

NIDA CTN Protocol 0048

**Cocaine Use Reduction with
Buprenorphine
(CURB)**

Lead Investigator: Walter Ling, M.D.

March 6, 2012

Version 4.0

CONTACT INFORMATION

Lead Investigator: Walter Ling, MD
Pacific Region Node
Director, UCLA Integrated Substance Abuse Programs
University of California, Los Angeles
11075 Santa Monica Blvd., Suite 200
Los Angeles, CA 90025
Phone: (310) 267-5888
Fax: (310) 312-0552
lwalter@ucla.edu

Co-Lead Investigator: Andrew Saxon, MD
Pacific Northwest Node
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
Andrew.saxon@va.gov

Co-Lead Investigator: Larissa Mooney, MD
Pacific Region Node
Integrated Substance Abuse Programs
University of California, Los Angeles
11075 Santa Monica Blvd., Suite 200
Los Angeles, CA 90025
Phone: (310) 267-5419
Fax: (310) 312-0552
lmooney@mednet.ucla.edu

CCTN Project Coordinator: David S. Liu, MD
Health Science Administrator
Center for the Clinical Trials Network
National Institute on Drug Abuse
Neuro Science Center, 3125
6001 E. Executive Blvd.
Rockville, MD
Phone: (301) 443-9802
Fax: (301) 443-2317
david.liu2@nih.gov

Community Treatment Liaison: Allan J. Cohen, MA, MFT
Pacific Region Node
Director of Research and Training
Bay Area Addiction Research & Treatment, Inc.
1926 West Beverly Blvd.
Los Angeles, CA 90057
Phone: (818) 212-8893
Fax: (213) 607-1434
AllanJCohen@aol.com

Project Director: Albert L. Hasson, MSW
Pacific Region Node
Integrated Substance Abuse Programs
University of California, Los Angeles
11075 Santa Monica Blvd, Suite 200
Los Angeles, CA 90025
Phone: (310) 267-5224
Fax: (310) 312-0552
alhasson@ucla.edu

Co-Project Director: Christie M. Thomas, MPH
Pacific Region Node
Integrated Substance Abuse Programs
University of California, Los Angeles
11075 Santa Monica Blvd., Suite 200
Los Angeles, CA 90025
Phone: (310) 267-5319
Fax: (310) 312-0552
cthomas@friendsresearch.org

Clinical Coordinating Center: Robert Lindblad, MD
Medical Monitor
The EMMES Corporation
401 N. Washington St, Suite 700
Rockville, MD 20850
Phone: (301) 251-1161
Fax: (301) 576-3924
rlindblad@emmes.com

Data Coordinating Center: Don Stablein, PhD
Senior Statistician
The EMMES Corporation
401 N. Washington St, Suite 700
Rockville, MD 20850
Phone: (301) 251-1161
Fax: (301) 576-3924
dstablein@emmes.com

Collaborators:

Alkermes, Inc. (Vivitrol®)
852 Winter Street
Waltham, MA 02451

Reckitt Benckiser Pharmaceuticals, Inc. (Suboxone®)
The Fairfax Building
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

TABLE OF CONTENTS

1.0	LIST OF ABBREVIATIONS	7
2.0	ABSTRACT	8
2.1	Study Objectives	8
2.2	Study Design.....	8
2.3	Study Population	8
2.4	Treatment	8
2.5	Safety Assessments.....	8
2.6	Efficacy Assessments	9
2.7	Analyses	9
3.0	STUDY SCHEMA	10
4.0	INTRODUCTION	11
4.1	Background and Rationale	11
4.1.1	Buprenorphine	12
4.1.2	Naltrexone	14
4.1.3	Psychosocial/Behavioral Treatment for Drug Dependence: Cognitive Behavioral Therapy (CBT)	15
4.1.4	Significance of the Project to the Field	16
4.2	Objectives	16
4.2.1	Primary Objective.....	16
4.2.2	Secondary Objectives	16
5.0	STUDY DESIGN	18
5.1	Overview of Study Design	18
5.2	Duration of Study and Visit Schedule	18
5.3	Study Population	18
5.3.1	Inclusion Criteria	18
5.3.2	Exclusion Criteria	19
5.4	Participant Recruitment	20
5.5	Number of CTP Sites	20
5.6	CTP Characteristics	20
5.7	Rationale for CTP Selection	21
6.0	OUTCOME MEASURES	22
6.1	Primary Outcome Measure	22
6.2	Secondary Outcome Measures	22
7.0	STUDY PROCEDURES	23
7.1	Screening and Baseline	23
7.1.1	Pre-screening Assessment	23
7.1.2	Informed Consent Procedures	23
7.1.3	Pre-Induction Strategy	23
7.1.4	Naltrexone Induction	24
7.2	Randomization	24

7.3	Treatment	25
7.3.1	Pharmacotherapy.....	25
7.3.2	Cognitive Behavioral Therapy (CBT).....	26
7.4	Ancillary Medications	26
7.4.1	Concomitant Medications.....	27
7.5	Study Medication Management.....	27
7.5.1	Study Medication Storage.....	27
7.5.2	Used/Unused Medication	27
7.5.3	Lost Medication.....	28
7.5.4	Dispensing of Study Medications	28
7.5.5	Drug Packaging	28
7.6	Participant Withdrawal	28
7.7	Follow-Up.....	29
7.8	Blinding.....	29
7.8.1	Type of Blinding	29
7.8.2	Maintenance of the Blind.....	29
7.8.3	Breaking the Blind.....	29
7.9	Participant Reimbursement	29
8.0	STUDY ASSESSMENTS	31
8.1	General Measures.....	33
8.1.1	Inclusion/Exclusion	33
8.1.2	Locator Form	33
8.1.3	Demographics Form	33
8.1.4	Treatment Satisfaction Survey	33
8.1.5	End of Medication Form.....	33
8.1.6	End of Study Form.....	33
8.2	Safety and Medical Measures	33
8.2.1	Medical and Psychiatric History	34
8.2.2	Physical Examination.....	34
8.2.3	Injection Site Examination.....	34
8.2.4	Electrocardiogram (ECG).....	34
8.2.5	Clinical Laboratory Tests.....	34
8.2.6	Buprenorphine and Naltrexone Levels	35
8.2.7	Pregnancy and Birth Control Assessment.....	35
8.2.8	Vital Signs.....	35
8.2.9	Prior and Concomitant Medications	35
8.2.10	Adverse Events (AEs) and Serious Adverse Events (SAEs)	35
8.3	Drug Use Measures and Psychological Measures	35
8.3.1	Timeline Follow-back (TLFB)	35
8.3.2	Urine Drug Screen (UDS)	36
8.3.3	Visual Analog Craving Scale (VAS)	36

8.3.4	The Beck Depression Inventory (BDI)	36
8.3.5	Treatment Effect Assessment (TEA)	36
8.3.6	World Health Organization Quality of Life BREF (WHOQOL-BREF)	36
8.3.7	PRISM Suicide and Homicide Screening	36
8.3.8	Opioid Use Questionnaire	37
8.3.9	DSM-IV-TR Checklist.....	37
8.3.10	Risk Assessment Battery (RAB).....	37
8.3.11	Self-Help Assessment.....	37
8.3.12	Addiction Severity Index Lite (ASI-Lite)	37
8.3.13	Fagerström Test for Nicotine Dependence.....	37
8.4	Compliance Measures	37
8.4.1	Dose Logs (DL).....	37
8.4.2	CBT Attendance Log.....	38
9.0	TRAINING.....	39
10.0	STATISTICAL ANALYSES.....	40
10.1	General Design	40
10.1.1	Study Hypothesis	40
10.1.2	Primary Endpoint	40
10.2	Rationale for Sample Size and Statistical Power	40
10.2.1	Projected Number of Sites	41
10.2.2	Projected Number of Participants per Site	41
10.3	Statistical Methods for Primary and Secondary Outcomes.....	41
10.4	Significance Testing	42
10.5	Interim Analyses	42
10.6	Exploratory Analyses	42
10.7	Missing Data and Dropouts	42
10.8	Demographic and Baseline Characteristics.....	42
10.9	Safety Analysis	43
11.0	REGULATORY COMPLIANCE AND SAFETY MONITORING	44
11.1	Regulatory Compliance	44
11.2	Institutional Review Board Approval.....	44
11.3	Research Advisory Panel of California (California sites only)	44
11.4	Informed Consent.....	44
11.5	Drug Accountability	45
11.6	Quality Assurance and Safety Monitoring.....	45
11.7	Data and Safety Monitoring Board (DSMB)	45
11.8	Medical Monitor.....	45
11.9	Quality Assurance Monitor	45
11.10	Statement of Compliance.....	46
11.11	Confidentiality	46
11.12	Health Insurance Portability Accountability Act (HIPAA).....	46

11.13	Investigator Assurances	46
11.14	Financial Disclosure	47
11.15	DEA Registration.....	47
11.16	Inclusion of Women and Minorities.....	47
11.17	Description of Plans to Conduct Valid Analyses of Study Results by Gender and Race/Ethnicity	47
11.18	IND Requirements.....	47
11.19	Regulatory Files	47
11.20	Records Retention and Requirements.....	48
11.21	Audits.....	48
11.22	Reporting to Sponsor	48
11.23	Study Documentation.....	48
11.24	Protocol Deviations, Violations, and Reporting and Management	48
11.25	Safety Monitoring	49
11.25.1	Adverse Events (AEs).....	49
11.25.2	Definitions of Adverse Events and Serious Adverse Events.....	49
11.25.3	Reportable Adverse Events and Serious Adverse Events.....	49
11.25.4	Known Potential Toxicities of Study Drug/Intervention	50
12.0	DATA MANAGEMENT AND PROCEDURES	52
12.1	Design and Development.....	52
12.2	Operations Manual.....	52
12.3	Site Responsibilities	52
12.4	Data Center Responsibilities	52
12.5	Data Collection.....	52
12.6	Data Acquisition and Entry.....	52
12.7	Data Editing and Control	52
12.8	Study Documentation and Records Retention.....	53
12.9	Data Transfer/Lock.....	53
12.10	Data Training	53
12.11	Data QA	53
12.12	Confidentiality	54
12.12.1	Confidentiality of Data.....	54
12.12.2	Confidentiality of Participant Records.....	54
13.0	PUBLICATIONS AND OTHER RIGHTS	55
14.0	INVESTIGATOR(S) SIGNATURES.....	56
15.0	REFERENCES.....	57

1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT/SGPT	Alanine Aminotransferase/Serum Glutamic Pyruvic Transaminase
ASI-Lite	Addiction Severity-Index-Lite
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
BDI	Beck Depression Inventory
BUP	Buprenorphine+Naloxone
CAP	College of American Pathologists
CBT	Cognitive Behavioral Therapy
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DEA	Drug Enforcement Agency
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyltranspeptidase
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IND	Investigational New Drug
LFT	Liver Function Test
Mg	Milligrams
NDA	New Drug Application
NTX	Naltrexone
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
PI	Principal Investigator
PLB	Placebo
RAB	Risk Assessment Battery
RAP-C	Research Advisory Panel of California
SAE	Serious Adverse Event
TES	Treatment Effectiveness Score
UDS	Urine Drug Screen
VAS	Visual Analog Scale
WHOQOL-BREF	World Health Organization Quality of Life BREF
XR-NTX	Extended-Release Naltrexone

2.0 ABSTRACT

2.1 Study Objectives

The aim of this study is to investigate the safety and effectiveness of buprenorphine in the presence of naltrexone for the treatment of cocaine dependence.

2.2 Study Design

This multi-centered double-blind, placebo-controlled study will randomly assign participants to one of three conditions: experimental (4mg buprenorphine plus naltrexone or 16mg buprenorphine plus naltrexone) or control (placebo plus naltrexone). Participants will be treated with pharmacotherapy for 8 weeks, with clinic visits to occur thrice weekly for observed medication administration, provision of take-home medication, collection of urine samples, safety and other assessments, and once-weekly cognitive behavioral therapy (CBT). Participants will be tapered from study medication in the final two days of week 8. Follow-up assessments will occur at 1 month and 3 months post-treatment.

2.3 Study Population

Participants will be 300 cocaine-dependent individuals who have successfully met all eligibility criteria, including either past-year opioid dependence or past-year opioid abuse or past-year opioid use with a history of opioid dependence during the lifetime. Participants will be males and non-pregnant, non-lactating females age 18-65.

2.4 Treatment

Participants will be randomly assigned 1:1:1 to one of three conditions: 4mg buprenorphine plus naltrexone, 16mg buprenorphine plus naltrexone, or placebo plus naltrexone to be provided for 8 weeks. Naltrexone will be extended-release naltrexone by injection (XR-NTX; Vivitrol®). Buprenorphine will be provided as sublingual buprenorphine+naloxone (BUP; Suboxone®). The abbreviations BUP and XR-NTX will be used in the protocol to refer to buprenorphine+naloxone and extended-release injectable naltrexone. Other formulations of buprenorphine or naltrexone will be specified. All participants will be scheduled for once-weekly CBT sessions.

2.5 Safety Assessments

Screening/baseline assessments will include a physical examination, medical and psychiatric history, clinical laboratory tests (blood chemistry, hematology, liver function and coagulation tests, urinalysis, HIV and hepatitis screening), a pregnancy test, 12-lead electrocardiogram (ECG), and vital signs. A urine pregnancy test will be administered to all females at screening and every 4 weeks (including prior to naloxone challenge and prior to each XR-NTX injection) during the study. Blood levels of buprenorphine and naltrexone will be drawn at two time points: before re-administration of XR-NTX (i.e., first visit of Week 5), and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (last visit of Week 8). Adverse events (AEs) and concomitant medications will be assessed and documented at each clinic visit. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end-of-medication visit to assure safety and to document end-of-medication outcomes.

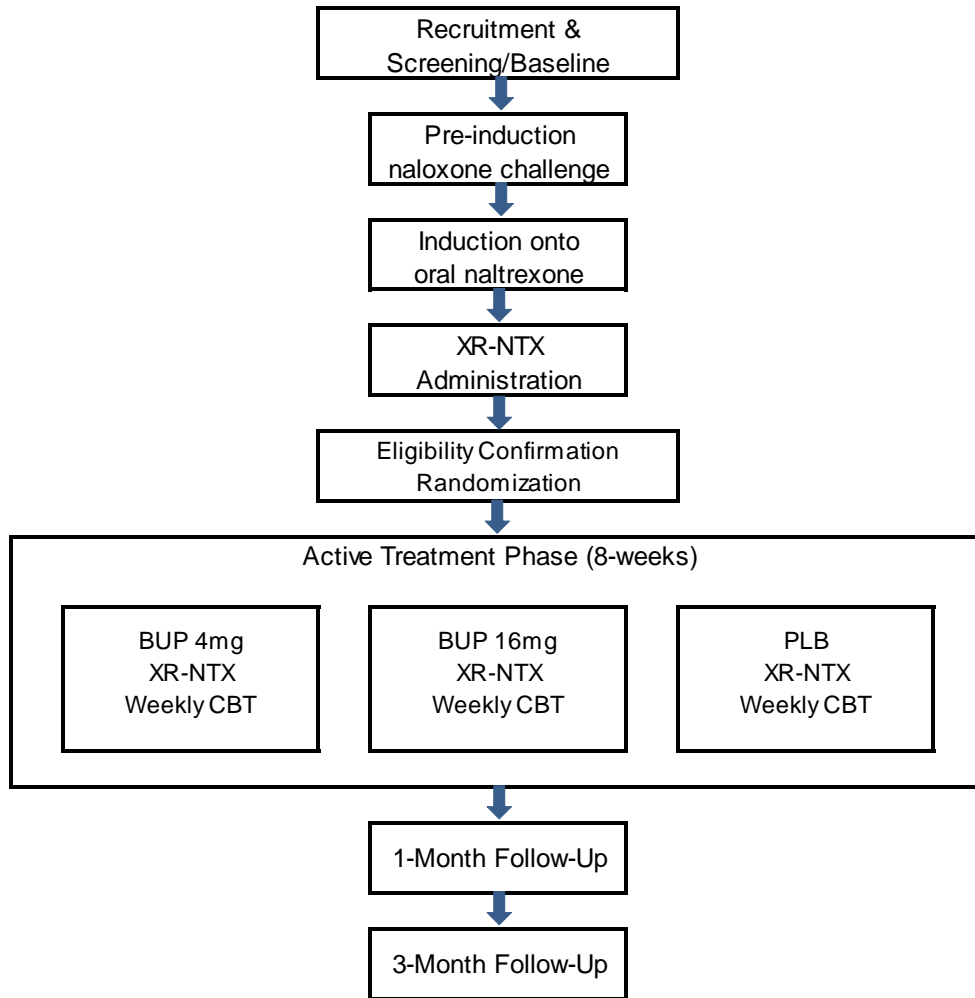
2.6 Efficacy Assessments

The effectiveness of buprenorphine for the treatment of cocaine dependence will be assessed via self-reported days of cocaine use, corroborated with urine drug screens collected thrice weekly over the 8-week active medication period. Unless consent is withdrawn, effort will be made to continue thrice-weekly visits throughout the duration of the planned treatment phase (weeks 1 – 8) with all participants who prematurely discontinue medication administration during the active treatment phase, including completion of the 1-month, and 3-month follow-up visits.

2.7 Analyses

The primary endpoint is the number of cocaine use days during the 30-day evaluation period (the final 30 days of active medication administration prior to taper; days 25-54). This will be analyzed using appropriate statistical methods for the intent-to-treat and evaluable samples. Statistical tests will be two one-sided 2.5% level tests contrasting buprenorphine-containing regimens versus the control (no buprenorphine) for an overall experimentwise 5% Type I error rate. Other analyses will include summaries of the characteristics of the participants in each condition. Analyses will address abstinence, reduction in drug use, treatment retention, and treatment completion.

3.0 STUDY SCHEMA



Extended-release injectable naltrexone (Vivitrol) = XR-NTX
Buprenorphine+naloxone (Suboxone) = BUP

4.0 INTRODUCTION

4.1 Background and Rationale

Cocaine dependence remains a serious problem throughout the United States and in many parts of the world. In 2009, 1.1 million persons age 12 or older were cocaine abusers or were dependent on cocaine, and there were 1.6 million past-month users of cocaine. SAMHSA's National Survey of Drug Use and Health (NSDUH) estimated 36.6 million Americans age 12 and over had used cocaine at least once in their lifetime, and 8.4 million of that number had used crack. SAMHSA estimates indicated at least 787,000 persons received formal treatment for cocaine abuse or dependence in the past year. Data from the Treatment Episode Data Set showed that only 25% of individuals in outpatient-based treatment for cocaine-related problems completed the program (SAMHSA, 2009a).

Despite considerable research efforts, effective strategies to treat cocaine dependence remain elusive. Behavioral approaches are deemed crucial to a comprehensive treatment program, but pharmacotherapies may also be important to reduce drug use and more effectively engage and retain cocaine-dependent individuals in psychosocial treatment. No medications are currently available to specifically treat cocaine dependence, although extensive research is striving to identify and test new medications. A pharmacotherapy that has shown promise is buprenorphine, which has not been adequately examined for its definitive efficacy in reducing cocaine use.

Recent pharmacotherapy research has rekindled interest in buprenorphine (a partial mu-opioid agonist and a kappa-opioid antagonist) as a medication for treating cocaine dependence. Buprenorphine's effectiveness in reducing cocaine use has been documented for more than a decade (e.g., Amass et al., 2002; Ling et al., 2005; Schottenfeld et al., 1997, 2005; Woody et al., 2008), but these observations were restricted to opioid abusers in treatment who were also cocaine abusers. To date, no experimental research with buprenorphine has occurred in non-opioid-using cocaine abusers because of the fear of potentially eliciting opioid craving and habituation by exposing opioid-naïve individuals to the effects of buprenorphine. Montoya and colleagues (2004; 2008) studied buprenorphine in participants who were abusers of opioids and cocaine, finding that "sublingual buprenorphine solution at 16mg daily is well tolerated and effective in reducing concomitant opioid and cocaine use." The therapeutic effect on cocaine use appears independent of that on opioid use, as noted in work by Gerra (2006) and by Rothman (2000).

Renewed interest in buprenorphine as a possible pharmacotherapy for cocaine dependence has developed. Concurrent administration of buprenorphine with an opioid antagonist such as naltrexone has been considered to minimize the risk of eliciting opioid craving or iatrogenic opioid dependence in cocaine-dependent individuals. Research by Rothman and colleagues (2000) and by Gerra and colleagues (2006) documented buprenorphine effects on cocaine use when administered in combination with naltrexone. Indeed, a recent review article by McCann (2008) observed that the Gerra work suggested that "buprenorphine is effective in reducing cocaine use even in the presence of naltrexone, the addition of which should alleviate concerns regarding physical dependence."

Findings from the Gerra study suggest that participants can be safely inducted onto a combination of buprenorphine and naltrexone and be maintained at therapeutic levels—negligible pupillary changes suggest significant mu blocking effects from the combination, mitigating the risks of opioid dependence while leading to significant reductions in cocaine use among the participants. Recent data from Phase I studies (Reese Jones, personal

communication, 2009) confirm that naltrexone effectively blocks the mu opioid receptor in the presence of therapeutic doses of buprenorphine. In these studies, buprenorphine challenges of 4, 8 and 16mg, when compared to a placebo challenge, elicited no significant effects on blood pressure, heart rate, respiratory rate, or pulse oximetry in volunteers pre-treated with naltrexone. Subjective ratings of medication effects were similarly unaffected. A dose-dependent reduction in pupil diameter was seen: the 16mg buprenorphine challenge produced a maximum reduction of 0.7 mm; the 4mg challenge produced a maximum reduction of only 0.3 mm. It should be noted that the Gerra study referenced above used a 4mg buprenorphine dose, and pupil diameter changes were noted only by gross observation.

The existing research and clinical observations described above provide a sound rationale for investigating the effectiveness of buprenorphine for reducing cocaine use in persons with cocaine dependence. Results of previous work suggest a viable approach—concurrent administration of buprenorphine and naltrexone—to examine the therapeutic potential of buprenorphine for reducing cocaine use while safeguarding against the risk of inducing opioid-seeking behavior. If buprenorphine in the presence of naltrexone is shown to reduce cocaine use in participants with cocaine dependence and opioid use disorders, findings could provide justification for studies where this pharmacotherapy combination would be tested in persons who are only cocaine dependent.

Prior studies investigating pharmacotherapy with buprenorphine treatment for opioid dependence provide evidence that individuals with concurrent cocaine and opioid use disorders can be successfully recruited. For example, of 516 opioid-dependent participants participating in a study of differing schedules of buprenorphine taper (CTN0003; Ling et al., 2009), 21% (n=107) were also diagnosed as cocaine dependent based on DSM-IV criteria. Analyses demonstrated a greater decrease in cocaine use for those who ceased opioid use, providing additional support for the contention that buprenorphine may be an effective treatment for cocaine dependence.

4.1.1 Buprenorphine

Opioid Dependence Treatment with Buprenorphine

One of the major focuses of NIDA initiatives has been the development of pharmacotherapies for the treatment of drug dependence. Of particular interest has been the use of buprenorphine (Subutex[®]) and its combination with naloxone (Suboxone[®]) as a treatment for opioid dependence. Buprenorphine is a mu-opioid partial agonist approved by the FDA in October of 2002 as a pharmacotherapy for the treatment of opioid dependence. Controlled clinical trials in several thousand participants over the past 15 years have provided overwhelming support for its therapeutic efficacy in opioid-dependent individuals (Amass, Kamien & Mikulich, 2000; FDA website, 2002; Fiellin, Rosenheck & Kosten, 2001; Fudala et al., 1998; Ling et al., 1996, 1998; Ling & Wesson, 2003; Woody et al, 2008). Treatment with buprenorphine in the United States emphasizes the use of Suboxone[®], a sublingual combination tablet containing buprenorphine and naloxone in a 4:1 ratio (Chiang & Hawks, 1994; Chiang et al., 1996a, 1996b, Fudala et al., 1998). This combination tablet was developed to help mitigate potential diversion and intravenous abuse of buprenorphine.

Although buprenorphine has abuse liability (Singh et al, 1992; de Jong, 1999; Ahmadi et al, 2003; Jenkinson et al, 2005), it appears to have less potential for psychological and/or physical dependence than traditional full agonist opioids like methadone (Comer et al, 2002; Alho et al, 2007). Buprenorphine has fewer side effects than methadone and its use in the office-based treatment setting provides the patient the opportunity to avoid the "stigma" sometimes associated with traditional opioid (methadone) maintenance treatment programs. Buprenorphine

treatment also allows patients to receive medication by prescription to be taken at home for days, weeks, or even months, thereby avoiding the more frequent (often daily) attendance required in methadone maintenance programs.

Buprenorphine Effects and Safety

Clinical research has established that buprenorphine (and as buprenorphine+naloxone) is a safe and effective alternative to methadone (Amass et al., 2000; Bickel et al., 1988a; Johnson et al., 1992; Ling et al., 1996, 1998; Strain et al., 1994; Uehlinger et al., 1998), and produces significant and substantial improvement over time in psychosocial functioning (Strain et al., 1996). In particular, buprenorphine has a favorable safety profile due to its ceiling effect on mu receptor activity, which minimizes respiratory depression and euphoric effects (Huestis et al., 1999; Lange et al., 1990), mitigates abuse liability (Walsh et al., 1994, 1995), and reduces overdose risk relative to full mu agonists. Maximal drug effects typically occur at approximately 8 to 16mg, although sublingual daily doses up to 32mg have been safely administered (Johnson et al., 1992; Ling et al., 1998; Walsh et al., 1994) for a period of up to one year.

Due to its unusually high affinity at the mu opioid receptor, buprenorphine blocks the effects of exogenously administered opioids (Bickel et al., 1988b; Walsh et al., 1995). Moreover, buprenorphine's slow dissociation from mu receptors not only results in a long duration of action but also diminishes symptoms and signs of withdrawal upon cessation (Amass et al., 1994; Fudala et al., 1990), thereby improving treatment outcomes by permitting accelerated tapering of buprenorphine.

Buprenorphine/Drug Interactions

Although buprenorphine has shown a ceiling effect for respiratory depression in clinical pharmacological testing (Walsh et al., 1994), the interaction of buprenorphine with other CNS depressants such as high doses of benzodiazepines and alcohol may be potentially dangerous (Faroqui, Cole, & Curran, 1983; Reynaud, Petit, Potard, & Courty, 1998). For this reason, excluding participants who meet DSM-IV criteria for abuse or dependence on these substances has been a standard practice in most clinical trials, and close monitoring by prescribing practitioners and patient education is required (Bridge, Fudala, Herbert, & Leiderman, 2003). Additionally, because buprenorphine is metabolized by Cytochrome P-450 3A4 (Iribarne et al., 1997), drugs that inhibit or induce this system could result in increased or decreased levels of buprenorphine. Known inhibitors of this system include erythromycin, ketoconazole, and grapefruit juice, and certain HIV protease inhibitors (Iribarne et al., 1998). Inducers of this system include phenobarbital, carbamazepine, and phenytoin, and could potentially lead to reduced levels of buprenorphine that might induce withdrawal symptoms (Bridge et al., 2003) though this effect has not been observed clinically. In a review of pharmacokinetic drug interactions, Armstrong and Cozza (2003) warn that drug interactions are likely with drugs such as azole-type antifungals, some macrolide antibiotics, nefazodone, rifampin and some antiepileptics.

Although there is some evidence of drug-drug interactions between buprenorphine and antiretroviral agents, Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and protease inhibitors, results from cohorts of HIV-infected patients in France indicate that buprenorphine treatment is associated with increased adherence to potent antiretroviral therapy and that patients experience appropriate increases in CD4+ cell count and reductions in viral load (Carrieri et al, 2000; Moatti et al, 2000). Other research has documented reductions in HIV risk behavior, overdose deaths, and improved outcomes from antiretroviral treatment in HIV-infected opioid users when treated with buprenorphine (Johnson et al., 2000), and strategies to expand access to opioid agonist treatment may combat the spread of HIV (Sullivan, Metzger, Fudala, &

Fiellin, 2005). Sublingual buprenorphine may result in liver function abnormalities, but hepatic toxicity is more likely with intravenous administration (Berson et al., 2001; Verrando et al., 2005).

4.1.2 Naltrexone

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

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

Overall, these study results suggest that naltrexone interferes with the beta-endorphin/dopamine reward system by attenuating the impact of alcohol-induced beta-endorphin release on dopamine release, thereby reducing the reinforcing properties of alcohol. Consistent with this finding has been the clinical observation that some alcoholics taking naltrexone did not relapse even if they drank, suggesting that naltrexone attenuated the usual relationship between drinking and relapse in persons trying to recover from alcohol dependence. Since adherence has been a problem in naltrexone studies using the 50mg tablet, an extended-release naltrexone formulation (e.g., Vivitrol[®]) may be a better formulation to use in relapse prevention because it does not depend on daily decisions to take a pill.

Extended-release Naltrexone by Injection: Vivitrol[®]

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

Vivitrol[®] Pharmacokinetics and Pharmacodynamics

After intramuscular injection there is a transient peak of naltrexone in about two hours, followed by a second peak 2-3 days later that reaches a level of around 25 ng/ml. This second peak is followed by a decline to about 12 ng/ml by Day 7, and then a more gradual reduction that

reaches 1-2 ng/ml in 30 days. The once/month injection reduces the first pass metabolism to 6-beta-naltrexol that occurs after the oral formulation, which allows for less total drug to be administered than the oral formulation, though total naltrexone exposure is 3-4 times higher over the 28 days following a Vivitrol® injection than with a 28-day course of the usual 50mg/day oral dose (PDR; 2009, pp 988-992).

The liver metabolizes naltrexone to 6-beta-naltrexol, its primary metabolite. The P450 system is not involved, thus reducing the chances for interactions with many other drugs including those used to treat hepatitis C and HIV. Naltrexone and its metabolites form glucuronide conjugates and are excreted in the urine. The elimination half-life of naltrexone and 6-beta-naltrexol is 5-10 days and dependent on the erosion of the PLG polymer.

Vivitrol® Safety

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

To prevent occurrence withdrawal symptoms in patients dependent on opioids, patients must be opioid-free for at least 7 days before starting Vivitrol® treatment. Patients should be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of treatment with Vivitrol®.

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

4.1.3 Psychosocial/Behavioral Treatment for Drug Dependence: Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy (CBT) has been extensively studied with various substance-abusing populations including alcohol (Annis & Davis, 1989), opioids (Church, Rothenberg, Sullivan, Bornstein, & Nunes, 2001; McAuliffe, 1990; Pollack et al., 2002; Stein et al., 2004), marijuana (Roffman, Stephens & Simpson, 1990), nicotine (Shoptaw, et al., 2002), and methamphetamine and cocaine (Azrin et al., 1996; Carroll et al., 1991, 1994a, 1994b, 1998, 2000; Rawson, et al., 1995, 1999, 2002; Shoptaw et al., 2005).

Many of the well-controlled studies that have demonstrated the efficacy of CBT have employed manuals to guide and standardize the delivery of the treatment material (Carroll, et al., 1994a; Rawson, et al., 1995, 1999, 2002; Shoptaw, et al., 1994). The overall goal of the CBT treatment model is to encourage and support abstinence of the targeted drug of choice. The specific CBT sessions focus on behavior change principles including identifying relapse triggers, development of coping skills, explanations of craving, discussions of “breaking the cycle” of addictive behaviors, the processes of maintaining new lifestyle behaviors, increasing self-efficacy, and the concept of abstinence.

Several research projects that have evaluated applications of the model have shown CBT to be associated with significant reductions in drug use (Carroll et al 1991, 1994a, 1998, 2000;

Rawson, et al., 2002,). Along with a reduction in use of the participant's drug of choice, CBT studies have also demonstrated reductions in HIV-risk behaviors (Shoptaw et al. 2005), which is extremely important when treating injection drug users. Treatment benefits of CBT appear to be sustained even after the discontinuation of treatment (Carroll et al, 1994b; Rawson et al., 2002). CBT is being extensively used in clinical practice with a variety of patients of every ethnicity, race, sexual orientation, and gender (McKay et al., 1997). The CBT approach is a well accepted form of therapy.

4.1.4 Significance of the Project to the Field

Investigation of the neurobiology of cocaine dependence has increased the understanding of involved brain mechanisms, leading to targeted research on medications that may be supportive of behavioral treatment and promote abstinence via negation of cocaine's rewarding effects. Relapse associated with currently available behavioral therapies is common, and a medication to help sustain abstinence or attenuate relapse episodes would be of great benefit, as cocaine dependence poses huge burdens on society and individuals. The examination of many medications for cocaine dependence has yielded no definitively and universally effective pharmacotherapy. Developing medication-based interventions for cocaine dependence has considerable scientific implications as well as clear public health ramifications, including reductions in criminal activity, social disruption, and infectious disease transmission related to drug use (Peck et al., 2005).

This project will assess the utility of buprenorphine in the presence of naltrexone as a potential medication useful in reducing cocaine use, commencing a research direction of great importance to both theoretical and practical addiction medicine. Naltrexone will be provided as extended-release naltrexone by injection (XR-NTX). Buprenorphine will be provided as buprenorphine+naloxone (BUP). This protocol will explore the effects of three conditions: 4mg of buprenorphine plus naltrexone (BUP4+XR-NTX), 16mg of buprenorphine plus naltrexone (BUP16+XR-NTX), or placebo plus naltrexone (PLB+XR-NTX) to test buprenorphine as a possible treatment for cocaine dependence. This study will advance the science, provide dosing information, and characterize the effects of the combination of the two medications in this population.

4.2 Objectives

The overall aim of this study is to examine the safety and effectiveness of buprenorphine in the presence of naltrexone for the treatment of cocaine dependence.

4.2.1 Primary Objective

The primary objective of this study is to determine whether buprenorphine can reduce cocaine use days as measured by self-report, corroborated by thrice-weekly urine drug screens, over the course of the 30-day evaluation period (the final 30 days of active medication administration prior to taper; days 25-54).

4.2.2 Secondary Objectives

Secondary objectives are:

1. To evaluate safety of the study conditions in the study population as measured by adverse events.
2. To assess cocaine use during the study using a variety of measures, including the Treatment Effectiveness Score (TES).

3. To assess use of other drugs of abuse across the duration of the study as measured by self-report and urine drug screens.
4. To examine cocaine and opioid craving using Visual Analog Scales (VAS).
5. To assess change in depressive symptoms as measured by the Beck Depression Inventory (BDI).
6. To assess the reduction in problems related to drug abuse.
7. To assess changes in quality of life as measured by the World Health Organization's Quality of Life BREF instrument.
8. To assess cocaine abstinence throughout the final two weeks of the evaluation period.
9. To assess retention in treatment across the duration of the active treatment phase.
10. To assess cocaine use during the follow-up period.

5.0 STUDY DESIGN

5.1 Overview of Study Design

This study is a randomized, double-blind, placebo-controlled trial to examine the safety and effectiveness of buprenorphine in the presence of naltrexone for individuals with cocaine dependence and either past-year opioid dependence or past-year opioid abuse or past-year opioid use with a history of opioid dependence during the lifetime.

Buprenorphine will be provided as sublingual buprenorphine+naloxone tablets (Suboxone®). Naltrexone will be provided as extended-release naltrexone by injection (Vivitrol®).

Participants will be randomly assigned to one of three medication conditions: 4mg buprenorphine plus naltrexone (BUP4+XR-NTX), 16mg buprenorphine plus naltrexone (BUP16+XR-NTX), or placebo plus naltrexone (PLB+XR-NTX) for 8 weeks of treatment. In addition, all participants will be scheduled for once-weekly CBT sessions. Thrice-weekly clinic visits will be scheduled for observed medication administration, provision of take-home medication, collection of safety, medical, drug use, psychological, and compliance measures.

5.2 Duration of Study and Visit Schedule

The duration of this study will be approximately 24 weeks from screening to completion of the 3-month follow-up visit, although this will differ on an individual basis depending on the length of time needed for screening, eligibility tests, and induction onto naltrexone. Screening and baseline assessments will take approximately 4 hours to complete, including the collection of laboratory samples and medical assessments. In addition, confirmation of detoxification status (urine drug screen, naloxone challenge, and naltrexone induction) will take approximately three hours. Thrice-weekly visits will last from 20–60 minutes depending on the assessments scheduled, and weekly CBT sessions will be completed in approximately 45 minutes.

Participants will be scheduled for clinic visits three times weekly (for a total of 24 visits across the 8-week treatment period). An 8-week active treatment period was selected to best reflect the typical treatment duration for the target population in outpatient CTPs and for pragmatic issues related to medication dosing. Participant tracking procedures will be employed to locate participants during the trial and at the two follow-ups at 1 month and 3 months post-treatment. Participants will be asked to provide urine samples and complete scheduled assessments at every clinic visit in accordance with the schedule of assessments (see Section 8.0). Follow up visits will take approximately 2 hours to complete.

5.3 Study Population

A total of 300 individuals will be randomized in this study, including males and females between 18 and 65 years of age who meet DSM-IV criteria for cocaine dependence and meet criteria for either past-year opioid dependence or past-year opioid abuse or past-year opioid use with a history of opioid dependence during the lifetime.

5.3.1 Inclusion Criteria

Study participants *must*:

1. Be 18 to 65 years of age;
2. Be in good general health;
3. Meet DSM-IV criteria for cocaine dependence;

4. Have either:
 - past-year opioid dependence (DSM-IV) or
 - past-year opioid abuse (DSM-IV) or
 - past-year opioid use and a history of opioid dependence during the lifetime (DSM-IV Addendum);
5. Be interested in receiving treatment for cocaine dependence;
6. Provide a negative urine drug test for opioids immediately prior to naloxone challenge;
7. Meet objective or subjective definition of being “opioid detoxified” as per study medical clinician’s determination;
8. Tolerate induction onto oral naltrexone and XR-NTX;
9. If female of childbearing potential, be willing to practice an effective method of birth control for the duration of participation in the study;
10. Be able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study.

5.3.2 Exclusion Criteria

Study participants *must not*:

1. Have evidence of an acute psychiatric disorder as assessed by the study medical clinician that would make participation difficult or unsafe;
2. Have suicidal or homicidal ideation that requires immediate attention;
3. Have a known allergy or sensitivity to buprenorphine, naloxone, naltrexone, PLG (polyactide-co-glycolide), carboxymethylcellulose or any other component of the XR-NTX diluent;
4. Have a serious medical illness that, in the opinion of the study medical clinician, would make participation medically hazardous;
5. Have evidence of second or third degree heart block, atrial fibrillation, atrial flutter, prolongation of the QTc; in addition, any other finding on the screening ECG that, in the opinion of the medical clinician, would preclude safe participation in the study will also be exclusionary;
6. Have any LFT value > 5 times the upper limit of normal as per laboratory criteria;
7. Have INR >1.5 or platelet count <100k;
8. Have body habitus that precludes gluteal intramuscular injection of naltrexone with provided needle;
9. Have taken an investigational drug in another study within 30 days of study consent;
10. Be receiving ongoing treatment with tricyclic antidepressants, chlorpromazine, modafinil, disulfuram, or any medication that, in the judgment of the study medical clinician, could interact adversely with study drugs;
11. Have been in methadone maintenance treatment within 15 days of consent;
12. Have been in buprenorphine maintenance treatment within 30 days of consent;

13. Have pending legal action or other situation that might prevent remaining in the area for the duration of the study;
14. Have a surgery planned or scheduled during the study period;
15. Require therapy with opioid-containing medicines (e.g., opioid analgesics) during the study period;
16. Have a current pattern of alcohol, benzodiazepine, or other sedative hypnotic use, as determined by the study medical clinician, which would preclude safe participation in the study;
17. Be currently pregnant or breastfeeding.

5.4 Participant Recruitment

Study participants will be recruited using a variety of methods including advertising and study announcement flyers posted in local inpatient and outpatient treatment settings or other community sites, word-of-mouth, and referrals.

5.5 Number of CTP Sites

The multi-site trial will involve 10-12 community treatment programs across the CTN.

5.6 CTP Characteristics

Participating CTPs must:

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

5.7 Rationale for CTP Selection

Assuming 10-12 sites and a target of 300 randomized participants, each site was selected, in part, based on ability to randomize and complete assessments on 30-35 participants during the trial, thus randomizing across all sites 100 to BUP4+XR-NTX, 100 to BUP16+XR-NTX and 100 to PLB+XR-NTX.

6.0 OUTCOME MEASURES

6.1 Primary Outcome Measure

Primary outcome will be number of cocaine use days as measured by self-report over the course of the 30-day evaluation period (the final 30 days of active medication administration prior to taper; days 25-54), corroborated by thrice-weekly urine drug screens.

6.2 Secondary Outcome Measures

1. Adverse events related to study medication across the duration of the study, measured at each clinic visit by appropriately qualified and trained medical personnel;
2. Cocaine use will be assessed by a number of outcome measures, including:
 - a. The Treatment Effectiveness Score using urine drug screen results;
 - b. Number of cocaine use days as measured by self-report during the period between randomization and end of treatment;
 - c. Percentage of participants who test free from cocaine use on three successive urine tests;
3. Number of days of use of other drugs of abuse as measured by self-report, corroborated by urine drug screen results;
4. Severity of cocaine and opioid craving using Visual Analog Craving Scales (VAS);
5. Change in depressive symptoms during the period between randomization and end of treatment as measured by the BDI.
6. Reduction in drug-related problems between randomization and end of treatment as indicated on the Addiction Severity Index;
7. Changes in quality of life between randomization and end of treatment as measured by the World Health Organization Quality of Life BREF instrument;
8. Percentage of participants who achieve cocaine abstinence throughout the final two weeks of the evaluation period.
9. Percentage of participants who are retained in treatment for the duration of the active treatment phase.
10. Number of cocaine use days as measured by self-report during the follow-up period.

7.0 STUDY PROCEDURES

7.1 Screening and Baseline

Assessments conducted during screening will determine whether participants meet eligibility criteria, and will also provide baseline measures of drug use and other life domains (HIV risk, psychiatric, family/social, legal problems, etc.) prior to beginning study treatment. Participants who do not pass all items listed below within 30 days of consent, including the naloxone challenge and naltrexone induction, will be considered screen fails.

7.1.1 Pre-screening Assessment

Individuals responding to recruitment materials or otherwise referred to the study will be pre-screened on the phone or in person to ascertain preliminary eligibility status. A series of questions will determine preliminary eligibility, and full screening appointments will be scheduled for those who meet these eligibility criteria.

7.1.2 Informed Consent Procedures

At the start of screening appointments, qualified study personnel will explain the study to prospective participants including the use of XR-NTX (Vivitrol®) and random assignment to BUP (Suboxone®) or placebo. Participants will be given a copy of the IRB-approved consent form and asked to read it either on site or at home in accordance with the consent process approved by the local IRB. Participants who remain interested after receiving an explanation of the study will be given a short quiz to test his/her understanding of the project, the purpose and procedures involved, and the voluntary nature of his/her participation. Those who cannot successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form and proceed with the screening assessments.

7.1.3 Pre-Induction Strategy

- Self-report of no opioid use in the previous seven days, as measured with the Timeline Follow-Back and Prior and Concomitant Medication assessment. Participants reporting no opioid use in the previous seven days will move to the next step.
- A urine drug screen that is negative for opioids. A one-step test will be used to measure opioid use. Individuals who are opioid-negative will continue in the pre-induction process. Individuals can have two additional attempts to provide a subsequent urine drug screen negative for opioids on a different day if the study medical clinician determines that repeat specimens are appropriate to meet these requirements.
- Completion of all pertinent psychosocial and medical screening assessments (see Sections 5.3.1, 5.3.2, 8.0).
- A naloxone challenge must be performed to confirm the absence of physiological dependence on opioids. The method of naloxone challenge administration is up to the discretion of the medical clinician. An example of a challenge could begin with the delivery of 0.1mg naloxone I.V., I.M., or subcutaneous. If no significant levels of opioid withdrawal symptoms or discomfort appear after a few minutes, a second dose of 0.3mg would then be provided followed by a brief observation period. With no observed discomfort, 0.8mg naloxone would then be administered as the final dose, followed by an observation period. In any case, a minimum 0.8mg bolus must be given before determining that a naloxone

challenge is negative. The determination as to whether the participant is eligible to continue on to the oral naltrexone induction will be made by the study medical clinician based on clinical judgment, including both objective and subjective assessments. Attention to individual symptoms and changes in these symptoms should guide the medical clinician. New signs of discomfort or increase in withdrawal symptoms following naloxone administration should be taken as a positive result of the challenge. In this case the oral naltrexone induction should be delayed until a negative challenge result is achieved.

7.1.4 Naltrexone Induction

Oral Naltrexone. All participants will receive oral naltrexone prior to the first XR-NTX administration. Oral naltrexone induction will be performed as determined by the study medical clinician, usually over 2 days, though may be completed in one day where a negligible risk of opioid withdrawal is determined to exist. Based on the study medical clinician's determination, oral naltrexone may be provided for a period greater than two days as necessary.

The initial dose of naltrexone is at the study medical clinician's discretion. A suggested dose range for the initial dose is 12.5-25mg oral naltrexone. Following the first dose of oral naltrexone the participant should be observed for emergence of opioid withdrawal symptoms. If the participant experiences no withdrawal, nausea or other adverse effects, another 12.5mg-25mg naltrexone can be given in clinic or as take-home medication. Irrespective of induction procedure, participants must receive a total of 50mg oral naltrexone as an in-clinic dose and show no signs of discomfort or opioid withdrawal on the day of the first XR-NTX administration.

Participants who experience withdrawal symptoms following the naloxone challenge or oral naltrexone induction can be treated with ancillary medications, observed until symptoms resolve, and given the opportunity to return another day and be re-challenged. Participants who relapse to opioid use and are not interested in continuing to participate, or who fail a repeat naloxone challenge, will be referred to the most appropriate local treatment facility and will not be eligible to continue in the study.

Participant vital signs should be clinically stable, as assessed by the medical clinician, and the participant should show no signs of withdrawal prior to discharge from the clinic after initial study drug administration.

Extended-release Naltrexone. XR-NTX will be provided to participants as a gluteal intramuscular injection (380mg) immediately prior to randomization. The XR-NTX injection shall be administered following the guidelines provided in the package insert.

An inadvertent subcutaneous injection of XR-NTX may increase the likelihood of severe injection site reactions. The needle provided in the kit is a customized needle, and XR-NTX must not be injected using any other needle. The needle length may not be adequate in every participant because of body habitus. Body habitus will be assessed during the screening physical examination for each participant to assure that needle length is adequate for intramuscular administration. The study medical clinician will ensure that the XR-NTX is given correctly, and will exclude from study participation participants whose body habitus precludes a gluteal intramuscular injection of naltrexone with the provided needle.

7.2 Randomization

Immediately following successful induction onto XR-NTX and a final assessment of eligibility, participants will be randomly assigned to one of the three conditions: (BUP4+XR-NTX), (BUP16+XR-NTX) or (PLB+XR-NTX) for 8 weeks of treatment. Random assignment will be on a 1:1:1 ratio to one of three conditions. Randomization will be stratified according to site and opioid use levels according to the following strata:

- *High*, defined as 1) ever injected an opioid; 2) greater than or equal to 2 years of regular opioid use (per ASI); or 3) opioid use on 20 or more days in the month preceding screening (per TLFb)
- *Low*, defined as not meeting criteria for high opioid use

The randomization procedure will be conducted in a centralized process through the CTN Data and Statistics Center (DSC), and randomization assignments will not be conveyed to staff or participants. The DSC statistician will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. The DSC statistician will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization slot, once used, will not be re-allocated.

7.3 Treatment

7.3.1 Pharmacotherapy

For the three conditions, administration of full daily doses of BUP or PLB will be observed in-clinic three times a week (recommended to occur on M-W-F) with sufficient take-home medication provided at each clinic visit for self-administration until the next clinic visit. XR-NTX will be administered by injection immediately prior to randomization and again at the first visit of Week 5.

Buprenorphine

The sublingual formulation of buprenorphine with naloxone (BUP) at 4:1 ratio will contain 2mg/0.5mg of buprenorphine/naloxone, or 8mg/2mg buprenorphine/naloxone. The tablets are manufactured by Reckitt-Benckiser Pharmaceuticals, Inc. (Hull, UK) and will be shipped to a NIDA contractor for distribution to the sites.

Although Suboxone® contains the opioid antagonist naloxone, the sublingual administration confers negligible bioavailability of naloxone. There is no additive or compound antagonist effect of naltrexone provided in the presence of Suboxone. To reflect clinical practice norms involving office-based prescribing of buprenorphine, we are using the Suboxone form rather than the mono-form (i.e., Subutex®).

Placebo

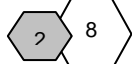
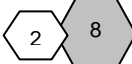
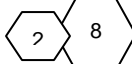
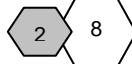
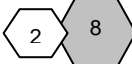
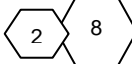
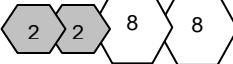

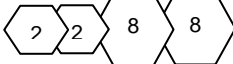
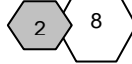
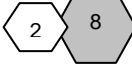
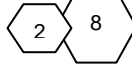
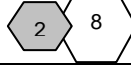

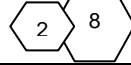
Placebo (PLB) will be prepared to look identical to the BUP preparation. Reckitt-Benckiser Pharmaceuticals, Inc. will provide the matched PLB.



Buprenorphine/Placebo Ramp-Up, Dosing, and Taper

Once randomized, participants will be inducted onto BUP (or PLB) by provision of half of their randomly assigned dose for the first two days of the treatment period (Days 1 and 2). Two tablets will be provided to each participant: one 2mg tablet and one 8mg tablet (active or placebo, depending on condition; see Fig. 2 for illustration of dosing). Vital signs will be assessed prior to the BUP (or PLB) induction and approximately one hour after administration to ensure stability before leaving the clinic on Day 1. On Day 3 daily dosage will be increased to the full assigned dose and will require the provision of 4 tablets. This dose will continue until the taper period during the last two days of the active treatment phase. If the participant reports intolerable side effects after receiving the full dose, and it is deemed appropriate by the study medical clinician, a dose reduction may occur. In this instance, the participant will be supplied with half of their randomly assigned dose such that only one 2mg and one 8mg tablet will be

provided daily. Continuing adverse side effects after a dose reduction will result in the participant's withdrawal from further medication administration. A taper will occur during the last two days of Week 8 of the active treatment phase (Days 55 and 56). The daily dose will be halved for the two taper days such that each participant will take one 2mg and one 8mg tablet daily. For any participant who is taking a reduced dose, no taper or additional reduction in dose will occur during the taper days. In the event a participant becomes pregnant during the active treatment phase, a taper is not indicated. The participant will be discontinued from further study medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

Figure 2. Buprenorphine/Placebo Induction, Maintenance, and Taper Dose by Study Day

Day	Dose of BUP (expressed as amount of buprenorphine)					
	4mg Group	Dispense	16mg Group	Dispense	Placebo Group	Dispense
1	2		8		0	
2	2		8		0	
3-54	4		16		0	
55	2		8		0	
56	2		8		0	

Key:  Active  Placebo

Extended-release Naltrexone

At Week 5, a second XR-NTX will be administered to study participants via gluteal intramuscular injection (380mg). An induction procedure may be repeated before the second XR-NTX injection if clinically indicated. No taper from XR-NTX will be necessary.

7.3.2 Cognitive Behavioral Therapy (CBT)

All participants are scheduled to receive once-weekly individual CBT conducted by a trained therapist over the 8-week treatment phase using a CBT treatment manual developed for this study. Each therapy session will be completed in approximately 45 minutes. Sessions will be guided by a worksheet from the treatment manual that presents a concept or a brief exercise explaining or illustrating one or more principles of CBT. Participants may not participate in other psychosocial addiction treatment services at the CTP during the active treatment phase of the study.

7.4 Ancillary Medications

Ancillary medications can be provided for opioid withdrawal symptoms or study medication-related side effects if clinically indicated. A range of prescription and over-the-counter ancillary

medications may be used. Ancillary medications are permitted for anxiety, bone pain and arthralgias, nausea, diarrhea, and insomnia.

7.4.1 Concomitant Medications

Participants will be instructed to contact the study medical clinician if they plan on taking any concomitant medications (including prescription, over-the-counter, and herbal supplements) during the course of the study.

As described in the eligibility criteria, participants will be excluded on the basis of potential medication interactions of clinical importance. Medications that may interact with buprenorphine will be excluded, including tricyclic antidepressants and chlorpromazine, which prolong the QTc interval. Participants who take modafinil and disulfiram will also be excluded, as these medications may impact cocaine use. The study medical clinician may also exclude any participant taking medications that could interact adversely with study drugs at his/her clinical discretion.

7.5 Study Medication Management

Each CTP is required to observe local, state, and federal regulations regarding receipt, custody, dispensing, and disposition of all medications used in this study.

Each CTP will use its own supply of naloxone and oral naltrexone in this study. Naloxone and oral naltrexone will not be supplied to the CTP by the NIDA contractor; therefore each CTP will be responsible for maintaining an adequate supply of naloxone and oral naltrexone to meet the needs of the study. Each CTP will use standard clinic practices for maintaining appropriate accountability for naloxone and oral naltrexone provided to study participants.

Each CTP will use XR-NTX and BUP/PLB supplied by the NIDA contractor. The following study-specific information on drug accountability and handling pertains only to study medication (i.e. XR-NTX and BUP/PLB) supplied by NIDA.

Appropriately qualified and trained medical personnel will maintain an accurate and current accounting of all study medication. Drug accountability records will be made available for verification by study monitors. Drug-accountability records including perpetual inventory, will be maintained at all times. These records will include the amount of XR-NTX and BUP/PLB ordered, received, transferred between areas of the study site (from pharmacy to clinic and back, for example), and those dispensed to and returned by an individual participant.

7.5.1 Study Medication Storage

Study medication will be stored in compliance with federal, state, and local laws and institutional policy. Study medication will be stored in a locked, secure, limited-access location under the conditions specified by the package insert.

7.5.2 Used/Unused Medication

Study medication returned by a participant may not be re-issued for use. Unused study medication will be returned and logged into a perpetual inventory of study medication returned. Returned medications will be accurately labeled, securely stored, and kept separately until the end of the study. Damaged, returned, expired or unused study medication will be accounted for by the NIDA contract monitor and sent to the central distributor or a reverse distributor for destruction. Expired XR-NTX will be destroyed on site per local institutional policies following a complete accounting by the NIDA contract monitor.

7.5.3 Lost Medication

There will be no replacement of any study medications that are prescribed and dispensed to the study participant.

7.5.4 Dispensing of Study Medications

All study medications shall be prepared and dispensed by a pharmacist or licensed medical practitioner appropriately trained and authorized to dispense study medications. XR-NTX will be administered at screening and again at week 5.. At each clinic visit over the 8-week active treatment phase BUP (or PLB) will be provided to the participant for an in-clinic, observed, sublingual dose. Take-home doses will be provided for non-clinic days, including weekends and holidays. Take-home medication dispensed will be sufficient to allow self administration until the next clinic visit.

7.5.5 Drug Packaging

XR-NTX will be supplied in single use kits. Each kit will contain one 380 mg vial of Vivitrol[®] microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of Vivitrol[®], one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1.5-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices. Lot number and medication expiration date will be included on the kit labels as supplied by the manufacturer. The BUP and PLB will be pre-packaged in individual participant medication kits containing 9 boxes (one for each study week, and an additional box of medication to be used only if supplied medication is damaged or needs to be replaced). Each weekly box in the participant's kit will contain two bottles of medication, BUP (or PLB) 2mg tablets and BUP (or PLB) 8mg tablets. Each bottle label will include kit and lot numbers, study week number, protocol number, participant ID, and study drug information. The label will also include: "Caution: New Drug- Limited by Federal Law to Investigational Use. Store at Controlled Room Temperature (20-25°C or 68-77°F)" as well as the manufacturer and distributor information.

7.6 Participant Withdrawal

Women who become pregnant during the active treatment period will be withdrawn from further study medication administration, referred for medical care, and the pregnancy will be followed until an outcome is known. Participants who continue to experience intolerable side effects after a dose reduction will also be withdrawn from further study medication administration.

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

- The initiation or recurrence of risky behaviors that had either never previously occurred or had not occurred recently (e.g., injection use, increased opioid use);
- Overdose;
- Emergence of psychosis, suicidal ideation, severe cognitive impairment or dangerous criminal behaviors;
- Evidence of medical deterioration; or
- New onset of psychiatric or medical conditions that would require intervention above and beyond or different from that prescribed in the study protocol.

If any of these situations occur, the medical clinician will evaluate and determine whether the participant should be withdrawn from further medication administration. In the event the

participant is withdrawn from further medication administration, referrals to treatment programs or recommendations for medical care should be provided. The study medical clinician in collaboration with the site principal investigator may consult with the lead investigator(s) and study medical monitor in making this decision. At any time, participants may notify study personnel that they no longer wish to continue in the study intervention. Study personnel will request that the participant complete an end-of-medication visit to assure safety and to document end-of-medication outcomes. Unless consent is withdrawn, effort will be made to continue thrice-weekly visits throughout the duration of the planned treatment phase (weeks 1 – 8) with all participants who prematurely discontinue medication administration during the active treatment phase.

7.7 Follow-Up

All randomized participants will be scheduled to complete 1-month and 3-month follow-up visits according to the schedule of assessments (see Table 2, section 8.0). Participant tracking strategies will be used to ensure the highest possible participant assessment completion rates, including obtaining detailed contact information from participants at intake. Research staff will update participant contact information regularly during the active treatment phase and at the 1-month follow-up.

7.8 Blinding

7.8.1 Type of Blinding

This is a double-blind, placebo-controlled trial.

7.8.2 Maintenance of the Blind

With the exception of the data management group managing the random assignment schedule and the NIDA contract research pharmacist preparing study medications, all other study personnel and participants will remain blinded to medication status until completion of the trial, nationwide. A Data Safety Monitoring Board (DSMB) will review study data.

7.8.3 Breaking the Blind

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

7.9 Participant Reimbursement

Study participants will be provided with study medication and counseling at no cost. In addition, participants will receive \$70 in gift cards or cash for completion of screening/baseline assessments (\$20 for the first three visits and \$10 for a fourth visit if required. If screening is completed in fewer visits, the remaining balance will be distributed on the day of randomization). Participants will receive \$30 in gift cards or cash for each Vivitrol injection visit (\$30 x 2 injections = \$60). A \$20 gift card or cash will be provided for completion of each of the 3 weekly clinic visits over the 8-week active treatment phase (24 visits x \$20 per visit = \$480). Participants will receive \$55 in gift cards or cash for completion of the additional end-of-

medication/end-of-treatment assessments and \$50 gift cards or cash for each of the two follow-up assessments. The total compensation possible is \$765 as outlined in Table 1 below. Compensation is intended to defray costs for participants' time, travel, and other related costs to improve clinic visit attendance. This compensation schedule may vary based upon site and local regulatory requirements.

Table 1 Compensation Schedule

Visit/Assessment	Amount	# of Payments	Total
Screening Assessments	\$70	1	\$70
Vivitrol Injection Visit	\$30	2	\$60
Active Treatment Visit	\$20	24	\$480
End of Medication/Treatment Visit Assessments	\$55	1	\$55
Follow-up Visit	\$50	2	\$100
Total			\$765

8.0 STUDY ASSESSMENTS

Study measures were chosen to minimize the research burden on participants yet collect adequate data to support analyses and assure safety. Similar to other pharmacotherapy and behavioral treatment research, measures have been included to ensure a comprehensive assessment of pertinent status and functioning variables. Importantly, many of the study measures were selected to record vital health information during buprenorphine treatment and are similar to other recent and ongoing studies of buprenorphine (e.g. Ling et al., 2005). Additional measures were selected to obtain information usually included in treatment studies, and include assessments of drug abuse and dependence diagnoses, psychological status, quality of life, and measures of craving. Safety is assessed at each visit. Additional forms are used to collect and document study-specific information such as enrollment, dosing, CBT participation, and contact information. Table 2 provides a representation of study assessments. On average, screening assessments will be completed in 7 hours, including confirmation of detoxification status. Thrice-weekly assessments will be completed in approximately 20 to 60 minutes. End-of-medication, end-of-treatment, and follow-up visits are expected to take approximately 2 hours.

Table 2 - Schedule of Assessments

Study Phase	Scrn/Baseline	Active Treatment																								End of Med	Follow-up			
		1			2			3			4			5			6			7			8				5 or 8	12	20	
Study Week	0	101	102	103	201	202	203	301	302	303	401	402	403	501	502	503	601	602	603	701	702	703	801	802	803	501 or 803	M1FU	M3FU		
Informed Consent	X																													
General Measures																														
Inclusion/Exclusion	X																													
Locator Form	X	X						X						X							X				X	X	X			
Demographics Form	X																													
Family Origin	X																													
Treatment Satisfaction Survey																									X	X				
End of Medication Form																								X	X					
End of Study Form																													X	
Safety and Medical Measures																														
Medical and Psychiatric History	X																													
Physical Examination	X																							X	X					
Injection Site Examination		X													X															
Electrocardiogram	X													X										X	X					
Clinical Laboratory Tests	X									X														X	X					
Buprenorphine and Naltrexone Blood Levels														X										X	X					
Pregnancy and Birth Control Assessment ^A	X	X												X									X	X						
Vital Signs ^B	O	X			X			X			X			O			X			X			X	O	O					
Prior and 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	X	X	X
Adverse Events and Serious Adverse Events	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	X	X	X
Drug Use and Psychological Measures																														
Timeline Follow-back	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Drug Screen	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visual Analog Craving Scale	X	X			X			X			X			X			X			X			X	X	X	X	X	X	X	
Beck Depression Inventory	X	X			X			X			X			X			X			X			X	X	X	X	X	X	X	
Treatment Effect Assessment	X													X										X	X	X	X	X	X	
WHO Quality of Life BREF	X																							X	X				X	
PRISM - Suicide and Homicide Screening	X													X										X	X					
Opioid Use Questionnaire	X																													
DSM IV-TR Checklist	X																													
Risk Assessment Battery	X																							X	X					
Self-Help Assessment	X																							X	X	X	X	X	X	
Addiction Severity Index Lite	X																							X	X	X	X	X	X	
Fagerström Test for Nicotine Dependence	X																							X	X					
Compliance Measures																														
Dose Logs	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	X	X	
CBT Attendance Log				X			X						X			X				X				X	X					

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

^B Collected according to schedule of assessments, including BEFORE and AFTER administration of naloxone, first dose of oral naltrexone, XR-NTX, and first dose of BUP (or PLB).

O = Orthostatic vitals

8.1 General Measures

8.1.1 Inclusion/Exclusion

This form will include each inclusion and exclusion criterion to document eligibility. Eligibility will be assessed continually as appropriate. Only participants who continue to meet study eligibility criteria will be allowed to continue with the screening process, pre-induction procedures, and randomization.

8.1.2 Locator Form

A locator form will be used to obtain information to assist in finding participants during treatment and at follow-up. This form will collect participants' current address, email address, and phone numbers, as well as names, addresses and phone numbers of family/friends who may know how to reach the participant if direct contact efforts are unsuccessful. This information will be collected at screening, and will be updated at least every two weeks during the active treatment phase, at the end-of-medication visit, at the end-of-treatment visit (last visit of Week 8), and at the 1-month follow-up. No information from this form will be used in data analyses.

8.1.3 Demographics Form

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

8.1.4 Family Origin

The family origin form is designed to be interviewer administered. It collects information about the participant and her/his biological family members' race/ethnicity, place of birth, and ancestry. If a participant does not know the information requested, the participant may answer "unknown." This form will be completed at screening. This form can be completed at any time for participants who have completed screening.

8.1.5 Treatment Satisfaction Survey

Satisfaction with treatment, both psychosocial and pharmacological, and participant impression as to treatment condition will be recorded on the Treatment Satisfaction Survey completed at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (last visit of Week 8).

8.1.6 End of Medication Form

This form tracks the participant's status with regard to the study intervention/medication. It will be completed at the time a participant is withdrawn from further medication administration or at the end-of-treatment visit (last visit of Week 8).

8.1.7 End of Study Form

This form tracks the participant's status in the study. It will be completed once participation in the study has ended, at the 3-month follow up visit or once the 3-month follow-up visit window elapses for participants who do not complete this final follow-up. This form will be used in data analyses to address variables such as treatment retention and completion.

8.2 Safety and Medical Measures

The study physician must review and approve all safety and eligibility assessments in order to confirm participant eligibility prior to randomization.

8.2.1 Medical and Psychiatric History

The study medical clinician will obtain a medical and psychiatric history from the participant covering past and present health conditions to help determine eligibility and to provide baseline information regarding the participant's medical health. This form will be collected at screening. Information from this form may be used in data analyses.

8.2.2 Physical Examination

The study medical clinician will complete a physical examination to ensure that there are no medical concerns regarding participation and to gather baseline information regarding the participant's physical health. During the screening physical exam a description of the participant's body habitus will be documented and the study medical clinician will examine the planned injection sites to ensure adequacy for XR-NTX gluteal intramuscular injection of naltrexone with the supplied needle. The physical examination will be collected at screening and will be repeated at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (last visit of Week 8).

8.2.3 Injection Site Examination

Appropriately qualified and trained medical personnel will examine the injection site on the next visit following the first and second XR-NTX administration. These examinations usually occur at visits 102 and 502 but may occur at other visits as required. Participants will be asked to immediately report any injection site reactions to study staff for evaluation, monitoring, and possible referral, as needed. Injection site reactions should be documented on the Injection Site Abnormality Log.

8.2.4 Electrocardiogram (ECG)

A 12-lead ECG will be administered by appropriately qualified and trained medical personnel. The screening ECG will assist in determining participant eligibility. The ECG will be repeated at week 5, and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (last visit of Week 8).

8.2.5 Clinical Laboratory Tests

A comprehensive blood chemistry including liver function tests (LFTs: including AST, ALT, GGT, ALP, and bilirubin), PT w/INR (Prothrombin Time/International Normalized Ratio) and PTT (Partial Thromboplastin Time), a hematology panel, and a standard urinalysis will be performed to help determine eligibility at screening. Although receipt of laboratory test results is not necessary before conducting the naloxone challenge, the lab results must be received and reviewed prior to administration of XR-NTX.

At screening, hepatitis B and C serology tests will be conducted including hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (Anti-HBs), hepatitis B core IGM antibody (Anti-HBc), hepatitis C virus antibody (HCV Ab), and HIV testing.

Clinical lab tests will also be repeated in the study week prior to the second XR-NTX administration, and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (last visit of Week 8).

A central laboratory that is accredited by the College of American Pathologists (CAP) or equivalent, and participates in the Clinical Laboratory Improvement Act of 1998 (CLIA) will perform these analyses. The central laboratory will provide normal values and proof of lab certifications.

8.2.6 Buprenorphine and Naltrexone Levels

Pharmacokinetic assessments will establish blood levels of buprenorphine and naltrexone prior to the second XR-NTX administration at Week 5 and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (last visit of Week 8). Samples will be drawn and sent to a designated laboratory for testing and analysis purposes and results will not be shared with the study sites.

8.2.7 Pregnancy and Birth Control Assessment

This form will document whether pregnancy tests were administered, test results, and female participants' self-reports of birth control method(s). The pregnancy and birth control assessment form, including on-site urine pregnancy tests will be collected at screening prior to the naloxone challenge and the first XR-NTX administration, at week 5 prior to the second XR-NTX administration, and at the end-of-medication visit (if medication is stopped early) or at the end-of-treatment visit (last visit of Week 8).

8.2.8 Vital Signs

Vital signs will be recorded at screening and once weekly throughout the active treatment phase, at the end-of-medication visit (if medication is stopped early), and at the end-of-treatment visit (last visit of Week 8). Vital signs will also be recorded before and after administration of naloxone, first dose of oral naltrexone, XR-NTX, and first dose of BUP (or PLB). In addition, orthostatic vital signs will be recorded at screening, at Week 5, at the end-of-medication visit, and at the end-of-treatment visit (last visit of Week 8).

8.2.9 Prior and Concomitant Medications

Appropriately qualified and trained medical personnel will use this form to collect information about prescription and over-the-counter medications used by participants. At screening, the form will be used to record medications taken by the participant in the 2-week period prior to screening. At weekly, end-of-medication/treatment, and follow-up visits the form will document medications taken since the previous data collection visit.

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

Appropriately qualified and trained medical personnel will assess for any medical or psychiatric side effects, by asking: "How have you been feeling since your last visit?" AEs will be recorded at each visit after consent according to the adverse event reporting definitions and procedures outlined in the protocol. If a reported AE suggests medical or psychological deterioration, it will be brought to the attention of the study medical clinician for further evaluation. SAEs will be medically managed, reported, and followed in accordance with applicable regulatory requirements.

8.3 Drug Use Measures and Psychological Measures

8.3.1 Timeline Follow-back (TLFB)

The Timeline Follow-back procedure (Sobell & Sobell, 1992; Fals-Stewart, 2000) will be used to elicit the participant's self-reported use of alcohol and illicit substances before and during the entire study period. At screening, this form will be used to assess substance use reported by the participant for the 30-day period prior to screening. The TLFB will be administered at each study visit throughout the active treatment phase and through the end of the follow up period to document the participant's self-reported use of substances for each day since the previous TLFB assessment.

8.3.2 Urine Drug Screen (UDS)

Urine drug screens will be collected at every clinic visit, in most cases, before assessing self-reported drug use or dispensing medications. All urine specimens will be collected using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. The UDS will test for the presence of the following drugs: opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamines, marijuana, methadone, and Ecstasy (MDMA). A further validity check will be performed using a commercially available adulterant test strip that indicates normal ranges for creatinine, pH (at minimum), nitrate, glutaraldehyde, specific gravity, bleach and pyridinium chloromate in human urine. In the event urine specimen tampering is suspected, study staff should request a second sample and may observe the urine collection process according to clinic standard operating procedures.

8.3.3 Visual Analog Craving Scale (VAS)

Participants' craving for opioids and cocaine will be documented on a visual analog scale (VAS) that ranges from 0 (no craving) to 100 (most intense craving possible). This scale will be completed at screening and once weekly throughout the active treatment phase, at the end-of-medication visit (if medication is stopped early), at the end-of-treatment visit (last visit of Week 8), and at each follow-up.

8.3.4 The Beck Depression Inventory (BDI)

The Beck Depression Inventory (Beck & Steer, 1993) will be used to assess symptoms of depression. A participant who scores in the range for possible depression (score of 15 or higher) or reports possible suicidal ideation will be assessed by a qualified clinician before leaving the clinic. This self-administered assessment will be completed at screening and once weekly throughout the active treatment phase, at the end-of-medication visit (if medication is stopped early), at the end-of-treatment visit (last visit of Week 8), and at each follow-up.

8.3.5 Treatment Effect Assessment (TEA)

The TEA (Ling, 2009) is a 4-item self-administered assessment that uses a Likert scale (1-10) to document changes in four life domains: substance use, personal responsibilities, health, and citizenship. Analyses are underway addressing psychometric properties of this measure. The TEA will be collected at screening, at week 5, at the end-of-medication visit (if medication is stopped early), at the end-of-treatment visit (last visit of Week 8), and at each follow-up.

8.3.6 World Health Organization Quality of Life BREF (WHOQOL-BREF)

The WHOQOL-BREF (The WHOQOL Group, 2004) instrument comprises 26 items, which measure domains of physical health, psychological health, social relationships, and environment. The WHOQOL-BREF is a shortened version of the original instrument that may be more convenient for use in large research studies or clinical trials. It assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns. The WHOQOL instruments were developed collaboratively in a number of centers worldwide, and have been widely field-tested. The WHOQOL-BREF will be self-administered at screening, at the end-of-medication visit (if medication is stopped early), at the end-of-treatment visit (last visit of Week 8), and at the 3-month follow up.

8.3.7 PRISM Suicide and Homicide Screening

The PRISM Suicide and Homicide Screening form is a structured, reliable interview modified from the Psychiatric Research Interview for Substance and Mental Disorders- PRISM (Hasin, et al. 1996). The form will be used as a periodic assessment of suicide and homicide risk

throughout the study. Participants who represent a significant suicidal/homicidal risk must be assessed by a qualified clinician before leaving the clinic. The PRISM Suicide and Homicide Screening Assessment will be collected at screening, at week 5, at the end-of-medication visit (if medication is stopped early), and at the end-of-treatment visit (last visit of Week 8).

8.3.8 Opioid Use Questionnaire

An abbreviated version of the Opioid Use Questionnaire will distinguish the main type of opioid used by the participant, whether a prescription opioid or heroin. Also assessed will be the onset of the use, the participant's perception of the substance that is most problematic, and their present treatment goal. This questionnaire will be self-administered at screening.

8.3.9 DSM-IV-TR Checklist

The DSM-IV-TR Checklist is a semi-structured interviewer administered instrument that provides current diagnoses for substance use disorders based on DSM-IV diagnostic criteria. The DSM-IV Checklist will be completed at screening to determine eligibility.

8.3.10 Risk Assessment Battery (RAB)

The Risk Assessment Battery (RAB) (Navaline et al., 1994) is a self-administered assessment of engagement in activities that increase the likelihood of contracting HIV. Several scores that measure drug risk, sex risk, and total risk will be computed. This measure will be completed at screening, at the end-of-medication visit (if medication is stopped early), and at the end-of-treatment visit (last visit of Week 8).

8.3.11 Self-Help Assessment

The Self-Help Assessment includes items to assess previous self-help participation. This measure was adapted from the Alcoholics Anonymous Involvement Scale (AAIS; Tonigan et al., 1996). This self-administered assessment will be completed at screening, at the end-of-medication visit (if medication is stopped early), at the end-of-treatment visit (last visit of Week 8), and at each follow-up.

8.3.12 Addiction Severity Index Lite (ASI-Lite)

The ASI-Lite is derived from the Fifth Edition of the ASI (McLellan et al., 1992), a structured clinical interview that yields scores for seven areas of functioning typically impacted by addiction, including medical status, employment status, drug use, alcohol use, family status, legal status, and psychiatric status. The ASI-Lite will be completed at screening, at the end-of-medication visit (if medication is stopped early), at the end-of-treatment visit (last visit of Week 8), and at each follow-up.

8.3.13 Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND) is used for assessing nicotine dependence (Fagerström and Schneider, 1989; Heatherton et al., 1991) and will be self-administered at screening, at the end-of-medication visit (if medication is stopped early), and at the end-of-treatment visit (last visit of Week 8).

8.4 Compliance Measures

8.4.1 Dose Logs (DL)

These forms will document amount of medication administered in-clinic, dispensed for take-home dosing, and reported as taken by the participant. Medications to be recorded on these

forms include naloxone, oral naltrexone, XR-NTX, and BUP (or PLB). These forms will be completed at relevant clinic visits through the end of the active treatment phase.

8.4.2 CBT Attendance Log

A CBT attendance log will be completed to document attendance or non-attendance at each weekly CBT session during the active treatment phase.

9.0 TRAINING

The study staff will be trained and certified as specified in the study Training Plan. Training will cover standard NIDA training for all CTN trials (e.g., Good Clinical Practices), as well as protocol-specific training as needed (e.g., assessments, study interventions, fidelity to the protocol and safety procedures, data management and collection, research procedures including understanding reliability and validity, and problem solving). Support mechanisms are identified (e.g., who to contact for aid, questions, resources). All study staff will also be required to complete any local training requirements per their study sites and IRBs. Further details are presented in the study Training Plan.

10.0 STATISTICAL ANALYSES

10.1 General Design

10.1.1 Study Hypothesis

The primary hypothesis is that buprenorphine, administered in the presence of naltrexone, can reduce the number of cocaine use days occurring over the 30-day evaluation period (days 25-54).

10.1.2 Primary Endpoint

The primary endpoint is the number of cocaine use days during the 30-day evaluation period. The evaluation period will be the last 30 days of the active medication period and will end on the day prior to initiation of the taper. Under the protocol schedule this would be days 25 to 54 inclusive. Cocaine use will be measured by self-report, corroborated with thrice-weekly urine drug screens. Scores for individuals who initiate the evaluation period will be included, and those who discontinue participation will have their score at the time of withdrawal scaled to the 30-day evaluation period.

10.2 Rationale for Sample Size and Statistical Power

The study has been designed to include 300 individuals randomly assigned at a 1:1:1 ratio to the 3 treatment arms. The sample size was developed from a simulation study of the anticipated trial characteristics considering the number of abuse days, withdrawal probabilities, probability of underreporting abuse and effect size. Prior studies of a similar population (NIDA CTN-0007 Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics) indicates that in a thirty day period, participants had about 9 cocaine abuse days, with a standard deviation nearly the size of the mean (mean=9.5, sd=8.5). The endpoint of this study is the number of cocaine use days during the 30 day evaluation period. Absent a treatment effect, it is assumed that each individual's daily use follows a Bernoulli distribution, but that individual's use risk varies, with sufficient population variability to match the anticipated extra-binomial variability noted from the prior study. Specifically a beta-binomial distribution is assumed for daily use with parameters ($b_1 = .45$, $b_2 = 1$). Since the mean of the beta binomial is b_1/b_1+b_2 , then the expected number of use days in a 30 day period is 9.31 and the standard deviation is 9.08.

While verification of some daily reports will be substantiated with urine testing, underreporting of use may occur. We anticipate that this underreporting may vary among individuals. In the simulation underreporting of use is modeled under assumptions of complete accuracy (0% underreporting), 20% underreporting and 40% underreporting of use days. Conditional on use, the probability of underreporting is modeled with a beta-binomial distribution with parameters of (.2, .8) for the 20% level and (.4, .6) for the 40% level.

Losses to follow-up are assumed to occur in 5% of the participants prior to initiation of the evaluation period. In addition, a daily loss probability is presumed that is scaled by the individuals mean use probability from the initial beta-binomial distribution. Thus, individuals with higher use rates are more likely to discontinue. In the simulation, the unscaled daily probability is set at .008 and this results in an 18% dropout rate during the evaluation period.

The test statistic used in the simulation is a nonparametric test (Wilcoxon) comparing use-free days in the 2 active treatment arms using an experimentwise 5% Type 1 error from performing 2 pairwise tests of the buprenorphine arms versus control each at the 2.5% one-tailed level. In individuals who withdraw during the evaluation period, the score is the percentage of use-free days during the completed period scaled up for the entire 30-day observation period. Note that

the simulation utilized the number of use-free days as the endpoint, however, this analysis is comparable to one in which the endpoint is defined as number of use days.

Note that an alternative statistic, the t-test, was examined in the simulation but power was consistently less (and on the order of 20 percentage points less) for several key situations. Simulated power was also less when analyzing the main effect from a repeated measurement linear model.

Under these assumptions, the following results were obtained with the randomized sample size of 300 (i.e. 100/arm) and 1,000 replications of each condition.

Simulated study pairwise power with N=100 randomized individuals per arm

Increased # of Non-Use Days With Treatment	Use 0%	Underreporting 20%	Percentage 40%
2.27	.635	.570	.515
3.16	.886	.873	.777
3.94	.974	.968	.915

Under these assumptions, an improvement of 3.16 days in the 30 day evaluation period can be reliably detected with >85% power if the underreporting percentage is bounded by 20%. When delta approaches 4, in excess of 90% power is available. Note that the standard errors for the first column results are .015, .010 and .005.

The above excludes the 5% of the randomized individuals who fail to enter the evaluation period. If one were to impute the maximally pessimistic situation (all treated use daily, all control use never) for these cases then simulated power is 77% for the difference of 3.94 days, no underreporting.

10.2.1 Projected Number of Sites

It is anticipated that 10-12 sites will participate in the trial.

10.2.2 Projected Number of Participants per Site

It is anticipated that at least 10 sites will target accrual of 30 randomized cases per site, at least 1.5 per month over a 20-month recruitment period.

10.3 Statistical Methods for Primary and Secondary Outcomes

The primary endpoint will be analyzed with the 2 sample Wilcoxon statistic.

The rich data set will permit a series of additional analyses addressing secondary objectives 1-10. Safety analyses are outlined in Section 10.9. The Treatment Effectiveness Score (TES) (Ling et al. 1997) is the percentage of the scheduled urine drug screens that were both provided and negative. TES will be evaluated during the evaluation period for both cocaine and opioid use. Simple contrasts of the treatment arms will be performed with the Wilcoxon statistic. Additional analyses will examine the primary endpoint adjusting for strata and other covariate effects including gender, age and race. Repeated-measurement analysis models will be used to explore presence of time-related treatment effects, including severity of cravings and level of mood disturbance. Additional analyses will include assessment of treatment effect in the pre-evaluation period (Days 1-24), over the course of the entire treatment period and during the follow-up period. Changes occurring over the treatment period in severity and type of drug-related problems and in quality of life will be summarized and compared between treatment groups using the two sample Wilcoxon test for continuous outcomes or the chi-square test or Fisher’s Exact Test for categorical outcomes.

10.4 Significance Testing

A 5% level test will be used for the analysis of the primary endpoint comprised of 2 pairwise 2.5% level one sided tests of the two buprenorphine arms versus the no-buprenorphine arm.

10.5 Interim Analyses

Given the relatively small sample size, short duration of the study and needs for precise estimation of multiple outcome measures, early termination for efficacy is not planned. Any claim of treatment difference between the active and control treatments will be made after testing at the end of the trial at which time all Type 1 error will be spent.

It may be that accumulating information shows little treatment effect. After endpoint information for half of the planned study sample is available, each buprenorphine treatment arm will be evaluated versus the no-buprenorphine arm. In the absence of observed benefit for the treatment, the treatment arm will be terminated (i.e. the treatment versus placebo contrast must favor the treatment). This stopping rule corresponds to about 20% conditional power under plausible (i.e. 95% confidence limit of current effect estimate) projections of the study result at the time of the analysis. Such termination does not affect type 1 error.

This assessment will be made by the DSMB who will be provided information necessary to make the decision by the unblinded statistician at the NIDA Data and Statistical Center. Only a single interim inspection for futility is planned a priori, and any subsequent inspections would be at the direction of the DSMB.

10.6 Exploratory Analyses

The primary endpoint will be analyzed with the 2 sample Wilcoxon statistic. If the opioid history strata is identified as a significant predictor of cocaine use days with a mean difference >3.0 days, then the primary endpoint will be analyzed with a stratified Wilcoxon test.

The effect in the “high” versus “low” opioid involvement strata is of interest; strata-specific assessment of the primary outcome will be evaluated.

10.7 Missing Data and Dropouts

The primary analysis will be performed in the group of individuals who initiate the evaluation period. Minimal loss is anticipated between randomization and this time point given the short time period. Intent-to-treat analysis with all cases will be performed assuming both the maximally pessimistic situation (all treated use daily, all control use never) and baseline use levels for these early withdrawals. The primary endpoint score imputes dropouts during the evaluation period to have use rates equal to that observed through the period prior to dropout. The TES will be used as a secondary analysis to assist with evaluating this effect. Note that in the design simulations, the TES 12-day analysis was observed to be less powerful than the analysis of the selected primary endpoint. But design assumptions did not assume interactions with treatment for either underreporting or withdrawal events.

10.8 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for each arm of the study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages. Since randomization is expected to produce balance at baseline between the three arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics should be

more informal. In case differences between treatments arms are suspected, statistical testing will be performed. For comparisons of treatment groups with respect to continuous baseline variables we will use the two sample Wilcoxon test. Group comparisons with respect to discrete baseline variables will use the chi-square test or Fisher's Exact Test as appropriate.

10.9 Safety Analysis

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, body system, and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available. Treatment arm differences will be monitored by the DSMB.

11.0 REGULATORY COMPLIANCE AND SAFETY MONITORING

11.1 Regulatory Compliance

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

11.2 Institutional Review Board Approval

Prior to initiating the study, site investigators will obtain written local IRB approval to conduct the study at their respective site. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials (e.g., CBT Manual) given to the participant. Annual reports and progress reports will be submitted to the IRBs annually or at a frequency requested by each IRB. The lead investigator is responsible for maintaining in his research files copies of all performance site(s) current IRB/IEC approval notice(s), IRB-approved consent document(s), including approval for all protocol modifications. These materials must be received by the lead investigator prior to the initiation of research activities at a given site, and must be available at any time for audit.

11.3 Research Advisory Panel of California (California sites only)

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

11.4 Informed Consent

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

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a study participant's

participation in the trial. Each study site must have the study informed consent approved by their local IRB(s). The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their local IRB and institutional policies and that is accessible for quality assurance review and regulatory compliance. Every study participant should be given a copy of the signed consent form to keep for reference. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

11.5 Drug Accountability

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

11.6 Quality Assurance and Safety Monitoring

Research oversight bodies at all levels require assurance that the protection of the rights and welfare of study participants be a vigilant process conducted by the research team and by the sponsors of the research. Therefore, in addition to the data and safety monitoring procedures described in the preceding paragraphs, additional safety monitoring through the Data and Safety Monitoring Board will be conducted regularly throughout the duration of the study.

11.7 Data and Safety Monitoring Board (DSMB)

This study will utilize the CTN DSMB to oversee ongoing trial progress. The purpose of this board is to determine whether risks emerge during the conduct of the trial that make continuation unethical (e.g., clear and significant superiority of one condition over another). This process is intended to assure the IRBs, the sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in CTN research trials. Safety monitoring begins with the initial review of the protocol during the study development process. If serious or unexpected adverse events occur during the trial, the site medical clinician reports these occurrences within the specified time frames to the IRBs, NIDA, RAP-C (in California sites), and the FDA as required. The DSMB will meet twice annually.

11.8 Medical Monitor

A NIDA-assigned Medical Safety Monitor will be responsible for overseeing safety and for evaluating all Adverse Events (AEs). He/She will review all Serious Adverse Events (SAEs) within five days of their occurrence and all other Adverse Events on a regular basis. It is the responsibility of the site principal investigator to provide this information to the medical safety monitor. It is also the site principal investigators' responsibility to inform the IRBs per local IRB guidelines.

11.9 Quality Assurance Monitor

The monitoring of the study site will be conducted on a regular basis using a combination of NIDA-contracted monitors and local quality assurance monitors. Investigators will host periodic visits by NIDA contract monitors and local QA monitors. The purpose of these visits is to encourage and assess compliance with GCP requirements and to document the integrity of the trial progress.

NIDA contract monitors will assure that submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents,

participant records, study drug accountability, and principal investigator supervision and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA.

Qualified Node personnel (Node QA monitors) will provide site management for each site during the trial. This will take place as specified by the local protocol team, Node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will ensure site staff is trained and able to conduct the protocol appropriately and that study procedures are properly followed. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training. Details of the contract monitoring, node QA, and data monitoring are found in the study QA monitoring plan.

11.10 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

11.11 Confidentiality

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The Department of Health and Human Services (HHS) office that issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary.

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

11.12 Health Insurance Portability Accountability Act (HIPAA)

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

11.13 Investigator Assurances

Each community treatment program site (CTP) must file (or have previously filed) a Federal Wide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the

protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator and sub-investigators at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

11.14 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. It is the responsibility of the investigator to maintain appropriate disclosure to their individual institution according to their requirements.

11.15 DEA Registration

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

11.16 Inclusion of Women and Minorities

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

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

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

11.18 IND Requirements

An IND application that was submitted for this study was reviewed, put into effect and given an IND number of 110,824 by the FDA. Going forward, any amendments to this clinical trial submitted to the FDA for review, will reflect awareness of and compliance with U.S Code of Federal Regulations 45 CFR 46 and it's subparts as well as the International Conference on Harmonization, Good Clinical Practice (ICH E6). This IND study will also be conducted in accordance with all applicable FDA regulations and will comply with all applicable laws and regulations at clinical research sites.

11.19 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for

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

11.20 Records Retention and Requirements

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

11.21 Audits

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

11.22 Reporting to Sponsor

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

11.23 Study Documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved current and previous consent forms and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. The original recording of an observation should be retained as the source document.

11.24 Protocol Deviations, Violations, and Reporting and Management

Any departure from procedures and requirements outlined in the protocol will be classified as either a protocol deviation or protocol violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be

monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The decision about whether a departure from the protocol will be designated as a protocol deviation or a protocol violation will be made by the protocol's Lead Investigator(s) in conjunction with the CCC. The consequences will be specified and participating sites will be informed.

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

11.25 Safety Monitoring

11.25.1 Adverse Events (AEs)

The Lead Investigator (LI) may appoint a Study Clinician (MD, PA, or NP) for this study, who will review or provide consultation for each serious event as needed. These reviews will include an assessment of the severity and causality to the study drug or study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide site principal investigators a Safety Letter when necessary. The medical monitor will determine which safety events require expedited reporting to NIDA, the DSMB, Alkermes, Reckitt Benckiser Pharmaceuticals Inc and regulatory authorities. This will include all suspected adverse reactions that are serious and unexpected. The study staff will be trained to monitor for and report adverse events and serious events.

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

11.25.2 Definitions of Adverse Events and Serious Adverse Events

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

11.25.3 Reportable Adverse Events and Serious Adverse Events

Adverse Events

For the purpose of this study, the following AE will not require reporting in the data system but will be captured in the source documentation as medically indicated:

- Grade 1 (mild) adverse events

This would typically include mild physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Serious Adverse Events

For the purpose of this study, admission to a hospital or freestanding residential facility for drug detoxification for the purpose of meeting eligibility criteria prior to randomization will not be

recorded as an SAE in the data system but will be documented in the source documentation as medically indicated. Such admissions would be reported to local IRBs per local IRB guidelines.

11.25.4 Known Potential Toxicities of Study Drug/Intervention

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

Common side effects from BUP 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 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, he/she may experience opioid 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 opioids while receiving the BUP tablet could also result in opioid withdrawal symptoms.

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

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

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

XR-NTX will precipitate or exacerbate opioid withdrawal in people dependent on opioids unless they have been opioid-free for 7-10 days. Any attempt to overcome the blockade produced by

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

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

The commercial formulations of BUP (Suboxone®) and of XR-NTX (Vivitrol®) have been classified Pregnancy Category C. Female participants of childbearing potential will be required to practice acceptable birth control. Female participants will also be required to have a negative pregnancy test prior to the naloxone challenge and prior to administration XR-NTX and monthly thereafter while receiving medications.

12.0 DATA MANAGEMENT AND PROCEDURES

12.1 Design and Development

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

12.2 Operations Manual

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

12.3 Site Responsibilities

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

12.4 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities which include, but are not limited to, method for ensuring subject confidentiality in the database, 2) provide final paper CRFs and eCRFs with instructions for the collection of all data required by the study, 3) provide data dictionaries for each paper CRF and eCRF that will comprehensively define each data element, 4) conduct ongoing data validation and cleaning activities on study data from all participating CTPs through database lock.

12.5 Data Collection

Data will be collected at the study sites either on source documents, which will be entered at the site into eCRFs or through direct electronic data capture. The eCRFs will be supplied by the DSC. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. Paper CRFs and eCRFs should be completed according to the CRF instruction manual and relevant instructions in the study operations manual.

12.6 Data Acquisition and Entry

Completed forms and electronic data will be entered into the data management system in accordance with the CRF Completion Guidelines established by the DSC. Only authorized individuals shall have access to electronic CRFs.

12.7 Data Editing and Control

Data will be entered into the DSC automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated and distributed to treatment programs for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the DSC automated data acquisition and management system. Data status reports will be issued on a regular basis to assist the site, the

corresponding RRTC (node) and the lead investigator to monitor the site's progress in responding to queries.

Participating investigators agree to routine data audits conducted by DSC staff. Monitors will routinely visit each site to assure that data entered on the appropriate eCRFs are in agreement with source documents. They will also verify that investigational products have been properly stored and accounted for, participant informed consent for study participation has been obtained and documented, all essential documents required by GCP regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the established procedures specified in the study operations manual.

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's statisticians in accordance with the analytical plan section of this protocol.

12.8 Study Documentation and Records Retention

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

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, participant diaries, biopsy reports, ultrasound photographs, participant progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. In an IND study, these documents must be kept for a minimum of two years after discontinuation of the IND, 3 years after the approval of the NDA, or as directed by the study sponsor.

12.9 Data Transfer/Lock

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA and the lead investigator, as requested, for storage and archive.

12.10 Data Training

The training includes provisions for training on assessments, CRF completion guidelines, and computerized systems.

12.11 Data QA

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

12.12 Confidentiality

12.12.1 Confidentiality of Data

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

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

12.12.2 Confidentiality of Participant Records

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

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

13.0 PUBLICATIONS AND OTHER RIGHTS

Per NIH policy, the results of the proposed trial are to be made available to the research community and to the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

14.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____
CCTN Designee		

INVESTIGATOR(S)

- I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only deviate from 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 in 21 CFR Part 50 and institutional review board (IRB) review and approval in 45 CFR 46 and 21 CFR Part 56 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 and 21 CFR 312.64.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 45 CFR 46 and 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 45 CFR 46 and 21 CFR Part 56 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 sponsor, lead investigator, and 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.
- I agree to comply with all the applicable federal, state, local, and institutional regulations regarding the obligations of clinical investigators and other pertinent requirements in 21 CFR 312.

Site Name	_____	
Typed Name	Signature	Date
_____	_____	_____
Principal Investigator		
_____	_____	_____
Principal Investigator (if applicable)		
_____	_____	_____
Sub-Investigator		
_____	_____	_____
Sub-Investigator		

15.0 REFERENCES

- Ahmadi J, Maany I & Ahmadi M. (2003) Treatment of Intravenous buprenorphine Dependence A Randomized Open Clinical Trial, *German Journal of Psychiatry*, 6: 23-29
- Alho H, Sinclair D, Vuori E and Holopainen A. (2007) Abuse liability of buprenorphine–naloxone tablets in untreated IV drug users, *Drug and Alcohol Dependence*, 88 (1): 75-78
- Amass, L., Bickel, W. K., Higgins, S. T., & Badger, G. J. (1994). Alternate-day dosing during buprenorphine treatment of opioid dependence. *Life Science*, 54, 1215-1228.
- Amass, L., Kamien, J. B., & Mikulich, S. K. (2000). Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. *Drug and Alcohol Dependence*, 58, 143-52.
- Amass L, Ling W. Ready, set, go: bringing buprenorphine to the U.S.treatment market. In: Harris LS, ed. Problems of Drug Dependence NIDA Research Monograph Series, No. 182. NIH Publication No. 02–5097. Washington D.C.: U.S. Government Printing Office; 2002:27–37.
- Armstrong, S. C. & Cozza, K. L. (2003). Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, part I. *Psychosomatics*, 44, 167-171.
- Annis, H. M. & Davis, C. S. (1989). Relapse prevention. In R. K. Hester & W. R. Miller (Eds.), *Handbook of alcoholism treatment approaches: Alternative approaches* (pp. 170-182). New York: Pergamon Press.
- Azrin, N., Acierno, R., Kogan, E., Donohue, B., Besalel, V., McMahon, P. (1996) Follow-up results of Supportive versus Behavioral Therapy for illicit drug use *Behav. Res. Ther.* Vol. 34, No. 1. pp. 41-46
- Beck, A. T. & Steer, R. A. (1993). *Beck Depression Inventory Manual*. New York: Harcourt Brace & Company.
- Berson, A., Gervais, A., Cazals, D., Boyer, N., Durant, F., Bernuau, J., Marcellin, P., Degott, C., Valla, C., & Pessayre, D. (2001). Hepatitis after intravenous buprenorphine misuse in heroin addicts. *Journal of Hepatology*, 34, 346-350. (2001)
- Bickel, W. K., Stitzer, M. L., Bigelow, G. E., Liebson, I. A., Jasinski, D. R., & Johnson, R. E., (1988a). A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. *Clinical Pharmacology and Experimental Therapeutics*, 43, 72-78.
- Bickel, W. K., Stitzer, M. L., Bigelow, G. E., Liebson, I. A., Jasinski, D. R., & Johnson, R. E. (1988b). Buprenorphine: Dose-related blockade of opioid challenge effects in opioid dependent humans. *Journal of Pharmacology and Experimental Therapeutics*, 247, 47-53.
- Bridge, T. P., Fudala, P. J., Herbert, S., & Leiderman, D. B. (2003). Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence. *Drug and Alcohol Dependence*, 70, S79-S85
- Carrieri, M. P., Vlahov, D., Dellamonica, P. et al. (2000). Use of buprenorphine in HIV-infected injection drug users: Negligible impact on virologic response to HAART. The Manif-2000 Study Group. *Drug and Alcohol Dependence*, 60, 51-54.
- Carroll, K. M., Nich, C., Ball, S. A., McCance-Katz, E., & Rounsaville, B. J. (1998). Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction*, 93, 713-728.

- Carroll, K. M., Nich, C., Ball, S. A., McCance-Katz, E. F., Frankforter, T. F., & Rounsaville, B. J. (2000). One year follow-up of disulfiram and psychotherapy for cocaine-alcohol abusers: Sustained effects of treatment. *Addiction, 95*, 1335-1349.
- Carroll, K. M., Rounsaville, B. J., & Gawin, F. H. (1991). A comparative trial of psychotherapies for ambulatory cocaine abusers: Relapse prevention and interpersonal psychotherapy. *American Journal of Drug and Alcohol Abuse, 17*, 229-247.
- Carroll, K. M., Rounsaville, B. J., Gordon, L. T., Nich, C., Jatlow, P. M., Bisighini, R. M., et al. (1994a). Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Archives of General Psychiatry, 51*, 177-197.
- Carroll, K. M., Rounsaville, B. J., Nich, C., Gordon, L. T., Wirtz, P. W., & Gawin, F. H. (1994b). One year follow-up of psychotherapy and pharmacotherapy for cocaine dependence: Delayed emergence of psychotherapy effects. *Archives of General Psychiatry, 51*, 989-997.
- Chiang, C. N., Bridge, P., Creedon, K., Hawks, R. L., Herbert, S., Hill, J., Maghrablian, L., Terrill, J., Walsh, R. (1996a). Buprenorphine-naloxone combination product for treating opioid addiction (abstract). Proceedings of the Fifty-eighth Annual Scientific Meeting of the College on Problems of Drug Dependence. San Juan, Puerto Rico, June.
- Chiang, C. N., Bridge, P., Hawks, R. L., Herbert, S., Hill, J., Maghrablian, L., Terrill, J., & Walsh, R. (1996b). The development of buprenorphine-naloxone products for treating opiate dependence. In L. S. Harris (Ed.), *Problems of Drug Dependence 1995* (p.117). NIDA Research Monograph No.162. U.S. Government Printing Office, Washington, DC.
- Chiang, C.N. & Hawks, R. (1994). Development of a buprenorphine-naloxone combination drug for the treatment of drug addiction. In L.S. Harris (Ed.), *Problems of Drug Dependence 1993* (p.458). NIDA Research Monograph No. 141. U.S. Government Printing Office, Washington, DC.
- Church, S. H., Rothenberg, J. L., Sullivan, M. A., Bornstein, G., & Nunes, E. V. (2001). Concurrent substance use and outcome in combined behavioral and naltrexone therapy for opiate dependence. *American Journal of Drug & Alcohol Abuse, 27*, 441-452.
- Comer SD, Collins ED, Fischman MW. (2002) Intravenous buprenorphine self-administration by detoxified heroin abusers, *Journal of Pharmacology and Experimental Therapeutics* 301:266–276, 2002.
- de Jong W, Tsegarelli T and Schouten E. (1999) Rapid Assessment of Injection Drug Use and HIV in the Republic of Georgia. *Journal of Drug Issues* 29, 843-860.
- Fagerström and Schneider, 1989. K.-O. Fagerström and N.G. Schneider , Measuring nicotine dependence: A review of the Fagerström Tolerance Questionnaire. *Journal of Behavioral Medicine* 12 (1989), pp. 159–182.
- Fals-Stewart, W., O'Farrell, T., Freitas, T., McFarlin, S., Rutigliano, P. (2000) The Timeline Followback Reports of Psychoactive Substance Use by Drug-Abusing Patients: Psychometric Properties. *Journal of Consulting and Clinical Psychology* 68, 134-144.
- Faroqui, M. H., Cole, M., & Curran, J. (1983). Buprenorphine, benzodiazepines and respiratory depression. *Anaesthesia, 38*, 1002-1003.
- Fiellin, D. A., Rosenheck, R. A. & Kosten, T. R. (2001). Office-based treatment for opioid dependence: Reaching new patient populations. *American Journal of Psychiatry, 158*, 1200-1204.
- Fudala, P. J., Bridge, T. P., Herbert, S., Chiang, C. N., Leiderman, D. B., and the Buprenorphine/Naloxone Collaborative Study Group. (1998). A multisite efficacy

- evaluation of a buprenorphine/naloxone product for opioid dependence treatment. NIDA Research Monograph 179. Rockville: DHHS/NIH/NIDA: 105
- Fudala, P. J., Jaffe, J. H., Dax, E. M., & Johnson, R. E. (1990). Use of buprenorphine in the treatment of opioid addiction II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clinical Pharmacology Therapeutics*, 47, 525-534.
- Gerra G, Fantoma A, and Zaimovic A. (2006) "Naltrexone and buprenorphine combination in the treatment of opioid dependence." *Journal of Psychopharmacology*; 20(6): 806-14.
- Hasin D, Trautman K, Miele G, Samet S, Smith M, Endicott J. (1996) Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry*, 153, 1195-201.
- Heatherton T, Kozlowski L, Freckler R, Fagerstrom K. (1991) The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *Brit. J. Addiction*, 86, 1119-1127.
- Huestis, M. A., Umbricht, A., Preston, K. L., & Cone, E. J. (1999). Safety of buprenorphine: No clinically relevant cardio-respiratory depression at high IV doses. Harris, L. S. [179], 62. Rockville, MD, National Institute on Drug Abuse. Problems in Drug Dependence, NIDA Research Monograph Series/Iribarne.
- Iribarne, C., Picart, D., Dreano, Y., Bail, J. P., & Berthou, F. (1997). Involvement of cytochrome P-450 3A4 in N-dealkylation of buprenorphine in human liver microsomes. *Life Science*, 60, 1953-1964.
- Iribarne, C., Berthou, F., Carlhart, D., Dreano, Y., Picart, D., Lohezic, F., & Riche, C. (1998). Inhibition of methadone and buprenorphine N-dealkylatins by three HIV-1 protease inhibitors. *Drug Metabolism and Disposition*, 26, 257-260.
- Jenkinson RA, Clark NC, Fry CL, Dobbin M. (2005) Buprenorphine Diversion and Injection in Melbourne, Australia: An Emerging Issue? *Addiction*. 2005 Feb;100 (2):197-205.
- Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *Journal of the American Medical Association*, 267, 2750-2755.
- Johnson, R. E., Chutuape, M. A., Strain, E. C., Walsh, S. L., Stitzer, M. L., & Bigelow, G. E. (2000). A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *New England Journal of Medicine*, 343, 1290-7.
- Jones, R. (2009). Personal Communication:
- Lange, W. R., Fudala, P. J., Dax, E. M., & Johnson, R. E. (1990). Safety and side-effects of buprenorphine in the clinical management of heroin addiction. *Drug and Alcohol Dependence*, 26, 19-28.
- Ling, W. (2009). *The Treatment Effects Assessment*. Unpublished ; UCLA Integrated Substance Abuse Programs.
- Ling, W., Amass, L., Shoptaw, S., Annon, J., Hillhouse, M., Babcock, D., Brigham, G., Harrer, J., Reid, M., Muir, J., Buchan, B., Orr, D., Woody, G., Krejcija, J. and the Buprenorphine Study Protocol Group. (2005). A multi center randomized trial of burprenorphine-naloxone and clonidine for opioid detoxification: Findings from the National Institute on Drug Abuse Clinical Trials Network. In press, *Addiction*.
- Ling, W., Charuvastra, V. C., Collins, J. F., Batki, S., Brown, L. S., Jr., Kintaudi, P., Wesson, D.R., McNicholas, L., Tusel, D. J., Malkerneker, U., Renner, J. A., Jr., Santos, E., Casadonte, P., Fye, C., Stine, S., Want, R. I. H., & Segal, D. (1998). Buprenorphine maintenance treatment of opioid dependence: A multicenter randomized clinical trial. *Addiction*, 93, 475-486.

- Ling, W., Hillhouse, M., Domier, C., Doraimani, G., Hunter, J., Thomas, C., et al. (2009). Buprenorphine tapering schedule and illicit opioid use. *Addiction*, 104, 256–265.
- Ling, W., Shoptaw, S., Wesson, D., Rawson, R. A., Compton, M., & Klett, C. J. (1997). Treatment effectiveness score as an outcome measure in clinical trials. *NIDA Research Monographs*, 175, 208-220.
- Ling, W. & Wesson, D. R. (2003). Clinical efficacy of buprenorphine: Comparisons to methadone and placebo. *Drug and Alcohol Dependence*, 70(2 Suppl), S49-57.
- Ling, W., Wesson, D. R., Charuvastra, C., & Klett, C.J. (1996). A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Archives of General Psychiatry*, 53, 401-407.
- Lobmaier P, Kornor H, Kunoe N, Bjørndal A. Sustained-Release Naltrexone For Opioid Dependence. *Cochrane Database of Systematic Reviews 2008*, Issue 2. Art. No.: CD006140. DOI: 10.1002/14651858.CD006140.pub2
- Lucey MR, Silverman BL, Illeperuma A, O'Brien CP. (2008) Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. *Alcoholism: Clinical and Experimental Research* Res 32, 498-504.
- Moatti, J. P., Carrieri, M. P., Spire, B., Gastaut, J. A., Cassuto, J. P., & Moreau, J. (2000). Adherence to HAART in French HIV-infected injecting drug users: The contribution of buprenorphine drug maintenance treatment. The Manif-2000 study group. *AIDS*, 14, 151-155
- McCann, D. J. (2008). "Potential of buprenorphine/naltrexone in treating polydrug addiction and co-occurring psychiatric disorders." *Clinical Pharmacology & Therapeutics* 83(4): 627-30.
- McAuliffe, W. E. (1990). A randomized control trial of recovery training for opioid addicts in New England and Hong Kong. *Journal of Psychoactive Drugs*, 22, 197-209.
- McKay, J. R., Alterman, A. I., Cacciola, J. S., Rutherford, M. J., O'Brien, C. P., & Koppenhaver, J. (1997). Group counseling versus individualized relapse prevention aftercare following intensive outpatient treatment for cocaine dependence: Initial results. *Journal of Consulting and Clinical Psychology*, 65, 778-788.
- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, & Argeriou M. (1992). The fifth edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment* 9 (199-213).
- Montoya, Ivan, MD, MPH, David A. Gorelick, MD, PhD, Kenzie L. Preston, PhD, Jennifer R. Schroeder, PhD, Annie Umbricht, MD, Lawrence J. Cheskin, MD, W. Robert Lange, MD, MPH, Carlo Contoreggi, MD, Rolley E. Johnson, PharmD, and Paul J. Fudala, PhD. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence *Clin Pharmacol Ther.* 2004 January ; 75(1): 34–48.
doi:10.1016/j.cpt.2003.09.004
- Montoya, Ivan, MD, MPH, and Frank Vocci, PhD Novel Medications to Treat Addictive Disorders. *Curr Psychiatry Rep.* 2008 October ; 10(5): 392–398
- Navaline HA, Snider EC, Petro C, Tobin D, Metzger, D, Alterman A, & Woody GE. (1994) An Automated Version of the Risk Assessment Battery (RAB): Enhancing the Assessment of Risk Behaviors. *AIDS Research & Human Retroviruses* 10(2).
- O'Brien, Charles P. (2001). Drug Addiction and Drug Abuse. In Goodman & Gillman's *The Pharmacological Basis of Therapeutics Tenth Edition* edited by Joel G. Hardman, Ph.D. and Lee E. Limbird, Ph.D. New York: McGraw-Hill.
- O'Brien CP. (2008) Prospects for a genomic approach to the treatment of alcoholism. *Archives of General Psychiatry* 65, 132-3.

- Peck, J.A., Shoptaw, S., Rotheram-Fuller, E., Reback, C.J., & Bierman, B. (2005). HIV-associated medical, behavioral, and psychiatric characteristics of treatment-seeking, methamphetamine-dependent men who have sex with men. *Journal of Addictive Diseases, 24*(3), 115-132.
- PDR (2009). *Physicians Desk Reference*, Medical Economics Company:Montdale, NJ
- Pollack, M. H., Penava, S. A., Bolton, E., Worthington III, J. J., Allen, G. L., Farach, F. J., & Otto, M. W. (2002). A novel cognitive-behavioral approach for treatment-resistant drug dependence. *Journal of Substance Abuse Treatment, 23*, 335-342
- Rawson, R. A., Huber, A., McCann, M. J., Shoptaw, S., Farabee, D., Reiber, C., et al. (2002). A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance for cocaine dependence. *Archives of General Psychiatry, 59*, 817-824.
- Rawson, R. A., McCann, M., Huber, A., & Shoptaw, S. (1999). Contingency management and relapse prevention as stimulant abuse treatment interventions. In S. T. Higgins & K. Silverman, (Eds.), *Motivating Behavior Change Among Illicit Drug Abusers* (pp. 57-74). Washington D.C.: American Psychological Association.
- Rawson, R. A., Obert, J. L., McCann, M. J., Smith, D. P., & Scheffey, E. H. (1989). *The Neurobehavioral Treatment Manual*. Beverly Hills, CA, Matrix Institute.
- Rawson, R., Shoptaw, S., Obert, J., McCann, M., Hasson, A., Marinelli-Casey, P., Brethen, P., & Ling, W. (1995). An intensive outpatient approach for cocaine abuse treatment: The Matrix model. *Journal of Substance Abuse Treatment, 12*, 117-127.
- Reynaud, M., Petit, G., Potard, D., & Courty, P. (1998). Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction, 93*, 1385-1392.
- Roffman, R. A., Stephens, R. S., & Simpson, E. E. (1990). *Relapse prevention and the treatment of marijuana dependence: Long-term outcomes*. Paper presented at the annual meeting of the Association for Advancement of Behavior Therapy, San Francisco. November
- Rothenberg, J. L., Sullivan, M. A., Church, S. H., Seracini, A., Collins, E., Kleber, H. D. & Nunes, E. V. (2002) Behavioral naltrexone therapy: an integrated treatment for opiate dependence. *Journal of Substance Abuse Treatment, 23*, 351–360.
- Rothman RB, Gorelick DA, Heishman SJ, Eichmiller PR, Hill BH, Norbeck J and Liberto JG. (2000). "An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence." *Journal of Substance Abuse Treatment 18*(3): 277-81.
- Schottenfeld, Richard S.1; Chawarski, Marek C.; Pakes, Juliana R.; Pantaloni, Michael V.; Carroll, Kathleen M.; Kosten, Thomas R. Methadone Versus Buprenorphine With Contingency Management or Performance Feedback for Cocaine and Opioid Dependence. *The American Journal of Psychiatry. Vol 162*(2), Feb 2005, pp. 340-349
- Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine versus methadone maintenance for concurrent opiate dependence and cocaine abuse. *Arch Gen Psychiatry 1997*;54:713–720. [PubMed: 9283506]
- SAMHSA, (Substance Abuse and Mental Health Services Administration). 2009a <http://www.oas.samhsa.gov/2k9/outputTX/outputTX.htm>.
- Substance Abuse and Mental Health Services Administration. (2010). Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586Findings). Rockville, MD.

- Shoptaw, S., Rawson, R., McCann, M., Obert, J. (1994) The Matrix model of outpatient stimulant abuse treatment: Evidence of efficacy. *Journal of Addictive Diseases* 13, 25–34.
- Shoptaw, S., Rotheram-Fuller, E., Yang, X., Frosch, D., Nahom, D., Jarvik, M. E., Rawson, R. A., & Ling, W. (2002). Smoking cessation in methadone maintenance. *Addiction*, 97, 1317-1328.
- Shoptaw, S., Reback, C. J., Peck, J. A., Yang, X., Rotheram-Fuller, E., Larkins, S., Veniegas, R. C., Freese, T. E., & Hucks-Ortiz, C. (2005). Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug and Alcohol Dependence*, 78, 125-134.
- Sobell LC, Sobell MB. (1992) Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In: Measuring Alcohol Consumption, Eds. R.Litten, J.Allen. *The Human Press Inc.*
- Singh RA, Mattoo SK, Malhotra A, Varma VK. (1992) Cases of buprenorphine abuse in India. *Acta Psychiatrica Scandinavica* 1992 Jul;86(1):46-8.
- Stein, M. D., Herman, D. S., Solomon, D. A., Anthony, J. L., Anderson, B. J., Ramsey, S. E., & Miller, I. W. (2004). Adherence to treatment of depression in active injection drug users: The Minerva Study. *Journal of Substance Abuse Treatment*, 26, 87-93.
- Strain, E. C., Stitzer, M. L., Biebson, I. A., & Bigelow, G. E. (1994). Comparison of buprenorphine and methadone in the treatment of opioid dependence. *American Journal of Psychiatry*, 151, 1025-1030.
- Strain, E. C., Stitze, M. L., Liebson, I. A., & Bigelow, G. E. (1996). Buprenorphine versus methadone in the treatment of opioid dependence: Self-reports, urinalysis, and Addiction Severity Index. *Journal of Clinical Psychopharmacology*, 16, 58-67.
- Sullivan, L. E., Metzger, D. S., Fudala, P. J., & Fiellin, D. A. (2005). Decreasing international HIV transmission: The role of expanding access to opioid agonist therapies for injection drug users. *Addiction*, 100, 150-158.
- Tabachnik B, & Fidell LS. Using multivariate statistics (4th Edn.), 2000, Boston: Allyn and Bacon.
- Tonigan, J. S., Connors, G. J., & Miller, W. R. (1996). The Alcoholics Anonymous Involvement (AAI) scale: Reliability and norms. *Psychology of Addictive Behaviors*, 10, 75-80.
- Uehlinger, C., Deglon, J., Livoti, S., Petitjean, S., Waldvogel, D., & Ladewig, D. (1998). Comparison of buprenorphine and methadone in the treatment of opioid dependence. Swiss multicentre study. *European Addiction Research*, 4 Suppl 1, 13-18.
- Verrando R, Robaey G, Matheï C and Buntinx F (2005) Methadone and buprenorphine maintenance therapies for patients with hepatitis C virus infected after intravenous drug use. *Acta Gastroenterol Belg*.;68(1):81-
- Volpicelli, J. R., Rhines, K. C., Rhines, J. S., Volpicelli, L. A., Alterman, A. I. & O'Brien, C. P. (1997) Naltrexone and alcohol dependence. Role of subject compliance. *Archives of General Psychiatry*, 54, 737–742.
- Walsh, S. L., Preston, K. L., Stitzer, M. L., Cone, E. J., & Bigelow, G. E. (1994). Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clinical Pharmacology Therapeutics*, 55, 569-580.
- Walsh, S. L., Preston, K. L., Bigelow, G. E., & Stitzer, M., L. (1995). Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *Journal of Pharmacology and Experimental Therapeutics*, 274, 361-372.

- The WHOQOL Group, *Development of the WHOQOL-BREF Quality of Life Assessment*, Psychological Medicine, 28 551-558, 1998. Skevington SM, Lofty M, OConnell K & The WHOQOL Group, *The World Health Organisation's WHOQOL-Bref quality of life assessment: Psychometric properties and the results of the international field trial. A Report from the WHOQOL Group*, Quality of Life Research, 13 (2), 299-310, 2004.
- Woody GE, Poole S, Subramaniam G, Dugosh K, Bogenschutz M, Abbot P, Patkar A, Publicker M, McCain K, Potter JS, Forman R, Vetter V, McNicholas L, Blaine J, Lynch KG, Fudala P. (2008) Extended vs. short-term buprenorphine-naloxone for treatment of opioid addicted youth: A randomized trial. *Journal of the American Medical Association*, 300, 2002-2011.

APPENDIX A

Adverse Event Reporting Definitions and Procedures

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

Definition of Adverse Events and Serious Adverse Events

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

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

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

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

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

Definition of Expectedness

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

Pregnancy

Any pregnancies that occur to a participant enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Women who become pregnant

during the active treatment period will be discontinued from further medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

Medical and Psychiatric History

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

Site's Role in Eliciting and Reporting Adverse Events

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

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

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

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

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

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

Guidelines for Assessing Severity

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

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

Guidelines for Determining Causality

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

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

Site's Role in Monitoring Adverse Events

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

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

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

Regulatory Reporting for an IND study

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

Participant Withdrawal

The study medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be withdrawn from further study medication administration. The study medical clinician should consult with the site principal investigator, the lead investigator and/or Medical Monitor as needed. If necessary, a study medical clinician may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end-of-medication visit to assure safety and to document end-of-medication outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.

