40 mg on day 1, they should receive a MET dose of 50 mg on day 2.

- On day 3, it is recommended that participants receive a MET dose 10 mg higher than the MET dose they received on day 2. For example, if they received a MET dose of 40 mg on day 2, they should receive a MET dose of 50 mg on day 3. If they received a MET dose of 50 mg on day 2, they should receive a MET dose of 60 mg on day 3.

If in the clinical judgment of the physician a slower induction is needed, a slower induction is acceptable. The first three days' dosing can be adjusted dependent on physician's clinical judgment.

Dosing after first 3 days until week 4

Dosing on day 4 and thereafter can remain at the day 3 dose of MET or can be adjusted upward or downward as needed dependent on physician's clinical judgment. As with BUP, people will vary in their response to treatment with MET, and a flexible dosing schema should be employed to meet clinical needs of the participants. Dose changes are to be made following participant's request and/or upon physician discretion. Stabilization will have been achieved when the study physician judges that the participant has few or no signs and symptoms of sedation or withdrawal during the 24-hour dosing interval. Further dose adjustments aimed to suppress opioid use or craving, or to stop residual withdrawal symptoms can be made. Study physicians are encouraged to adjust methadone doses so that participants are generally on a stable dose of methadone within 4 weeks of the initial dose. It is recommended, although not required, that the minimum daily dose for participants on MET is 50 mg.

Dosing from week 4 until termination

It is recommended (though not required) that methadone doses not be changed more than 20 mg within any discrete 7 day period unless the participant is being placed on an administrative taper or the participant has missed 3 or more consecutive days of medication.

11.6.3 Adjustments to Dosage

To help determine appropriate adequate doses for both medications, participants should receive careful clinical evaluation checking for signs and symptoms of opioid withdrawal or opioid intoxication. Signs or symptoms of opioid withdrawal and/or craving may indicate the need for an increase in dose. Signs or symptoms of opioid intoxication may indicate the need for a decrease in dose unless urine toxicology suggests evidence of illicit opioid use. Ongoing use of illicit opioids generally indicates the need for an increase in dose to help suppress the illicit use.

The Clinical Opiate Withdrawal Scale (COWS) will be administered to confirm the presence of mild to moderate opioid withdrawal prior to participant induction onto study medications.

Participants should score a minimum of 8 on the COWS before receiving the first dose of study medications, although the study physician can begin study medication with a lower COWS score if the reasons for this plan are documented in progress notes. [WARNING: The lower the COWS score, the more likely precipitated withdrawal will occur with buprenorphine administration.] For BUP/NX, participants will be told to hold the study medication under their tongue until the tablet(s) is dissolved. An explanation of dosing will be provided so the participant understands that BUP/NX will be inactivated if swallowed and that it is likely to cause opioid withdrawal if dissolved and injected by opioid-dependent individuals.

11.6.3.1. Dose Adjustments for Medication Interactions

MET and BUP/NX may interact with a number of other medications. A listing of known medication interactions will be provided to investigators for their use in dosage adjustment of either study medication.

11.6.4 Missed Doses

BUP/NX and MET will be stopped if study participants miss three or more consecutive days of medication, and can be restarted only within 14 days of the last medication dose. Participants who miss three to 13 days of medication dosing will need to be re-inducted on medication. For BUP and MET treated participants, the re-induction can use the identical dosing schedule as the initial dosing or an alternate schedule deemed clinically appropriate by the study physician. Participants who miss 14 or more consecutive days of medication will not have it restarted but will be encouraged to continue with non-research medical and/or psychosocial treatment. Participants who miss ≥14 consecutive days of medication prior to completion of the 24 week active treatment phase will be terminated from the study and an attempt will be made to contact these participants to complete termination visit assessments and liver tests.

11.6.5 Take Home Doses

Study medication will be dispensed daily or 3 times weekly for BUP/NX participants (clinic schedule permitting) by a nurse, physician or pharmacist at each CTP in accordance with opioid treatment regulations. Access to take-home study medication will be determined in accordance with all pertinent federal, state and local rules and in keeping with each CTP's SOPs. Take-home study medication will be provided in properly labeled, child-resistant containers. There will be no replacement of any lost or stolen take home medication.

11.6.6 Post-Study Treatment

Participants will be maintained on study medications along with counseling and medical monitoring for 24 weeks. Upon completion of the active phase of the study, study week 24, options will be discussed with the participant in accordance with those available at the CTP or at other local providers. If the participant elects to discontinue medication, an appropriate medication taper agreed upon by study physician and participant will be carried out. Otherwise, participants will be provided the same medication and allowed to discontinue treatment by the end of 32 weeks or be referred to local treatment resources at their own expense. Study supplied medication will not be available after 32 weeks. All participants, regardless of the option chosen, will be asked to return to the clinic for a 32-week follow-up visit.

11.7 Counseling

The counseling procedures routinely provided at each CTP will be followed throughout the study. To ensure that a basic education on the two possible study treatments is provided, all CTPs will be provided with a self-help treatment booklet to hand out to research participants.

11.8 Emergencies

Each site must have standard procedures for responding to emergencies. Included in site-specific procedures will be a provision for 24-hour emergency medical response.

11.9 Clinical Follow-up

All participants will have completed the active treatment phase of the study at week 24. Study participants who complete the active phase of the study at 24 weeks will be followed through week 32. During weeks 25-32, study observations will be made as clinically appropriate (i.e., as clinical symptoms may indicate). A follow-up pregnancy test will be performed at week 28 for all female participants. Study participants who withdraw from the study for any reason after induction and prior to completion of the active treatment phase at week 24 will be asked to complete a termination visit (week 24 assessments) at the time of early withdrawal.

Study staff will make contact with participant 30 days after study completion and/or discontinuation of study medication to follow-up on any adverse events continuing at study end and to determine whether the participant experienced any adverse events within the 30 days after discontinuing study medication. Any participant with confirmed abnormal liver tests as defined in Section 11.13 will be followed until resolution, diagnosis, or until cause of liver test elevation is discovered.

No attempt will be made to contact or follow-up participants during the time in which they may be considered “prisoners” under 45CFR46.303(c) unless the site has obtained IRB and OHRP approval to do so. Sites that have not obtained both IRB and OHRP approval may attempt to follow-up such participants once they are no longer considered “prisoners” unless they are released more than 32 weeks following the date of their randomization.

11.10 Post Week 24 Treatment Options

Upon completion of the active treatment phase of the study, post 24-week treatment options will be discussed with the participants in accordance with those available at the CTP or at other local providers. Participants will be provided the same medication and allowed to discontinue treatment by the end of 32 weeks or be referred to local treatment resources at their own expense. Study supplied medication will not be available after 32 weeks.

11.11 Participant Compensation

Participants will be compensated in accordance with local site policies (decided by individual IRBs). Participants (or potential participants as in the case during the eligibility assessment phase) should be paid at intervals that are most convenient/acceptable locally. A bonus may be

awarded to participants who attend scheduled study visits and complete all required tests and follow-up assessments. The Study Chair, Protocol Executive Committee and the IRB should be informed of any changes in level of participant reimbursement.

11.12 Missed Visits and Study Termination

11.12.1 Missed Visits

BUP/NX or MET participants who miss three or more consecutive days of medication dosing will need to be re-inducted on medication. Medication can be restarted if the participant returns within 14 days of the last medication dose. For BUP/NX and MET treated participants, the re-induction can use the identical dosing schedule as the initial dosing or an alternate schedule deemed clinically appropriate by the study physician.

If study staff are unable to collect key medical assessments due to a participant's missed visit, those assessments may be collected at the next scheduled study visit, if deemed clinically necessary by the study investigator.

Participants who miss ≥14 consecutive days of medication will not be allowed to restart study medication. Participants who miss ≥14 consecutive days of medication prior to completion of the 24 week active treatment phase will be terminated from the study and an attempt will be made to contact these participants to complete termination visit assessments and liver tests. Participants who have been terminated will be encouraged to continue, at their own expense, with non-research medical and/or psychosocial treatment. BUP/NX and MET participants will be informed of this medication rule in the consent and at the beginning of treatment.

11.12.2 Discharge

Participants may be administratively discharged for serious behavioral problems (e.g. threats, diverting or selling drugs, assault, loitering, having weapons in the clinic), according to policies of their program. Efforts will be made to follow-up all participants at all follow-up points, even if dropped out, administratively discharged, or transferred. If a participant withdraws his/her consent for further participation in the study, the reason(s) given should be documented on the study termination form and no further contact should be made with the participant.

If at any time in the opinion of the investigator, it is not medically appropriate to continue on the study, the participant will be discharged from the study and referred to alternate treatment.

11.12.3 Voluntary Withdrawal

At any time during the study, participants may notify study personnel that they no longer wish to participate in the study. Study personnel may at this time request that the participant complete termination evaluation to assure their safety. However, if they do not wish to do so, or do not want to be contacted for follow-up evaluations, they will not be contacted further, and their data from that point on will be counted as missing. If a participant withdraws consent from further participation in the study, the reason(s) given must be documented by the study staff and recorded on the study termination CRF.

At study termination, participants will have the following assessments completed: Risk Behavior Survey, SF-36, Fagerstrom Test, TLFB, prior and concomitant medications, physical exam with vital signs, weight, blood chemistries, hematology, urinalysis, pregnancy test (females only), Hepatitis A, B, C serologies (if negative for any of these serologies during the Week 1 visit), HIV test (if HIV negative during the Week 1 visit), ALT, AST, total and direct bilirubin, ALP, prothrombin time, albumin, alcohol use test (Breathalyzer) and urine drug screen. Unless consent is withdrawn, an attempt will be made to contact any participants who miss 14 or more consecutive days of medication or drop out of the study for any other reason in order to complete a study termination assessment to include liver tests.

11.13 Liver Abnormalities

For the purposes of the study, liver abnormalities are defined as follows:

- an ALT or AST that increases, during the study, to more than 10 X UNL
- a total or direct bilirubin that increases, during the study, to 2 X ULN
- an INR that increases, during the study, to 1.5 X ULN

The above liver abnormalities must be reported as an adverse event.

If any of the above liver abnormalities are present and the participant is receiving BUP/NX, then he/she may be switched to MET at the discretion of the physician. If the participant is receiving MET, the physician can consider switching the participant to BUP/NX. The participant will be referred to a gastroenterologist. The participant should be continued on agonist therapy if clinically feasible. Participants who switch will be allowed to continue in the study but will not be included in the FDA mandated 600 participant, 24 week evaluable sample. Collection of study data will continue on these individuals.

12.0 ASSESSMENT METHODOLOGY

12.1 Participant Demographics

Demographic information will be collected during the eligibility assessment phase. Participants will be asked to provide locator information, including their residential 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 relative or friend who is not a substance abuser and can reach the participant in emergencies.

12.2 Vital Signs

Vital signs to be assessed include blood pressure, respiratory rate, pulse rate, and oral temperature. Vital signs will be assessed during the eligibility assessment phase for all study participants and periodically throughout the study (See Table 1).

12.3 Hematology

Blood samples will be collected for hematological assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, and total white blood cells will be performed. A designated central laboratory that is accredited by the College of American Pathologists (CAP) or equivalent, and participates in the Clinical Laboratory Improvement Act of 1988 (CLIA) will perform these analyses. Hematological tests will be performed during the eligibility assessment phase and at study week 24 (-/+7 days).

12.4 Liver Tests (LT)

For this study, liver tests describe the battery of screening tests routinely available in many clinical laboratories. These include: serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALP), total and direct bilirubin, serum total protein, serum albumin, serum gamma glutamyl transferase (GGT), and prothrombin time. Blood samples for liver tests, except prothrombin time, will be drawn during eligibility assessment, and then again 1 week (-/+ 2 days), 2 weeks (-/+ 2 days), and 4 weeks (-/+ 7 days) after randomization. Thereafter, blood samples will be drawn every 4 weeks: at study weeks 8 (-/+ 7 days), 12 (-/+ 7 days), 16 (-/+ 7 days), 20 (-/+ 7 days), 24 (-/+ 7 days) and then at week 32 (-/+ 14 days) (10 total blood samples) to monitor liver function during this study. Prothrombin time will be drawn during the eligibility assessment and repeated at week 8 (-/+ 7 days), week 16(-/+ 7 days), week 24(-/+ 7 days) and then again at week 32 (-/+ 14 days). All CTPs will send blood samples to a designated central laboratory for analysis.

12.5 Repeat Liver Tests (LT)

In the event of any of the following scenarios regarding liver tests, repeat liver tests will be obtained within 7 days of the day results are received:

1. AST/ALT values ≥ 3X ULN in participants normal during the eligibility assessment phase;

2. Doubling of pretreatment AST/ALT values in participants abnormal during the eligibility assessment phase;

3. A 50% increase in ALP, PT/INR compared to values obtained during the eligibility assessment phase;

4. A 50% increase in total or direct bilirubin that is also above the upper limits of normal compared to values obtained during the eligibility assessment phase;

Participants with confirmed abnormal tests will also be worked up fully to obtain additional information to rule out other, non-study causes of the abnormalities and followed weekly at the discretion of the treating physician. A gastroenterology consultation may be required to achieve this goal.

Treatment discontinuation of BUP/NX will be considered if there is evidence of hepatic abnormalities or significant worsening of a pre-existing abnormality defined as:

- an ALT or AST that increases, during the study, to more than 10 X UNL
- a total or direct bilirubin that increases, during the study, to 2 X ULN
- an INR that increases, during the study, to 1.5 X ULN

12.6 Urinalysis

Urine will be collected by clean catch and analyzed for specific gravity, pH, bilirubin, glucose, protein, ketones, blood, white blood cells, red blood cells and epithelial cells. Urinalysis will be performed during the eligibility assessment phase and at study week 24 (-/+ 7 days) by a central laboratory.

12.7 Urine Drug Screen

All urine specimens will be collected using a drug test cup with temperature controlled monitoring and test strips for opiates, benzoylecognine (a cocaine metabolite), amphetamines, cannabinoids and benzodiazepines. Urinalysis for drugs of abuse will be conducted during the eligibility assessment phase, weekly through week 24 and at week 32.

12.8 Alcohol Breathalyzer

A breath sample for alcohol breath level will be obtained during the eligibility assessment phase, weekly through week 24 and at week 32 using standard alcohol intoximeters, which will be calibrated on a regular schedule.

12.9 Self-reports of Substance Use

During the eligibility assessment phase and every 4 weeks through study week 24, and again at week 32, research staff will obtain self-reports of daily substance use including alcohol use for the period since the last assessment using the timeline follow back method (TLFB). The TLFB method obtains retrospective reports of daily drug use by using a calendar and other memory prompts to stimulate recall. It gathers daily information on specific drugs used and amount of use (number of drinks, hits, rocks, etc.). The TLFB yields consistently high test-retest correlations over periods of up to 1 year (Carey, 1997; Mason et al., 1994), and has been shown to correlate with other self-reports as well as with collateral reports (Sobell & Sobell, 1992).

12.10 Prior/Concomitant Medication Use

Information on prior medication use for the 30 days prior to the eligibility assessment phase will be collected during that phase, using a specially designed form. Once a participant is randomized, information on concomitant medication use will be collected weekly beginning at week 1 through week 32.

12.11 Pregnancy Testing

Female participants will be required to have a negative urine pregnancy test during the eligibility assessment phase and again within 48 hours prior to starting study medication, at week 4 and every four weeks thereafter through study week 24, and at study weeks 28 and 32. Women who test positive during the eligibility assessment phase will be referred to appropriate specialty clinics. BUP is a Pregnancy Category C medication. Female participants will also be expected to practice acceptable birth control. Those who become pregnant and are on BUP/NX will be given immediate access to MET maintenance services at the CTP or another local treatment provider. MET is currently considered the optimal treatment for pregnant opioid-dependent women. Women who switch from BUP/NX to MET prior to study week 24 will be allowed to continue in the study but will not be included in the evaluable sample N=600. Women who refuse MET may continue in the study on BUP (buprenorphine mono [Subutex]) only if the participant agrees to sign a release relating to medical information concerning the pregnancy. The study physician will discuss with the female participant the risks/benefits of continuing with BUP (buprenorphine mono [Subutex]). Such women will be allowed to continue in the study and will be included in the evaluable sample N=600. Women who become pregnant during the study will be requested to sign a release of information to allow study staff to access medical records to assess the outcome of the pregnancy.

12.12 Compliance

Study sites will maintain daily records of participant BUP/NX or MET use.

12.13 Adverse Events (AEs)

Adverse events (medical and/or psychiatric) assessment will initiate with participant randomization and will continue through 30 days post last dose of study medication administered to the participant. Study staff should contact each participant 30 days after study

completion and/or discontinuation of study medication to follow-up on any adverse events continuing at study end and to determine whether the participant experienced any adverse events within the 30 days after discontinuing study medication.

All AEs reported during the course of the study requiring medical attention will be reported to a study physician immediately. A study physician may then meet any participants for whom additional follow-up or AE assessment is indicated. The type of AE, severity of the AE and the relationship of the AE to the study treatments will be assessed by appropriately trained medical personnel and recorded on an AE CRF, according to the procedures described in Section 14.2. A study investigator will review AEs for seriousness, severity, and relatedness weekly.

13.0 REGULATORY AND REPORTING REQUIREMENTS

13.1 FDA Form 1572

Investigators at each study site will sign a Statement of Investigator (FDA Form 1572) prior to initiating the study. The FDA Form 1572 must be updated should any of the information change.

13.2 Investigator Assurances

Each community treatment program site must file (or have previously filed) a written assurance (FWA) with the Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Under no condition shall research covered by the regulations be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein. The original signed copy of this document will be sent to the Study EC Chair's site for record keeping and a copy will be maintained in the site's regulatory binder.

13.3 Conflict of Interest

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to-date signed conflict of interest disclosure form on file at NIDA.

13.4 Privacy

In compliance with the Health Insurance Portability and Accountability Act (HIPAA), authorization for use of protected health information will be obtained at each site prior to initiating the study. Principal Investigators at study sites will ensure that the length of authorization extends throughout the study period. Study participants will need to sign an authorization agreement or a consent form with the appropriate authorization language, as specified by the local IRBs.

13.5 DEA Registration

Controlled substances will be administered as part of the research protocol. The Study Chair and Protocol Executive Committee must ensure that the DEA requirements, including registration, inspection, and certification, as applicable, are met. Every person who dispenses any controlled substance shall obtain a registration unless exempted by law or pursuant to

Secs. 1301.22-1301.26. A separate registration is required for each principal place of business or professional practice at one general physical location where controlled substances are distributed or dispensed by a person.

13.6 IRB Approval

An appropriate Institutional Review Board (IRB) must approve the protocol and informed consents prior to study initiation. Documentation of this approval must be provided to the study sponsor or designee. The IRB must comply with current U.S. Regulations (21 CFR 56). Investigators are responsible for the following:

1. Obtain written IRB approval of the protocol, informed consent, any advertising materials used for study recruitment, and any educational materials provided to study participants; obtain written IRB approval for any protocol amendments and informed consent revisions before implementing the changes;
2. Provide the IRB with any information it requests before or during the study;
3. Submit progress reports to the IRB, as required, during the conduct of the study; request re-review and approval of the study as needed; provide copies of all IRB re-approvals and relevant communication with the sponsor (NIDA) or designee;
4. Notify the IRB of all serious and unexpected adverse events related to the study medications that occur at the investigational site or that are reported to the Investigator by NIDA within the time frame required by the IRB.

13.7 Informed Consent

All study candidates will be provided with a copy of the informed consent form to read. The investigator (or trained designee) will fully explain the nature of the study, methods, anticipated benefits and potential risks and discomforts that participation might entail. Further, study candidates will be asked to answer questions about the study to ensure they understand the purpose, duration and risks. No eligibility or other assessment procedures to be used in this study will be performed prior to obtaining informed consent. Candidates who refuse to participate or who withdraw from the study will be treated without prejudice. The reason for refusal or withdrawal will be noted on the CRF. A consent form template will be provided to each site. Minor changes may be required to these documents by local IRBs.

13.8 Medication Accountability

Upon receipt of BUP/NX and MET, the site investigator and/or pharmacist will be responsible for keeping an inventory and providing secure storage. Study medications will be prescribed, dispensed, or administered (furnished) by an individual legally qualified to do so in accordance with state regulations. Accurate recording of all study medications received, dispensed, prescribed or administered, and returned or destroyed will be made. A record of this inventory must be kept and medication usage must be documented. Upon completion or termination of the study, all unused and/or partially used study medication must be returned to NIDA or NIDA's designee or disposed of as directed by NIDA.

14.0 SAFETY MONITORING

14.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment). In a separate document, a Data Safety and Monitoring Plan is provided to address issues related to DSMB operations including safety monitoring (included in the protocol as Section 14.2), trial performance monitoring, and efficacy monitoring.

14.2 Safety Monitoring

14.2.1 Adverse Event Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the protocol. Adverse events (medical and/or psychiatric) assessment will initiate with participant randomization and will continue through 30 days post last dose of study medication.

14.2.1.1. Known Potential Adverse Events Related to the Study Medication/Intervention

BUP/NX

Potential adverse events related to BUP/NX include: death, which has been reported among people who abuse BUP in combination with benzodiazepines and other drugs; withdrawal, if BUP/NX is taken while actively taking methadone or various other opioids; increased risk of opiate dependence with continued use of heroin or other opiates; and possible impairment of mental or physical abilities for at least 6 hours after taking BUP/NX.

Common side effects from BUP/NX may include headache, constipation, difficulty sleeping, weakness, sleepiness, nausea, vomiting, sweating, and dizziness. Elevated liver enzyme levels have been reported in participants with hepatitis that are treated with buprenorphine.

As with any new medication, the long-term side effects of BUP/NX are unknown at the present time.

Buprenorphine itself may cause physical dependence. It can also cause intoxication and mild respiratory depression, as evidenced by possible drowsiness and breathing that is slower and shallower.

If the participant attempts to dissolve and inject BUP/NX, he/she may experience opiate withdrawal symptoms, including nausea, diarrhea, hot and cold sweats, hot flashes, muscle cramps, flushing, painful joints, yawning, restlessness, watery eyes, runny nose, chills, gooseflesh, sneezing, abdominal cramps, irritability, backache, tension and jitteriness, depression, sleepiness, shaking or tremor, sensitivity to noise, clammy or damp skin, or other unpleasant effects. Use of other opiates while receiving the BUP/NX tablet could also result in opiate withdrawal symptoms.

The commercial formulation of BUP/NX has been classified Pregnancy Category C. Female participants will be required to have a pregnancy test done before the first dose is given, and must agree to use an adequate method of contraception to avoid pregnancy while on BUP/NX.

14.2.1.2. Known Potential Adverse Events Related to the Study Medication/Intervention

MET

Potential adverse events related to MET include: death, which has been reported among people who abuse MET, especially in combination with benzodiazepines and various other drugs; respiratory depression, systemic hypotension; and increased risk of central nervous system depression when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Common side effects from MET may include light-headedness, dizziness, sedation, nausea, vomiting, and sweating.

MET can be abused in a manner similar to other opioids, and may itself cause physical dependence.

14.2.1.3. Definition of Adverse Event/Serious Adverse Event

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related or clinically significant. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. A thorough history during the eligibility assessment phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant to avoid reporting false AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. 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. A study investigator will classify each AE, as serious or non-serious, and follow appropriate reporting procedures.

For the purpose of this study, the symptoms associated with withdrawal will not be classified as AEs.

For the purpose of this study, the following will not be considered SAEs:

- Admission to a hospital or freestanding residential facility for drug detoxification; the event will be captured as an AE and documented on the AE form.

- Admission to a hospital/surgery center for preplanned/elective surgeries; the event will be captured as an AE and documented on the AE form.

- Admission to a hospital for scheduled labor and delivery; the event will be captured as an AE and documented on the AE form.

Laboratory Adverse Event

Any clinically significant abnormal laboratory value that occurs during the course of the study is considered an AE. The AE may be the first manifestation or the worsening of a previous condition, whether or not considered to be study agent related. For each AE, the date of test, severity, likelihood of a relationship to investigational agent, and treatment required will be recorded.

The following liver abnormalities must be reported as an adverse event:

- an ALT or AST that increases, during the study, to more than 10 X UNL

- a total or direct bilirubin that increases, during the study, to 2 X ULN

- an INR that increases, during the study, to 1.5 X ULN

Laboratory values that can be abnormal should be specified as an increased or decreased test result (e.g., “increased blood glucose,” “decreased blood potassium”) or as a term that implies an abnormality (e.g., hyperglycemia, hypokalemia, etc.). Any abnormal laboratory value that is considered not clinically significant will be documented as such on the clinical laboratory report by the investigator and will not be considered an adverse event.

Serious Adverse Event (SAE)

Any adverse therapy experience occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution will be defined as an SAE. This includes, but may not be limited to any of the following events: (This terminology is from Section B.2 on the FDA MedWatch form. For a copy of the current MedWatch Form 3500, see the list of PDF forms at: http://www.fda.gov/opacom/morechoices/fdaforms/cder.html)

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported

2. Life-threatening: Any adverse therapy experience that places the participant or participants, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death)

3. In-patient hospitalization or prolongation of existing hospitalization

4. Persistent or significant disability or incapacity

5. Congenital anomaly/birth defect

6. An event that required intervention to prevent one of the above outcomes.

Unexpected Adverse Event

Any adverse therapeutic experience, the specificity or severity of which is not consistent with the investigator brochure or currently amended IND.

14.2.1.4. Eliciting and Monitoring Adverse Events

Appropriately trained medical personnel will elicit participant reporting of AEs/SAEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant randomization and will continue through 30 days post last dose of study medication. The study nurse or medical clinician will obtain as much information as possible about the AE/SAE to complete the AE/SAE forms and will consult with the study physician or study site investigator as warranted. SAEs will be reported as indicated in Section 14.2.1.6. A study investigator will review AEs for seriousness, severity, and relatedness weekly. The medical clinician will review and enter all adverse event (AE) documentation and verify accuracy of assessments during each clinician visit with the participant to ensure that all AEs are appropriately reported and to identify any unreported SAEs. AEs/SAEs will be followed until resolution or stabilization even beyond the end of the study. Each participating site's Protocol PI is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained medical clinicians to assess, report, and monitor adverse events.

NIDA designated monitors will monitor the study sites and study data on a regular basis and will promptly report any previously unreported safety issues. NIDA designated monitors will monitor 100% of all SAEs and related documentation and ensure that the SAEs are being followed appropriately by the research staff. The NIDA designated monitors will ensure that any unreported or unidentified SAEs discovered during monitoring visits are promptly reported by the site to NIDA, the Study EC Chair's site, the Node or Protocol PI or designee, and the IRB per local IRB requirements and will be reported on the monitoring report. Staff re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified AEs or SAEs are discovered, to ensure future identification and timely reporting by the site. The NIDA CTN DSMB will also review data related to safety monitoring for this trial periodically at regularly scheduled meetings.

14.2.1.5. Assessment of Severity

14.2.1.5.1. Severity

A study investigator will review each AE for seriousness, relatedness, and severity. A study investigator will review all AEs and SAEs for severity and relatedness during each clinician visit with the participant, and will consult with the study nurse and other research personnel as needed. The severity of the experience refers to the intensity of the event. The relatedness of the event refers to causality of the event to the study. Relatedness requires an assessment of temporal relationships, underlying diseases or other causative factors, medication challenge/re-challenge and plausibility.

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

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

14.2.1.5.2. Relatedness

Relationship to Therapy is defined as:

- **Definitely related:** An adverse event that follows a temporal sequence from administration of the test product and/or procedure; follows a known response pattern to the test article and/or procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the test product (positive dechallenge: and by reappearance of the reaction after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

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

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

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

dechallenge and/or rechallenge to the test article and/or procedure would support an unrelated relationship.

14.2.1.6. SAE Reporting and Management Procedures

Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for *serious* adverse events (including death and life-threatening events). A participating site must alert the Study EC Chair's site and the NIDA-assigned Safety Monitor of SAEs within 24 hours of learning of the event. The completed AE form for the SAE should be submitted to the Study EC Chair's site and NIDA within 24 hours or the next business day of learning of the event. The SAE form and summary and any other relevant documentation should also be submitted with the AE CRF if adequate information is available at the time of the initial report to evaluate the event and provide a complete report. The following attributes must be assigned:

- Description
- Date of onset and resolution (if known when reported)
- Severity
- Assessment of relatedness to therapy/procedure
- Action taken

Additional information may need to be gathered to evaluate the SAE and to complete the AE and SAE forms. This process may include obtaining hospital discharge reports, physician records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event. Within 5 days of learning of the event, an SAE form and related documents must be completed and sent to the Study EC Chair's site and the NIDA-assigned Safety Monitor. This form must be signed and dated by the medical clinician, i.e. study physician, Protocol PI (PPI), or other qualified clinician as delegated by the PPI. If the SAE is not resolved or stabilized at this time or if new information becomes available after the SAE form and summary is submitted, an updated SAE report must be submitted as soon as possible, but at least within 5 days after the site learns the information.

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

A NIDA-assigned Safety Monitor is responsible for reviewing all serious adverse event reports. The monitor will also report events to the sponsor and the Data & Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum.

Serious adverse events will be followed until resolved or considered stable, with reporting to the NIDA assigned Safety Monitor through the follow-up period. The site must actively seek information about the SAE as appropriate until the SAE is resolved or stabilized or until the participant is lost to follow-up and terminated from the study. The Study EC Chair's site or the NIDA- assigned Safety Monitor may also request additional and updated information. Details regarding remarkable adverse events, their treatment and resolution, should be summarized by the Investigator in writing upon request for review by the NIDA-assigned Safety Monitor, local ethics Committee/IRBs or regulatory authorities.

For any death, unexpected or study related SAE, the site should contact the Study EC Chair, NIDA assigned Safety Monitor and NIDA to discuss the event and to discuss the measures, if any, that may need to be taken. The NIDA assigned Safety Monitor will recommend to NIDA whether or not the SAE should be presented to the DSMB. An urgent meeting with DSMB members may be called to address any emergent safety concern.

For SAEs that are unexpected and related, an SAE Summary Report must be completed and sent to the Study EC Chair's site, the NIDA assigned Safety Monitor and NIDA within 5 business days of the initial report. These documents must be signed and dated by the site physician/Protocol PI and Study EC Chair. If the SAE is not resolved or stabilized at this time or if new information becomes available after the SAE form and summary is submitted, an updated SAE report must be submitted as soon as possible, but at least within 5 days after receipt of the information.

The IND holder is required by FDA regulations to report SAEs to the FDA in a timely manner. The NIDA assigned Safety Monitor must report all SAEs that are unexpected and related to the FDA in writing, within 15 business days of notification of the event. If the SAE is related, and fatal or life threatening, there is an additional obligation of the sponsor to notify FDA by telephone within 7 business days. The CTP PI and Study EC Chair must assure that their local IRB reporting requirements are met.

Figure 14-1. SAE Reporting Procedure Flowchart

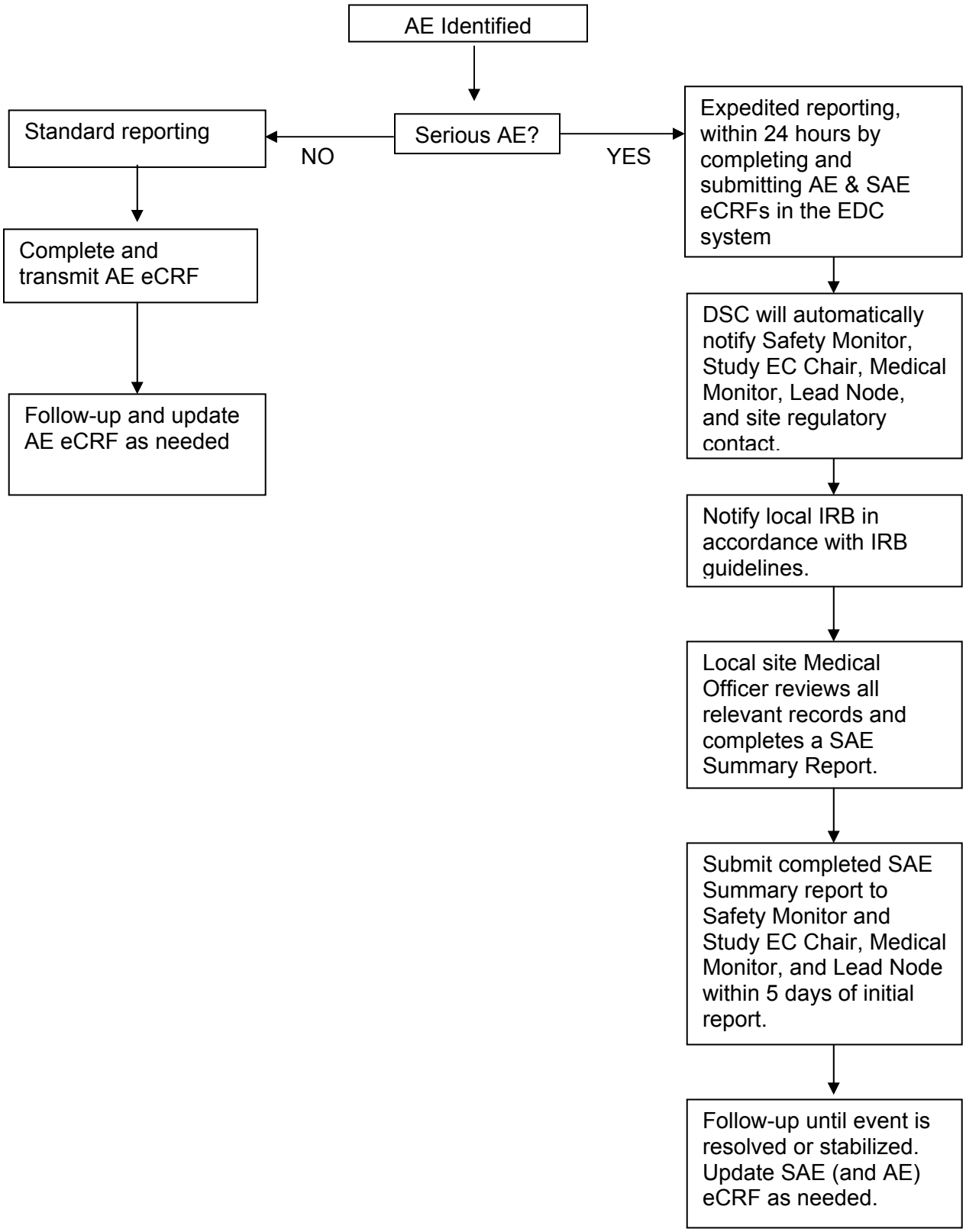
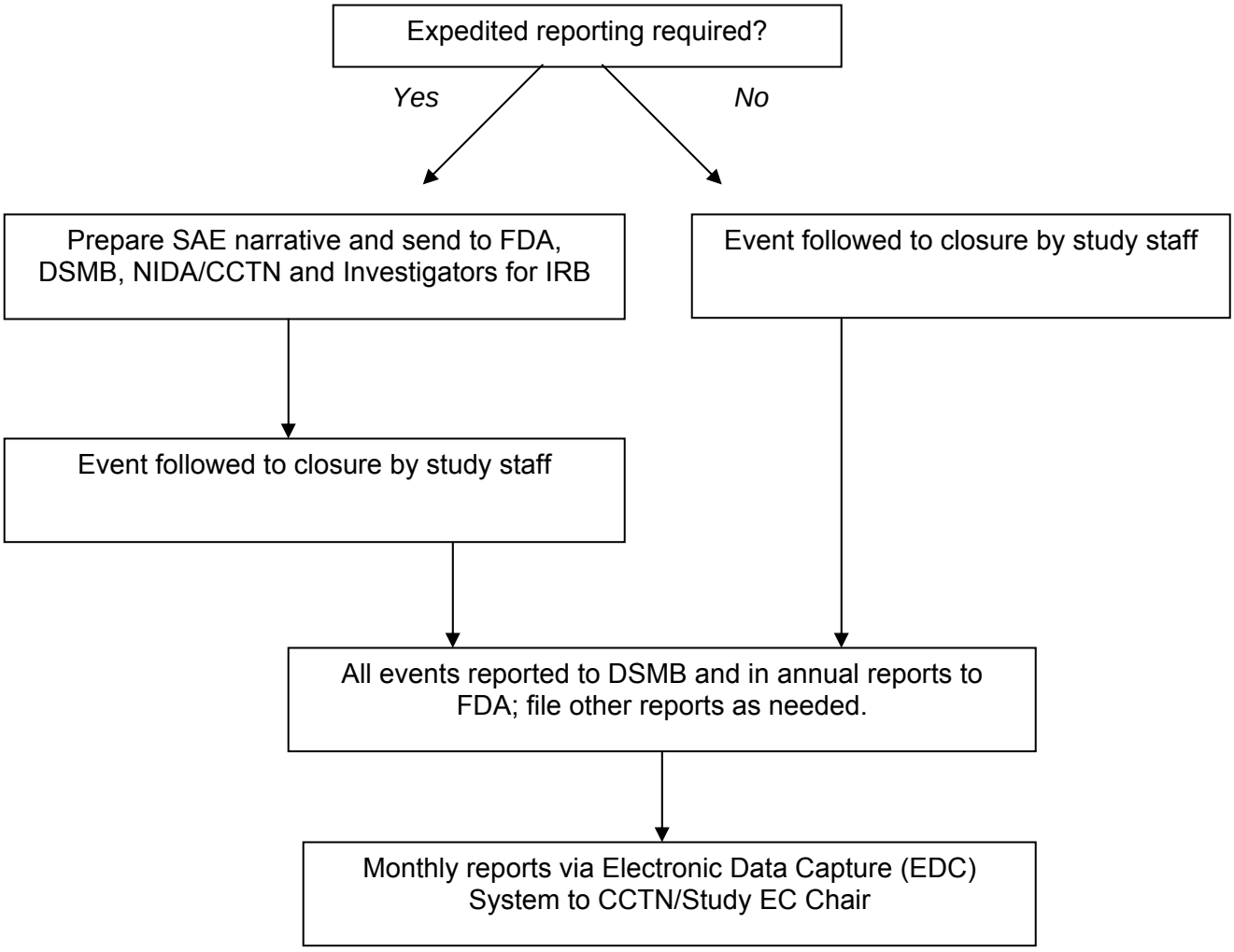


Figure 14-2. FDA Reporting Process Flowchart



15.0 ANALYTICAL PLAN

15.1 Outcomes

15.1.1 Primary Outcomes

The primary outcome measure will be changes in liver enzymes in participants treated with BUP/NX compared to participants treated with MET. Outcomes measured will be the proportion of participants who enter treatment with:

1. Eligibility transaminases (both ALT and AST) that are ≤ 2 X ULN and remain ≤2 X ULN throughout the study.

2. Eligibility transaminases that are ≤ 2 X ULN and that increase (either ALT or AST) to > 2 X ULN at any time during the study.

3. Eligibility transaminases that are > 2 X ULN (either ALT or AST), decrease to ≤ 2 X ULN (both ALT and AST), and do not subsequently increase to > 2 X ULN at any time during the study (both ALT and AST).

4. Eligibility transaminases (both ALT and AST) that are > 2 X ULN, that do not decrease below ≤ 2 X ULN, and that do not increase to ≥ 2 X the eligibility value at any time during the study;

5. Eligibility transaminases that are > 2 X ULN and that increase to ≥ 2 X the eligibility value at any time during the study (either ALT or AST).

The threshold of 2 X ULN was chosen because it is likely that a large proportion of participants in this study will enter the study with minor elevations in transaminase levels as a consequence of pre-existing liver disease such as Hepatitis C. Participants who enter with transaminases between 3 X and 5 X ULN will also be categorized and tracked, and their outcomes as a function of study medication assignment will be analyzed descriptively. Other primary events of interest will be serious liver disease, including events meeting the regulatory definition of "serious" (see Definition of Adverse Event/Serious Adverse Event, Section 14.2.1.2), or the occurrence of, or significant alterations in, laboratory parameters, e.g., participants with a combination of elevations of transaminases and increases of direct bilirubin or prothrombin time to 1.5 x ULN (see Repeat Liver Tests, Section 12.5 above).

15.1.2 Secondary Outcomes

The secondary outcome measures will be:

1. Identification of risk factors during eligibility assessment and during treatment that could contribute to liver dysfunction or hepatocellular injury.

2. Abstinence from illicit opiates, amphetamines, cocaine, cannabinoids, and

benzodiazepines, as determined by self-report and urine drug screen measured during eligibility assessment, at weekly (urine drug screen) and at 4 week intervals (self report) during the active study period, and at follow-up.

3. Abstinence from alcohol as determined by self-report and Breathalyzer.

15.2 Data Analysis Plan

Treatment effect will be summarized over the 24-week study period. Baseline summary characteristics of study participants in both treatment groups will be compared to values obtained throughout the study period. To test the primary outcomes, shift tables will be prepared to depict the number of participants at baseline with LT values in the normal range and the number of participants whose LT values move into the abnormal range.

Statistical methods: This study of the changes in liver enzymes of BUP and MET is not intended to confirm a hypothesis. It is primarily a descriptive study. Therefore, the primary analysis of the study will be done using descriptive, and not inferential statistics (see above).

However, it is recognized that some potentially valuable information could be neglected by ignoring data from study non-completers, and additional knowledge could be gained by examining trajectories of change in transaminases as continuous measures over time. Therefore, the following secondary data analysis strategies using inferential statistics will be applied to the primary outcomes after the primary analysis using shift tables is completed.

As written in section 3.7.3 of the protocol, the measurement of ALT and AST will occur at scheduled intervals, at weeks, 1, 2, 4, 8, 12, 16, 20, 24 and 32 post randomization. To analyze these primary aims, we will employ discrete survival analysis (see, for example, Allison, 1995). Using the discrete points, as a first step, Kaplan-Meier survival curves will be estimated, and the difference between the groups will be estimated using the log-rank test.

Dropouts will be censored for all data points subsequent to dropping out. If a participant should miss a single, interim point, the last value will be carried forward for that single interim point. If a participant misses 2 or more consecutive points, the participant will be censored at that point. While it is expected that 600 participants (of 1000) will provide full information, as noted below, participants who provide as little as 2 weeks of data will be included in the secondary analysis of the primary outcomes, and the impact of dropping out on the final estimates will be evaluated.

Randomization should insure that the groups are initially equal. However, we are aware of possible confounders and covariates to drug group-LT relationship, including
(a.) use of dirty needles
(b.) alcohol use
(c.) presence or absence of HIV
(d.) Heavy cigarette smoking
(e.) Hepatitis B or C +
(f.) illicit drug use

To assess the impact of these variables on the drug to LT parameter estimates, two secondary analyses will be performed. First, to assess the impact of the variables acting as covariates, the

variables will be added as a block or 'chunk' (Kleinbaum et al., 1998) to the model and the impact (parameters) of both the individual covariates as well as the change in the group effect will be reported. In a second step, the interaction of the arm with each of the covariates will be computed, and the chunk of interactions will be added to the model. To provide additional control for Type-I error, only if the chunk is significant (by the change in log-likelihood test), will the follow-up individual tests of interactions be assessed.

Missing Values: Missing data problems are ubiquitous in drug abuse research, and the amount of missing data increases as time increases. In the context of the current problem, missing values for LT can also occur when particular items of a CRF are skipped or left blank accidentally. Use of QC and eCRF should insure that these critical variables are collected if available negating the necessity for imputation. In most cases, the data are truly missing, and a value cannot reasonably be reconstructed. Missing values have a non-trivial effect on estimation, and one common strategy is to ignore missing values, knowing that, for most techniques, estimates can be derived in the presence of missing data. However, unless data are missing at random or completely at random, the estimates derived may be biased. First, participants with missing values will be given lesser 'weights' or are censored and second, if the missing values could have been measured, they may have greatly impacted the estimated survival curves. At a general level, two methods have been derived to address the problem: selection models and pattern mixture models. Selection models simultaneously try to model the dropout process and the observed data. Here, the pattern is expected to be particularly simple (triangular) – missing values after dropout. Pattern mixture models (Little & Rubin, 1987) compare the outcomes (or trajectories) across the various patterns of missing data. Several authors (Hedeker & Gibbons, 1997; Kenward, 1998) have pointed out that selection models are most useful when the dropout process is understood and that the variables thought to influence missingness are measured. In drug abuse populations, these variables might include age, gender, use of other drugs, or socio-economic status. Of greatest importance, of course, is the impact of arm on the pattern.

To give a flavor for how the analysis proceeds, participants are grouped on the basis of their pattern of missing values. This grouping then defines an indicator variable, which can then be utilized in the analysis. The regression coefficients from the models adding these indicator variables, and, more particularly, the interaction of the indicator variables with the predictors of interest provide an estimate of the impact of the missing pattern on the estimates.

Analysis of the Outcomes:

We address each outcome in order:
H1: *Eligibility transaminases (both ALT and AST) that are ≤2 X ULN and remain ≤2 X ULN throughout the study*. To assess this outcome, participants with initial ALT and AST values ≤2 X ULN will be analyzed. Using the discrete survival model listed above, differences between arms over time will be assessed for+ participants who survive until the end of the study with all values remaining below ≤2 X ULN. An alpha below 0.05 will provide a rejection of no difference between the arms. Any value above 2X ULN for either AST or ALT will be labeled as an 'event' in this analysis. Dropouts and missing values will be censored as listed above, and the impact of that censoring will be assessed.

H2: *Eligibility transaminases that are ≤2 X ULN and that increase (either ALT or AST) to > 2 X ULN at any time during the study.* Hypothesis 2 is a mirror image of H1. Rather than restricting interest to 'survival' (all values remaining below 2 X ULN), the 'event' (the first value above 2X

ULN) will be assessed. The difference between arms will be supported if the test listed for H1 is rejected.

H3: *Eligibility transaminases that are > 2 X ULN (either ALT or AST), decrease to ≤ 2 X ULN (both ALT and AST), and do not subsequently increase to > 2 X ULN at any time during the study (both ALT and AST).* This analysis will employ the methods listed above. A subset of participants will be included if they have one ALT or AST value above 2 X ULN at baseline and will go 'on study' at the first point the values of both ALT and AST decrease to or below 2 X ULN. An 'event' will be any subsequent value above 2 X ULN for both ALT and AST at a measurement point. Thus, conditional on the 2 conditions for inclusion in the study, differences between the arms will be assessed using the discrete survival model listed above. Censoring for dropout and missing values will continue to be defined as above.

H4: *Eligibility transaminases (both ALT and AST) that are > 2 X ULN, that do not decrease below ≤ 2 X ULN, and that do not increase to ≥ 2 X the eligibility value at any time during the study*. This analysis will again employ a subset of the participants with entry conditional on both ALT and AST values > 2X ULN. After randomization, an 'event' will be defined as (1) either AST or ALT value below 2 X ULN, or (2) an AST or ALT value above 2 X the eligibility value. The difference between arms will be assessed using the discrete survival model above, to assess if there is a difference in survival probability by treatment arm.

H5: *Eligibility transaminases that are > 2 X ULN and that increase to $\underline{\geq}$ 2 X the eligibility value at any time during the study (either ALT or AST).* Like H3 and H4, the sample to be employed is a conditional subset of the full sample. Conditional on an initial value above 2 X ULN, any subsequent increases above 2 X the eligibility value will be considered as an 'event'. The discrete survival model will be employed to assess if there is a difference in survival probability by treatment arm.

With 5 outcomes and 4 tests, the possibility of a Type-I error is increased. Therefore, the alpha level will be adjusted via a Bonferroni correction, and all tests will be performed at an alpha level of 0.0125.

Additional Secondary Analyses:

Use of the binary outcomes and time to event (above) does not utilize the full information of the data. In particular, the level and change in level for ALT and AST are not analyzed. To incorporate the information in the original values, and to utilize all points (not just those where a threshold has been crossed), a class of models variously called mixed-models (c.f., Laird & Ware) or trajectory analysis (c.f. Bryk and Raudenbush) will also be used for analyzing the original values. Separately for AST and ALT, controlling for the individual value at baseline, the trajectory of LT over time and differences in those trajectories by arm will be assessed.

The primary method for estimation of 'trajectories' is the class of Empirical Bayes estimation models variously called Hierarchical Linear Models, Random Coefficient Models, or Growth Curve Models (Raudenbush, 2001). In these equations, individual change is represented through a two-level hierarchical model. At level one, for a given outcome (ALT or AST) the change across time in each participant's outcome is measured separately for each person. At the second level, the regression parameters estimated from this first level become the outcome variables, which are regressed against the between-person or time invariant independent variables (e.g., sex, age, race), and other control variables. The functional form for these models with a single Level-1 (e.g., time) and one Level-2 predictor (e.g., age, sex, genetic/biomarker status) is described below:

(1) Level-1 (within-person) Model: $Y_{ij} = \beta_{0i} + \beta_{1i} Time_{ij} + \beta_{2i} Z_{ij} + e_{ij}$

Where the subscripts outcome across time for i-th individual at time j, and Z_{ij} references a time-varying covariate of interest. These models can be extended to incorporate time varying effects.

(2) Level-2 (between-person) Model : $\beta_{0i} = \gamma_{00} + \gamma_{01}X_i + u_{0i}$
$\beta_{1i} = \gamma_{10} + \gamma_{11}X_i + u_{1i}$

where X_i is the level-2 variable (e.g., sex, age, genetic status, medication group, and, in particular, the baseline value of the indicator), which affects the intercept (β_{0i}) and slope over time (β_{1i}) for each individual. The Level-1 and Level-2 models can be extended to include other multiple explanatory variables (i.e., Z's and X's at Level-1 and Level-2 respectively). The assumptions of the model are: 1) e_{ij} is independent and identically distributed with a mean zero and a variance of σ^2 for all i and j (i.e., homoscedastic, no autocorrelation - however, one can explicitly model some forms of heteroscedasticity and autocorrelation); 2) If there are 'q' level-1 predictors, the level-1 predictors, X_{qij} are independent of e_{ij}. ; 3) the level-2 predictors, X_{si} , are independent of every $u_{.i}$, and (4) e_{ij} and $u_{.i}$ are uncorrelated.

In this case, the γ's will be of ultimate interest as they will assess how, for example, the groups differ in LT over time. However, here the intent is to derive the optimal estimate of the trajectory itself. As shown in numerous places (e.g. Bryk & Raudenbush), a Bayesian or weighted estimate of the trajectory estimated in the 2 stages (β_{1i} from stage 1, $\hat{\beta}_{1i}$ from stage 2) using the appropriate variance estimates from the 2 stages has optimal statistical properties. A test of the time by group effect (γ_{11} for the variable, group, above) will provide a test of the differential change over time between arms.

AST and ALT will be modeled separately. However, it is possible that estimation jointly of the multivariate outcome (i.e. joint modeling of the ALT & AST trajectory) could both provide information about the general effect as well as increase precision of the estimates for any individual effect. In the multivariate multilevel model, longitudinal indicator data can be modeled in 3-levels with a separate model at each level. From before, Level 1 is the within-participant model with individual growth trajectories. Level-2 gives the between-participant model. Here, individual growth parameters (i.e., intercept, linear and any non-linear components) from level 1 are modeled to vary across the individuals. In level 2, individuals are nested within indicator pairs i.e., individual (participant-level) covariates and independent variables are included at this level. At level 3, indicator growth parameters from level 2 are modeled to vary across AST or ALT indicator pairs; covariates and independent variables at the indicator level are included here. Initial descriptive work on this model is shown in Fieuws and Verbeke (2004) and is discussed minimally in Snijders and Bosker (1999).

Missing values provide no particular difficulty in estimation for the models above, indeed, relative to standard repeated measures designs; incorporation of all data is a strength of mixed models. However, we will take care to assess the impact of drop-out and missing values using the methods listed above.

16.0 DATA MANAGEMENT AND CASE REPORT FORMS

16.1 Data Collection and Data Entry

Data will be collected and entered at the site using electronic CRFs. The Data and Statistical Center (DSC) will implement the electronic data capture (EDC) system for data collection to be performed by the sites. The DSC will function as the data management center for the study. The medical record, laboratory reports and all guidedsource documents will be the source of verification of data entered onto the eCRFs. The eCRFs should be completed on an ongoing basis throughout the study and in accordance with the instructions in the study operations manual. The site principal investigator is responsible for maintaining accurate, complete and up-to-date records for each participant. The site investigator is also responsible for maintaining any source documentation related to the study.

The DSC will be responsible for the validation of the clinical database, ensuring data integrity, and for training all participating staff on applicable data management procedures. Data entered into the EDC system will be reviewed, edited, and verified at the sites. Correction of inaccurate and incomplete data is the responsibility of the sites and can be maintained in the system. In addition, sites will resolve data inconsistencies and errors by utilizing EDC system functionality. The DSC will provide technical support as needed to clarify processes or assist in query resolution. NIDA PMCD, NIDA CCTN, the NIDA CTN RRTCs and the participating sites will receive monthly reports regarding the quality and quantity of data managed by the DSC.

When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the DSC statisticians in accordance with the Analytical Plan section of this protocol. Periodically, during the investigation, the DSC will prepare summary reports of the data so that progress of the study can be monitored. Various reports will be prepared for NIDA PMCD, NIDA DSMB, central data repository and others, as appropriate.

A copy of the final analysis dataset will be sent to NIDA for storage and archive. Reckitt Benckiser Pharmaceuticals, Inc. will have access to all stored and archived data.

16.2 Study Documentation and Records Retention

Study documentation includes all CRFs, data correction forms, data clarification requests, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed 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 study. Thus, source documents include, but are not limited to, laboratory reports, X-rays, radiologist reports, patient diaries and progress notes, hospital charts or pharmacy records and any other 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.

Research records for all study participants including history and physical findings, laboratory data, and results of consultations are to be maintained by the investigator in a secure storage facility for 3 years or until notified by NIDA. These records are to be maintained in compliance with IRB, federal, state, and local requirements; the statute with the most stringent requirements has precedence. Exceptions to the 3-year retention requirement can be found in 45 CFR 74.53 and 92.42 (e.g., if any litigation, claim, financial management review, or audit is started before the expiration of the 3-year period, the records must be retained until all litigation, claims, or audit findings involving the records have been resolved and final action taken). It is the investigator's responsibility to retain copies of the completed case report forms until notified in writing by NIDA that they can be destroyed. In all instances, the site must get permission from NIDA prior to disposition of any study documentation and materials.

17.0 QUALITY ASSURANCE

A monitoring plan is in place to ensure all study procedures are conducted and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. Investigators will host periodic visits by NIDA contract monitors to audit, at mutually agreed upon times, all case report forms (CRFs) and corresponding source documents for each participant.

Qualified node personnel will provide site management for each site during the trial. This will take place as specified by the protocol team or node PI and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will verify that study procedures are properly followed and that site staffs are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training.

18.0 CONFIDENTIALITY

18.1 Confidentiality of Data

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

By participating in this protocol, the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, 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.

18.2 Confidentiality of Participant Records

To maintain participant confidentiality, all laboratory specimens, CRFs, reports and other records will be coded using alpha-numeric identifiers only. All research and clinical records will be stored in a secure area with limited access. Only research staff and NIDA program officials and its agents will have access to the records. Participant information will not be released without written permission, except as necessary for monitoring by the FDA or NIDA. NIDA will file for a certificate of confidentiality that will cover all sites participating in the study.

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

19.0 AVAILABILITY OF RESEARCH RESULTS: PUBLICATIONS, INTELLECTUAL PROPERTY RIGHTS, AND SHARING RESEARCH RESOURCES

Per NIH policy, the results of the proposed trial are to be made available to the research community and to the public at large. Sharing of copyrightable outcomes of research may be in the form of journal articles or other publications. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN. In addition, Reckitt-Benckiser will be provided a copy of any reports, manuscripts, etc. resulting from this research for review and comment (without need for writer to take action on comments) within 30 days prior to submission of such reports or manuscripts. The rights and privacy of individuals who participate must be protected at all times. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual participants. The proposed research will include data from approximately 1000 participants at 8 community treatment clinics. The final dataset will include self-reported demographic and behavioral data from interviews with the participants and laboratory data from blood and urine specimens provided. Even though the final dataset will be stripped of identifiers prior to release for sharing, there remains the possibility of deductive disclosure of participants with unusual characteristics. Thus, the data and associated documentation will be available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

20.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Name	Signature	Date
Frank Vocci, PhD DMPC Project Director	_____	_____
Mary Ellen Michel, PhD CCTN Project Director	_____	_____

INVESTIGATOR (S)

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

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

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22.0 TABLE 1: SCHEDULE OF EVENTS

Study Procedures:		24 Week Study Period with Follow-up Through Week 32																											
ELIGIBILITY ASSESSMENTS & METHODOLOGIES	**Comment**	**SCREEN**	**WK 0**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 5**	**WK 6**	**WK 7**	**WK 8**	**WK 9**	**WK 10**	**WK 11**	**WK 12**	**WK 13**	**WK 14**	**WK 15**	**WK 16**	**WK 17**	**WK 18**	**WK 19**	**WK 20**	**WK 21**	**WK 22**	**WK 23**	**WK 24[G]**	**WK 28**	**WK 32**
Main Study Informed Consent	Must be signed by the participant prior to performing ANY study related assessments.	X																											
Inclusion Criteria		X																											
Exclusion Criteria		X																											
Demographics		X																											
COWS[A, B]			X[A]	X[B]	X[B]		X[B]				X[B]				X[B]				X[B]				X[B]				X[B]		
DSM IV Checklist		X																											
HIV Risk Behavior Survey		X													X												X		
Health Survey (SF-36)		X					X																				X		
Fagerstrom Test for Nicotine Dependence		X													X												X		
Medical History		X																											
Physical Exam		X																									X		
Vital Signs (BP, respiration rate, pulse rate & oral temperature)		X		X	X		X				X				X				X				X				X		X
Weight		X																									X		
Blood Chemistry	Performed by Central Lab	X																									X		
Liver Tests (LTs)[C]	Performed by Central Lab	X		X[C]	X[C]		X[C]				X[C]				X[C]				X[C]				X[C]				X[C]		X[C]
Prothrombin Time/INR[C]	Performed by Central Lab	X									X[C]								X[C]								X[C]		X[C]
Hematology	Performed by Central Lab	X																									X		
Urinalysis	Performed by Central Lab	X																									X		
Hepatitis A, B, C Serologies[D]	Performed by Central Lab			X																							X[D]		
HIV Test[D]	Performed by Central Lab			X																							X[D]		
Pregnancy Test [Females only]	Performed at Site	X	X				X				X				X				X				X				X	X	X
Randomize	IVRS		X																										

Study Procedures:		**24 Week Study Period with Follow-up Through Week 32**																										
ELIGIBILITY ASSESSMENTS & METHODOLOGIES	**Comment**	**SCREEN**	**WK 0**	**WK 1**	**WK 2**	**WK 3**	**WK 4**	**WK 5**	**WK 6**	**WK 7**	**WK 8**	**WK 9**	**WK 10**	**WK 11**	**WK 12**	**WK 13**	**WK 14**	**WK 15**	**WK 16**	**WK 17**	**WK 18**	**WK 19**	**WK 20**	**WK 21**	**WK 22**	**WK 23**	**WK 24[G]**	**WK 28**	**WK 32**
Alcohol Use (Breathalyzer)	Performed at CTP Site; EVERY CALENDAR WEEK through week 24 & at week 32; only 1 per week	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Drug Screen	Performed at CTP Site; EVERY CALENDAR WEEK through week 24 & at week 32; only 1 per week	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Record Drug Use (Self-report) Timeline Follow Back (TLFB)		X					X				X				X				X				X				X		X
Adverse Event Evaluation[E]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BUP/NX dosing[F]: initial dosing as directed, with dose adjustment for individual participants as needed according to clinical judgment	16mg/4mg Day 1 32mg/8mg Day 2 adjust thereafter		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MET dosing[F]: initial dosing as directed, with dose adjustment for individual participants as needed according to clinical judgment	30 mg Day 1 40 mg Day 2 50 mg Day 3 adjust thereafter		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Study Termination Form in the EDC System[G]																										X[G]		X

[A] Performed prior to participant induction onto study medication and within 2 hours after first dose.

[B] Performed at the study physician's discretion.

[C] Repeat LTs if excessively elevated as per protocol section 12.5

[D] Performed if negative at Week 1

[E] Contact should be made with Ss 30 days after study completion and/or discontinuation of study medication to follow-up on any adverse events continuing at study end and to determine whether they experienced any adverse events within the 30 days after discontinuing study medication.

[F] After obtaining informed consent, completing all eligibility assessments, and documenting eligibility, participants will be randomized and inducted.

[G] Perform Week 24 assessments at the termination visit if the participant terminates before week 24.

APPENDIX A: Informed Consent Form

Principal Investigator's Name
Telephone Number
24-hour Emergency Phone Number

(*Insert your institution's name here*)

CONSENT TO PARTICIPATE IN RESEARCH

Starting Treatment with Agonist Replacement Therapies (START)
A Study of the NIDA Clinical Trials Network (CTN), Protocol 0027

You are invited to participate in a research study that will be conducted at the [Insert name of site]. Dr. [Insert name] is the Principal Investigator. The National Institute on Drug Abuse (NIDA) is the sponsor of this research study.

This consent form may contain words you do not understand. Please ask the study doctor and the study staff to explain any words or information that you do not clearly understand about this consent form and about the study. Please read the information carefully and do not be afraid to ask any questions now, or at any time during the study. Please initial and date the bottom of each page to show that you have read and understand the information on each page.

If you decide to participate, please sign and date the last page of this consent form to show that you understand the risks, benefits and purpose of this research study. You will be asked to answer questions (Attachment #1) about the information given in this consent form to show that you understand it.

TERMS

These are some words and abbreviations you may need to know and refer to while reading this consent form:

Opioid: Opioids are types of natural and man-made drugs used for pain relief. Opioids include drugs such as
Darvon ™, Percocet ™, Demerol ™, morphine, oxycodone, heroin and methadone.

Methadone [MET]: A man-made opioid drug that is used as a substitute treatment for morphine or heroin addiction in opioid treatment programs. The word methadone and its abbreviation [MET] will both be used throughout this form. Methadone is one of the study drugs you may receive if you participate in this research.

Buprenorphine [BUP]: A man-made opioid drug that both acts like and blocks the effects of opioids in the body. and is also used for the treatment of opioid addiction. The word Buprenorphine and its abbreviation [BUP] will both be used throughout this form.

Naloxone [NX]: A drug, which blocks the effects of opioids in the body. Naloxone is known by its trade name Narcan ™ and is often given to reverse the effects of overdose. Naloxone and its abbreviation [NX] will be used interchangeably throughout this form.

BUP/NX: Refers to a combination of drugs, buprenorphine and naloxone, which is also used for the treatment of opioid dependence. This combination of drugs in a single tablet, BUP/NX, is one of the study drugs you may receive if you participate in this research.

PURPOSE AND BACKGROUND OF THE STUDY

The U.S. Food and Drug Administration (FDA) has requested that this study be done to compare the effect of two different drugs, buprenorphine/naloxone (BUP/NX) and methadone (MET), on the liver. The FDA has approved both drugs for the treatment of opioid dependence. MET has been used for many years. BUP/NX is a newer drug and was approved by the FDA in October 2002.

You are being considered for participation in this study because you are addicted to opioids and are seeking treatment for your addiction.

Approximately 1,000 individuals at approximately 10 treatment clinics across the United States will participate in this study.

DESCRIPTION OF RESEARCH STUDY

This study will be performed in two (2) parts:

1. Part 1--**SCREENING PHASE**

If you agree to be in this study, you will first complete a number of tests to make sure that you are healthy enough to participate and that you meet all of the requirements for participation. The time required to complete the screening phase will be about three and a half (3 ½) hours. Screening may be done in one day or over several days. Screening must be completed within 30 days of signing this consent form.

During the screening phase and before you are given any study drug, the following will happen:

- You will be given a physical.
- We will ask you to give us information so that we can find you for assessments. To help with this process, you will be asked to name several people who might help us contact you if we are unable to find you. The contacts you name will not be asked to provide any information about your health, drug use, or any other personal information. The researcher who calls will only ask that you return a call to the number provided. We will ask you at each weekly visit if this information has changed since your last visit.
- You will be asked about your medical history, including a review of any medicines (prescription and “over the counter”) that you are taking or have taken in the past.
- You will be asked about your mental health and your current withdrawal symptoms.
- You will need to complete several questionnaires about how you are feeling and your drug use.
- We will need to take some blood. The amount of blood collected during the first part of the study will be about 4 tablespoons or 2 ounces. This blood will show the study doctor how various systems in your body are working, for example, your liver and kidneys.
- You will need to provide a urine sample. Some of this urine will be used to see how your kidneys and other parts of your body are working, and some of it will be tested for drugs, such as heroin and cocaine.

- You will need to have had an ECG performed within six months prior to first study medication dose if the investigator determines you are at risk for certain heart related problems. An ECG is a test that shows how your heart is working.

- You will need to provide a breath sample to test for alcohol use.

- You will be provided with the results of these tests.

FOR WOMEN ONLY
You will be required to have a negative urine pregnancy test. You may not be in this study if you the results of your test show that you are pregnant. If you are pregnant, you will be sent to an appropriate specialty clinic.

2. Part 2--**TREATMENT PHASE**

If you agree to be in this research study and meet the study entrance requirements, you will be enrolled in part two (2) of the study. This part will last for up to 32 weeks. You will come to the clinic [Clinic to specify] to get your dose of study drug. During one of these visits each week, you will meet with a member of the study staff to have some medical tests done and research staff will ask you some questions.

During the treatment phase, the following will happen:

- You will be randomized by chance (like the flip of a coin) into one of two treatment groups. One treatment group will get BUP/NX, and the other treatment group will get MET. You have a greater chance of being assigned to the BUP/NX group than the MET group. That is you have a 2 out of 3 chance of being assigned to receive BUP/NX and a 1 out of 3 chance of being assigned to receive MET. This assignment will be determined by chance, in a computerized process similar to flipping a coin. This means your assignment is based on chance rather than a medical decision made by the study doctor.

- You will get planned outpatient drug abuse counseling that is offered by the clinic. [Clinic to specify].

- Your blood will also be checked for signs of liver disease (hepatitis A, B and C). If the results of these tests show that you have liver damage, you may be referred to a medical specialist at your own expense.

- You will need to have a confidential test for human immunodeficiency virus (HIV). This is the virus that causes AIDS. You will receive counseling before and after you get the results of the test.

- You will need to give 9 blood samples during the second part (treatment phase) of this study. Blood samples will be taken at study weeks 1, 2, 4, 8, 12, 16, 20, 24 and 32. The total amount of blood taken from you will be about 22 tablespoons or 11 ounces. This blood will show the study doctor how various systems in your body are working, for example, your liver and kidneys.

- You will need to provide urine samples once a week during weeks 1 - 24 and again at week 32. Some of this urine will be used to see how your kidneys and other parts of your body are working, and some of it will be tested for drugs, such as heroin and cocaine.

- You will be required to provide breath samples once a week during weeks 1 - 24 and again at week 32 to test for alcohol use.

- You will be asked about any other medicines that you are taking and any side effects that may have occurred since your last visit. You will be asked these questions while you are in the study.

- You will be asked about your drug and alcohol use every four weeks up to study week 24 and at study week 32.

- You will be asked to complete several questionnaires about how you are feeling and your drug use.

- At study week 24, you will have another physical, you will have your vital signs taken, and you will be asked about risk behaviors. These questions will be set-up close to the time of the counseling meetings to make them easier for you to go to.

- Your blood will be checked for signs of liver disease (hepatitis A, B and C) at week 24 if your blood tests at the first part of the study did not show signs that you had previous infection with any of these forms of hepatitis. You will also have a confidential test for human immunodeficiency virus (HIV) at week 24 if your blood test from the first part of the study showed that you did not have this infection. You will receive counseling before the HIV test is performed and after you receive the results of the HIV test.

- You will be provided with the results of these tests.

STUDY DRUG DOSING:

If you are put into the **BUP/NX treatment group**, you will be given one or more tablets that must be dissolved under your tongue. It may take between 5-10 minutes until the tablets are completely dissolved.

If you are assigned to the **MET treatment group**, you will be given a liquid form of medicine to swallow.

You will have to come to the clinic [clinic to specify] to get your study drug. On the first day of dosing, you may have to stay in the clinic for up to 2 hours to be watched after receiving your first dose of the study drug. Further dose changes may be made over the next few days or weeks depending on how you respond to the study drug.

If you do not take the study drug for more than 3 days in a row, the study drug will be stopped and you must see a clinic medical care provider before it can be restarted.

If you do not take the study drug for 14 or more days in a row, you will not get anymore study drug. However, you will be asked to continue with outpatient counseling and/or medication treatment not associated with this research study. We will call or send you a letter in the mail to answer questions and have liver tests done. Your part in the study will end after this final assessment.

The longest time you can be on study drug, either BUP/NX or MET, during this study is 32 weeks. It is recommended that you take it for the full 32 weeks.

If you have any liver tests that are not normal at week 32, you may be asked to return to the clinic for additional health tests.

FOR WOMEN ONLY

During the treatment phase, you will have a urine pregnancy test within 48 hrs before you start the study drug. Additional pregnancy tests will be done every 4 weeks through week 32 while you are on study drug to be sure that you are not pregnant.

You must agree to use a medically acceptable type of birth control while being in the study. Types of birth control you can use are:

- Complete abstinence (not having sexual intercourse with anyone)
- An oral contraceptive (birth control pills)
- Norplant
- Depo-Provera
- A condom used with a spermicide (kills sperm)
- A cervical cap used with a spermicide (kills sperm)
- A diaphragm used with a spermicide (kills sperm)
- An Intrauterine device
- Surgical sterilization (having your tubes tied)

If you become pregnant during the study, and you are on BUP/NX, you will be offered MET treatment. MET is currently considered the best treatment for opioid-addicted pregnant women. If you refuse MET, you may continue in the study on BUP (Buprenorphine mono [Subutex]; study drug without Naloxone) only if you agree to sign the release of information form. This form will allow study staff to access your medical records to obtain information regarding the outcome of your pregnancy. The study physician will review with you the risks/benefits of continuing with BUP (buprenorphine mono [Subutex]) treatment during your pregnancy. If you refuse to sign the release of information form, you will be offered MET and discontinued from the study.

If you become pregnant during the study, you will be asked to sign a release of information form to allow study staff to access your medical records to obtain information regarding the outcome of your pregnancy.

COMPENSATION

You will be given cash or gift certificates/vouchers to cover your travel expenses and for time contributed to this research study. You will be awarded a bonus if you attend scheduled study visits and complete all required tests and follow-up assessments. The maximum payment you are eligible to receive is $300.

If you stop being in the study before week 32, you will be paid for all of the scheduled study visits you went to and for completing the required medical tests and study questions up until the time you stopped participating. If you choose to stop being in the study before week 32, you will also receive payment for completing one termination visit.

POTENTIAL RISKS AND DISCOMFORTS

- The drawing of blood may cause pain, bleeding, bruising, lightheadedness, and, on rare occasions, infection at the site of the needle insertion. Precautions will be taken to decrease these risks. The total amount of blood that you will be asked to give during the study is about 22 tablespoons or 11 ounces.

- Because BUP/NX must be taken under your tongue, it may cause some mild irritation or leave a bad taste in your mouth. As with any drug, there is also the rare chance of an allergic reaction. The exact frequency of allergic reactions is not known.

- Side effects associated with BUP/NX include headache (30%), constipation (11%), difficulty sleeping (25%), weakness (14%), sleepiness (5%), nausea (upset stomach) (10%), vomiting (5%), sweating (12%), and dizziness (4%).

- Side effects associated with MET include slowed or stopped breathing, dangerous changes in heart beat, drowsiness, dizziness, nausea (upset stomach), vomiting, sweating, headache, itching, skin rashes, decreased sex drive, constipation, flushing of the face, and difficulty sleeping. How often these possible side effects happen is not known.

- High liver test results have been reported among patients with liver disease (hepatitis) who took with BUP/NX or MET. It is unclear if these increases were caused by hepatitis, the specific study drugs, or by each working in combination. Liver enzyme levels often increase above normal when there has been some form of injury to the liver. To explore the possibility that BUP/NX or MET may increase liver enzyme levels in persons with hepatitis, everyone in this study will be tested for hepatitis and will have monthly tests for liver enzymes. You may be referred to a medical specialist if these tests show evidence of liver damage. The cost of any consultation with the specialist will be covered by you or by your insurance company.

- Taking BUP/NX within 24 hours of using MET may cause you to go into withdrawal.

- Taking BUP/NX or MET with alcohol or other drugs may be hazardous. A number of deaths have been reported among people who abuse BUP in combination with benzodiazepines, such as Valium, Xanax or sleeping pills. Do not drink beverages containing alcohol or take other drugs including benzodiazepines like Valium or Xanax, sleeping pills, or narcotic pain relievers while participating in this study without first talking your study doctor.

- BUP/NX and MET may cause addiction. They can also cause you to feel drunk and may slow your rate of breathing**.** If you abruptly stop taking your study drug, you may experience opioid withdrawal symptoms. You may also be more sensitive to the effects of opioids when you come off of heroin, BUP/NX, MET, or other opioids.

This increased sensitivity is one reason people overdose after being detoxified if they relapse and return to drug use.

Therefore, if you start using drug again after detoxifying from study drug (BUP/NX or MET), heroin or other opioids, it is important to use doses of opioids much lower than the doses you used when you enrolled in this study.

- BUP/NX and MET, like other drugs with opioid effects, may impair mental or physical abilities that are necessary for activities such as driving or operating machinery. Use caution if you engage in these activities.

- As with any new medicine, the long-term side effects of BUP/NX are unknown at the present time; however, no serious long-term adverse effects have been detected among 1000 or more adults who have received this medicine.

- NX is a drug that blocks the action of opioids in the body. When injected into a person dependent on opioids (e.g., heroin, morphine, oxycotin, oxycodone, Percocet™, MET, etc.) it can cause a withdrawal reaction. Very little NX gets into the body when taken under the tongue. When taken as directed (i.e., under the tongue), NX has no effect, and only the effects of BUP are felt. If the drug is swallowed into the stomach, neither the BUP nor the NX has any effect.

- There is a chance that you may experience opiate withdrawal symptoms during the study including nausea, vomiting, diarrhea, muscle pain, abdominal discomfort, sweating, runny nose, watery eyes, restlessness, tremors, chills, an increase in heart rate and blood pressure, and agitation.

- The study drug must be kept out of reach of children and anyone other than yourself.

- You may feel anxious or sad after receiving the results from your HIV test. A counselor will be available if you want to talk about how you are feeling.

- Results of your HIV test or other communicable disease test may need to be reported to the local and state health authorities, as required by law.

- Being involved in a research study requires time. Attending the visits and completing the study questions may be viewed as frustrating and time-consuming. Efforts will be made to schedule your study visits at times that are easy for you.

- Some of the questions about your personal habits, lifestyle and drug and alcohol use may embarrass you or may otherwise cause you distress.

- Participation in this study may involve risks that are currently unforeseeable. You will be told if the investigators find out about new risks associated with BUP/NX or MET that are not currently known.

PREGNANCY: The risks of BUP/NX in pregnancy are not known. Females must have a negative pregnancy test before the first dose and agree to use an acceptable method of birth control to avoid pregnancy while on BUP/NX. If you become pregnant, the study drug or procedures may involve currently unforeseeable risks to you or to your baby.

ANTICIPATED BENEFITS OF THE STUDY

You may or may not get a direct benefit from either of the treatments that are offered in this study. However, it is possible that either of them will provide a chance for you to stop drug use, reduce HIV risk behavior and improve your quality of life.

It is possible that the medical testing done in this study could reveal a medical condition that you might not have been aware of previously and for which you may need treatment. Study and clinic staff will refer you for additional treatment if such problems are identified.

The information that is obtained during this study may be helpful and may lead to greater knowledge about addiction treatment, and may help determine whether BUP/NX or MET has any effect on liver

function after 24 to 32 weeks of dosing. At present, little is known about the long-term effects of BUP/NX or MET on liver function.

ALTERNATIVES TO PARTICIPATION

If you decide not to be in this study, you can still come to the clinic for the standard treatment provided by this clinic. If you choose not to remain at this clinic, referral to the most appropriate treatment will be made. Referrals to behavioral (non-medication) treatments such as Narcotic's Anonymous, counseling, and other therapies will be provided according to their availability in the area where you live. Any referral is at your own cost.

WITHDRAWAL FROM THE STUDY

Your participation in this research is VOLUNTARY.

- If you choose *not to participate* or you are found *not eligible to participate*, your relationship with [Insert name of clinic], or your rights to health care or other services to which you are otherwise entitled will not be affected.

- You have the right to drop out of the study at any time. If you decide to *discontinue participation*, you should notify [Insert name of local PI here] in writing. You will be given information about other treatment programs in your area so that you can apply for treatment elsewhere.

- If you fail to follow the study procedures or the study staff feels that it is in your best interests, the investigator may *end your participation* in this study. For example, you may experience an allergic reaction to the study drug and therefore, you would not be able to continue in the study. You will be given information about other treatment clinics in your area so that you can apply for treatment elsewhere.

- If you decide not to participate, withdraw from the study, decide to leave [Insert name of clinic], or if you are suspended from the study for breaking study rules, you will be given information about other treatment programs in your area so that you can apply for treatment elsewhere.

- If you drop out or leave the study for any reason, we will contact you to obtain follow-up information on how you are doing, unless you instruct us not to do so. If you decide to withdraw your consent from further participation in this study, you will need to do so in writing.

- If you do not take the study drug for 14 days or longer for any reason, you will be withdrawn from this study. We will attempt to contact you to come in for a follow-up assessment.

- You will be informed of any significant new findings that become available during the course of the study that might influence your willingness to participate.

STUDY TERMINATION

The maximum time you can be on study drug, either BUP/NX or MET, during this study is 32 weeks. It is recommended that you take it for the full 32 weeks. This research study will not provide any type

of study drug or treatment for you after week 32. Options available to you at the end of this research study include:

1. You may enter non-study treatment with the same medicine or with a different medicine. You could enter treatment at the clinic where you participated in the study or at another clinic of your choice. You will be responsible for assuming the cost of your treatment after your involvement in this study ends.

2. You and your study medical provider may plan to taper your study drug prior to week 32, so that your dosage is very low by the time you reach the end of your study participation. This is likely to reduce the withdrawal symptoms you might have when you go off the study drug.

3. You will be maintained on study medications along with counseling and medical monitoring for 24 weeks. Upon completion of the active phase of the study, study week 24, options will be discussed with you in accordance with those available at the CTP or at other local providers. If you elect to discontinue medication, an appropriate medication taper agreed upon by study physician and you will be carried out through week 32.

FINANCIAL OBLIGATION

Neither you nor your insurance company or any other third party payer will be billed for any study drugs, blood or urine tests, or other procedures that are part of this study.

EMERGENCY CARE AND COMPENSATION FOR INJURY

Your participation in this research study is done at your own risk. If you are injured as a direct result of research procedures that are not part of regular clinic activities such as counseling, you will receive treatment for the injury at no cost. [Insert your clinic name here and any investigator's names and degrees] does not provide any other form of compensation for injury. No compensation for things such as lost wages, disability or discomfort is available. Participation in this study will in no way waive any legal claims, rights or remedies.

Should you believe that taking part in this research has injured you or if you experience an adverse reaction, you should immediately contact a member of the study staff: [List pertinent staff including name, degree, phone number and address here to the consent]**.** In case of an emergency in which you are unable to reach [List investigator's name here], please call 911 or go to the nearest emergency room.

CONFIDENTIALITY

To help us protect your privacy, a Certificate of Confidentiality has been obtained from the National Institutes of Health (NIH). With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court order, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you. Even with the Certificate of Confidentiality, the investigators still have ethical and legal obligations to report elder abuse, child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. Also, depending on state or local law, the investigators may be required to report diseases that you can pass on to others to health authorities. If keeping information private would immediately put you or someone else in danger, the investigators will release information to protect you or another person.

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 Food and Drug Administration (FDA). Staff from the FDA, the National Institute on Drug Abuse (NIDA) and its agents, Reckitt Benckiser Pharmaceuticals, Inc (the company that makes and sells BUP/NX) and its agents, and study monitors (people who look at the study to see if it is being done right), and other federal agencies may review records that identify you. However, it is the policy of these agencies and the study researchers that every effort will be made not to release information that identifies you.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer or other person obtains your written consent to receive research information, and then the researchers may not use the Certificate to withhold that information.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The investigator must get your authorization (permission) to use or give out any health information that might identify you.

If you choose to be in this study, the investigator will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research about
  HIV / AIDS
  Hepatitis infection
  Sexually transmitted diseases
  Other reportable infectious diseases
  Physical exams
  Laboratory test results
  The diagnosis and treatment of a mental health condition
- Records about any study drug you received

Information about your health may be used and given to others by the investigator and research staff as well as to NIDA and its agents.

Information about you and your health, which might identify you, may be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Other institutions or entities participating in this research
- [Insert IRB]

Information about you and your health that might identify you may be given to others to carry out the research study. NIDA and/or its agents will analyze and evaluate the results of the study. In addition,

people from NIDA and its agents will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for a new product resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by [insert IRB]. [insert IRB] is a group of people who perform independent review of research as required by regulations.

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

You can withdraw or cancel your permission, but this permission will be good until the end of research study. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by giving a written notice to the investigator. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information, which might identify you, will be gathered after that date. Information that has already been gathered may still be used and given to others.

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

QUESTIONS

If you have any medical problems or questions, you can contact [Insert names] at [Insert phone numbers/ and contact information]. *Identify all personnel involved in the research as listed in the following subheadings: Principal Investigator, Co-Investigator(s), and Other Study Personnel. Include the daytime telephone numbers and addresses for all listed individuals, including a night/emergency telephone number.

RIGHTS OF RESEARCH PARTICIPANTS

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you have questions regarding your rights as a research participant, you may contact the [Insert your IRB name, Chairman and phone number and address here].

SIGNATURE OF RESEARCH PARTICIPANT

I have read the information provided in this consent form. I understand that taking part in this study is voluntary. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I understand what the study is about and how and why it is being done. I have been told of the possible risks and discomforts, and the possible benefits of the study. I have been told of other treatments that may be available to me.

I understand that if I decide not to take part in this study, my refusal to participate will involve no penalty or loss of rights to health care or other services to which I am entitled. I may withdraw from this study at any time. I may do so without penalty or loss of rights to health care or other services to which I am entitled.

The results of this study may be published; however, I will not be identified by name or by any other personal identifiers.

I understand my rights as a research participant. I understand that giving false, incomplete, or misleading information about my medical history, including past and present drug use, could have serious consequences for my well-being.

By signing this form, I voluntarily agree to participate in this research study and give permission to the investigator and NIDA and its agents to use and give out the health information collected about me during my participation in this study. I will receive a signed copy of this consent form.

_____
Name of Participant

_____ _____
Signature of Participant Date

_____ _____
Signature of Authorized Staff Member Obtaining Participant's Consent Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the patient and answered all of his/her questions. He/she has verbalized understanding of the information described in this document and freely consents to participate.

_____ _____
Name of Investigator (as named on 1572)

_____ _____
Signature of Investigator Date

SIGNATURE OF WITNESS (Leave this section in if required by your institution or your IRB)

_____ _____
Signature of Witness (person other than study staff) Date

ATTACHMENT 1
CONSENT FORM QUESTIONS
Starting Treatment with Agonist Replacement Therapies (START)

	TRUE	FALSE
1. Your participation in this research study is voluntary.	☐	☐
2. The Food and Drug Administration (FDA) has approved methadone (MET) for many years as a treatment for opiate dependence.	☐	☐
3. There are no possible side effects from BUP/NX or Methadone, the 2 drugs in this research study.	☐	☐
4. Your participation in the study can last up to 32 weeks.	☐	☐
5. You will not have to give any blood or urine samples during the course of the study.	☐	☐
6. Your participation in the study will be kept confidential except as required by law.	☐	☐
7. The study staff can end your participation in this study if they feel that it is in your best interests.	☐	☐
8. You will be given cash or gift certificates/vouchers to cover your time and/or travel expenses for participating in this study.	☐	☐
9. Some of the questions you will be asked to answer in the study may be embarrassing to you.	☐	☐
10. You do not have to tell the staff of any new drugs that you take during the study.	☐	☐

The correct answers to the questions above have been discussed with me.

_____ _____
Participant's Signature Date

APPENDIX B:
TREATMENT CONTRACT

As a participant in the Buprenorphine/naloxone and Methadone study protocol, I freely and voluntarily agree to accept this treatment contract, as follows:

1. I agree to keep, and be on time to, all my scheduled appointments with the clinic and all clinic staff.

2. I agree to conduct myself in a polite manner in the clinic.

3. I agree not to arrive at the clinic drunk or high on drugs. If I do, the staff may cancel my appointment and, if necessary, take emergency measures to assure my safety, and I will not be given my medication until my next scheduled appointment.

4. I agree not to sell, share or give any of my medication to another person. I understand that such mishandling of my medication is a serious violation of this agreement and would result in my being taken out of the study without recourse for appeal.

5. I agree not to deal, steal or conduct any other illegal or disruptive activities in or near the clinic.

6. I agree that my medication (or prescriptions) can only be given to me at my regular clinic visits. Any missed clinic visits will result in my not being able to get medication until the next scheduled visit.

7. I agree that the medication I receive is my responsibility and that I will keep it in a safe, secure place. I agree that lost medication will not be replaced regardless of the reasons for such loss.

8. I agree not to obtain medications from any doctors, pharmacies, or other sources without telling my treating doctor and other clinic staff. I understand that mixing buprenorphine/naloxone or methadone with other medications, especially benzodiazepines, such as Valium, and other drugs of abuse can be dangerous, and that a number of deaths have been reported among persons mixing buprenorphine/naloxone and benzodiazepines.

9. I agree to take my medication as the doctor, and clinic staff have instructed and not to change the way I take my medication without first consulting the doctor or clinic staff.

10. I understand that medication alone is not sufficient treatment for my disease and I agree to participate in counseling, as provided, to assist me in my treatment.

_____ _____

Participant's Signature Date

APPENDIX C:
METHODS FOR CALCULATING THE MODEL ENDSTAGE LIVER DISEASE SCORE

MELD stands for Model End Stage Liver Disease, a disease severity scoring system applied to adult liver patients. MELD score is calculated using a relatively simple formula that relies on three readily available objective variables:

- Serum creatinine (Scr; mg/dL)
- Total bilirubin (Tbil; mg/dL)
- INR (international normalized ratio)

The following rules must observed when using this formula:

- 1 is the minimum acceptable value for any of the three variables.
- The maximum acceptable value for serum creatinine is 4.
- The maximum value for the MELD score is 40.

MELD Score = 10 **{**0.957 Ln (Scr) + 0.378 Ln (Tbil) + 1.12 Ln (INR) + 0.643**}**

Multiply the score by 10 and round to the nearest whole number.

Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation.

A computer program that automatically calculates the MELD score after the values for Scr, Tbil, and INR are entered will be supplied to the study sites or the MELD score will be calculated by the central laboratory and printed on the laboratory report along with the other lab results.

APPENDIX D:
MEDICATIONS* KNOWN TO HAVE A RISK OF QT INTERVAL PROLONGATION

Anti-arrhythmic:

amiodarone	Cordarone®, Pacerone®
disopyramide	Norpace®
dofetilide	Tikosyn®
flecainide	Tambocor®
procainamide	Pronestyl®, Procan®
quinidine	Cardioquin®, Quinaglute®

Anti-depressant: Selective serotonin reuptake inhibitors (SSRIs)

citalopram	Celexa®

Anti-depressant: Tricyclic antidepressants (TCAs)

amitriptyline	Elavil®
desipramine	Norpramin®
doxepin	Sinequan
imipramine	Tofranil®
nortriptyline	Aventyl®, Pamelor®
protriptyline	Vivactil®
trimipramine	Surmontil®

Anti-fungal agent:

ketoconazole	Nizoral®
itraconazole	Sporanox®

Macrolide antibiotic:

erythromycin	E.E.S.®, Erythrocin®, Eryzole®, Ilosone®
clarithromycin	Biaxin®, Prevpac®

This is NOT an all-inclusive listing.