IND #: 34,563

STUDY #: NIDA-CTN-0001

BUPRENORPHINE/NALOXONE VERSUS CLONIDINE FOR INPATIENT OPIATE DETOXIFICATION

Lead Investigator: Walter Ling, M.D., Integrated Substance Abuse Programs UCLA

Co-Investigator: Leslie Amass, Ph.D., Integrated Substance Abuse Programs UCLA

Protocol Development Team:
Walter Ling, M.D.
Leslie Amass, Ph.D.
Paul Fudala, Ph.D.
Rolley E. Johnson, Pharm.D.
Chris Reiber, Ph.D., M.P.H.
C.J. Klett, Ph.D. consultant

NIDA Collaborators: Nora Chiang, Ph.D., National Institute on Drug Abuse
Ming Shih, Ph.D., National Institute on Drug Abuse

Study Sponsor: Walter Ling, M.D.

Central Data Repository: Jim Glass, Ph.D., National Institute on Drug Abuse

CONTACT INFORMATION FOR INVESTIGATORS/COLLABORATORS

Walter Ling, M.D., 310-312-0500 ext. 317
lwalter@ix.netcom.com
Leslie Amass, Ph.D., 310-479-9330 ext. 238
lamass@friendsresearch.org
Chris Reiber, Ph.D., M.P.H., 310-312-0500 ext. 507
creiber@ucla.edu
Integrated Substance Abuse Programs (ISAP)
11075 Santa Monica Boulevard (Ling and Amass)
11050 Santa Monica Boulevard (Reiber)
Suite 200 (Ling), Suite 225 (Amass), Suite 100 (Reiber)
Los Angeles, CA 90025

Paul Fudala, Ph.D.
Department of Psychiatry, Ward 7 East (116-7 E)
VA Medical Center, University and Woodland Avenues
University of Pennsylvania, Philadelphia, PA 19104
Work Phone: (215) 823-6377
Fax Number: (215) 823-5919
E-Mail: fudala_p@research.trc.upenn.edu

Rolley E. Johnson, Pharm.D.
Associate Professor
Department of Psychiatry and Behavioral Sciences
Behavioral Pharmacology Research Center
Johns Hopkins University School of Medicine
5510 Nathan Shock Drive Bldg. G, Room 2725
Baltimore, Maryland 21224
E-Mail: RoEJohnson@aol.com

C.J. Klett, Ph.D. consultant
127 Briarcliff Lane
Bel Air, MD 21014
tel: 410-838-7542
fax: 410-638-0497
E-Mail: sklett@erols.com

Nora Chiang, Ph.D., 301-443-5280, nchiang@nih.gov
Ming Shih, Ph.D., 301-443-9982, mshih@mail.nih.gov
Jim Glass, 301-443-1112, jglass@nih.gov
Division of Treatment Research and Development
National Institute on Drug Abuse
6001 Executive Boulevard
Room 4123, MSC 9551
Bethesda, MD 20892

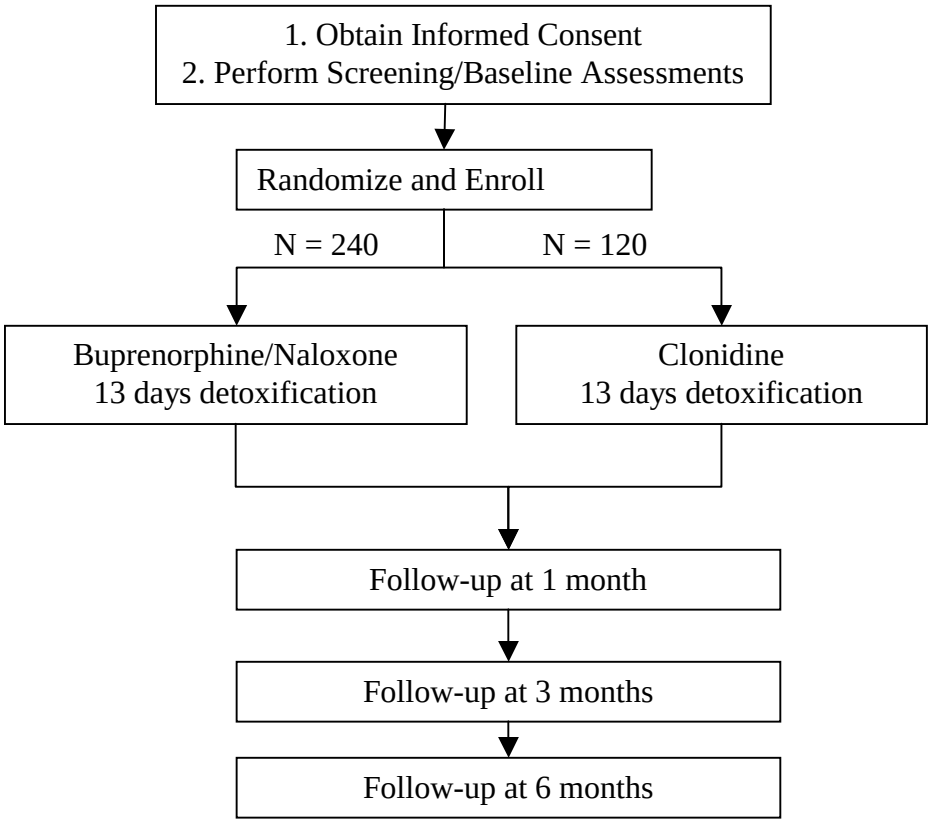
TABLE OF CONTENTS

APPENDICES

1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase
ARSW	Adjective Rating Scale for Withdrawal
ASI	Addiction Severity Index
AST/SGOT	aspartate aminotransferase
BUN	blood urea nitrogen
CLIA	Clinical Laboratory Improvement Amendment of 1988
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CPK	creatine phosphokinase
CSQ	Client Satisfaction Questionnaire
CTN	NIDA Clinical Trial Network
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
ECG	electrocardiogram
GGT	gamma glutamyltranspeptidase
HIV	human immunodeficiency virus
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
LDH	Lactic dehydrogenase
NIDA	National Institute on Drug Abuse
SAE	serious adverse event
DSM-IV	checklist for substance dependence and abuse disorders
SDR	study discharge report
VAS	Visual Analog Scales

2.0 STUDY SCHEMA



3.0 PROTOCOL SYNOPSIS

STUDY OBJECTIVES: To assess the relative clinical utility of buprenorphine-naloxone (BUP/NX) in comparison to clonidine for short term opiate detoxification initiated in the in-patient setting. It is hypothesized that BUP/NX detoxification will be more effective in sustaining treatment retention and abstinence, reducing the frequency of ancillary medications dispensed, and alleviating withdrawal symptoms than clonidine detoxification.

STUDY DESIGN: This is a randomized, open-label, parallel-group design study in which, after screening and baseline assessments are performed, patients will be randomly assigned, in a 2:1 ratio to either a BUP/NX or clonidine 13 day detoxification regimen, respectively. The standard counseling procedures used at each clinic, along with self-help detoxification handbooks, will be offered to all patients on the study. After the 13-day detoxification period, patients will be assessed for relapse, withdrawal symptoms, and treatment satisfaction at follow-up visits occurring 1, 3, and 6 months after starting detoxification.

STUDY POPULATION: Three hundred sixty (360) patients meeting Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for opiate dependence determined by DSM-IV checklist who are seeking treatment, and report experiencing symptoms of opiate withdrawal, are currently physically dependent on opioids, and are in need of medical assistance for opioid withdrawal, will be randomized into one of two treatment groups (240 in the BUP/NX group and 120 in the clonidine group).

ELIGIBILITY CRITERIA: Treatment seeking males and females, at least 15 years-of-age, with a DSM-IV diagnosis of opiate dependence with the ability to understand and provide written informed consent will be included. Women of childbearing capacity will be required to use an acceptable method of birth control.

Patients will be excluded if they have any medical condition that would make participation medically hazardous, have clinically significant abnormalities in ECG, have known allergy or sensitivity to buprenorphine, naloxone, or clonidine, or have acute severe psychiatric condition, or immediate suicide risk. Patients who are dependent upon alcohol, benzodiazepines, or other depressants or stimulants, requiring immediate medical attention or who have participated in another investigational study within the last 30 days will be excluded. Patients receiving beta-blockers, calcium channel blockers, tricyclics, digitalis and other medication which may interact adversely with clonidine, and patients who have had methadone or LAAM maintenance or detoxification within 30 days of enrollment will also be excluded. Patients who have pending legal actions or for any reason are unable to remain in the area for the duration of the active phase of treatment will be excluded.

STUDY INTERVENTIONS: Patients randomized to the BUP/NX arm will receive daily doses for 13 days with sublingual administration of 2 mg buprenorphine – 0.5 mg naloxone tablet(s) and/or an 8 mg buprenorphine – 2.0 mg naloxone tablet(s). The starting dose on day 1 is 4 mg/1 mg BUP/NX with an additional 4 mg/1 mg, if needed, escalating in a step-wise manner to 16 mg/4 mg BUP/NX on day 3 and tapering to 2 mg/ 0.5 mg BUP/NX by days 12 to13. Patients randomized to the clonidine arm will receive oral clonidine (0.05 to 0.1 mg depending upon weight) every 4 to 6 hours for 24 hours not to exceed 0.6 mg total on day 1 and, assuming oral clonidine is well tolerated, a clonidine transdermal patch will be applied (0.1 mg/day/7-day patch with number of patches adjusted by weight). Oral clonidine will continue to be given on the second day of detoxification and increased to 0.2 mg every 6 hours or 0.1 mg every 3 hours not to exceed 0.8 mg over 24 hours. Patches will be worn for up to 13 days of detoxification. The dose of clonidine will be adjusted according to the proposed detoxification schedule, patient's weight, tolerance, and systolic blood pressure. Patients will receive counseling according to procedures in existence at each CTP throughout the study. Self-help detoxification handbooks will be distributed to all study participants.

DURATION OF THE STUDY: The total duration of study participation for each patient will be a maximum of 6 months consisting of: screening and baseline assessments; detoxification (13 days); and, follow-up evaluations conducted at 1, 3, and 6 months after enrollment. It is estimated that 2 patients will be enrolled per site per week with a total of 6 sites. Thus, the estimated length of enrollment is 30 weeks.

SAFETY ASSESSMENTS: Before any study procedures are performed, patients will be required to provide signed informed consent. All candidates for study enrollment will have a physical examination including vital signs and weight, medical history and history of prior medication use assessment, and psychiatric evaluation (ASI Lite) including a DSM-IV checklist for substance dependence, HIV risk assessment, and clinical laboratory studies (blood chemistry, hematology, Hepatitis B and C serology, and urinalysis) performed during screening/ baseline. All patients will have a 12-lead electrocardiograph (ECG). Females will be given a pregnancy test. Assessments of adverse events (AEs) and concomitant medication use will be performed daily during detoxification and at the one-month visit. Serious Adverse Events (SAEs) will be reported during the treatment and follow-up phases of the study.

OUTCOME ASSESSMENTS: Abstinence from opiates, amphetamines, cocaine, cannabinoids, methadone, and benzodiazepines will be assessed by urine drug screen measured at baseline, throughout detoxification, and at follow-up. Treatment retention will be calculated as the number of days each patient received his/her detoxification medication. The patient's status in the study will be tracked with a Study discharge report (SDR). The dispensing of ancillary medications will be tallied and grouped according to symptomology (several medications are permitted for treating anxiety, insomnia, nausea, etc.) and day during detoxification. Withdrawal symptoms will be assessed using the clinical opiate withdrawal scale (COWS), the adjective rating scale for withdrawal (ARSW), and visual analog scales (VAS) during detoxification and at follow-up (COWS and ARSW only). Additional measures of overall treatment effect will include a

shortened version of the Addiction Severity Index (ASI Lite), a client satisfaction questionnaire (CSQ), and SF-36 Health-related Quality of Life questionnaire administered at baseline and all follow-ups.

4.0 BACKGROUND AND RATIONALE

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

Buprenorphine is a high affinity, partial μ-opioid agonist pending FDA approval as a pharmacotherapy for opioid dependence (Bickel and Amass, 1995; Ling *et al.*, 1994). Treatment with buprenorphine in the United States will employ a sublingual combination tablet containing buprenorphine and naloxone in a 4:1 ratio (Chiang and Hawks, 1994; Chiang *et al.*, 1996a, 1996b, Fudala *et al.,* 1998). This combination tablet was developed to help mitigate potential diversion and abuse of buprenorphine once it becomes available for widespread clinical use. Bioavailability studies with sublingual solution and tablet formulations of buprenorphine indicate tablet preparations of buprenorphine may be about 60-70% of the corresponding sublingual solution dose (Nath et al., 1999; Schuh and Johanson., 1999; Ling *et al*., unpublished). Thus, combination tablet dosages used in clinical practice may need to exceed those shown to be effective in prior controlled studies with the sublingual solution.

Clinical research in the last 10 years has established that buprenorphine (and BUP/NX) is a safe and effective alternative to methadone (Bickel *et al*., 1988a; Johnson *et al*., 1992; Strain *et al*., 1994; Ling *et al.*, 1996, 1998; Uehlinger *et al.,* 1988; Amass *et al.,* in press 2000a) and levomethadyl acetate hydrochloride (LAAM; Chutuape *et al*., 1999) that produces significant and substantial improvements over time in psychosocial functioning (Strain *et al*., 1996). Buprenorphine also has unique features that permit novel uses, which may alter current strategies for maintenance and detoxification (Bickel and Amass, 1995; Amass *et al*., 2000, in press 2000b). In particular, buprenorphine's ceiling on agonist activity decreases the danger of overdose, may limit its abuse liability (Walsh *et al*., l994, 1995) and confers low toxicity even at high intravenous doses (Lange *et al.*, 1990; Huestis *et al.,* 1999), increasing the dose range over which it may be safely administered. Buprenorphine can also produce sufficient tolerance to block the effects of exogenously administered opioids (Bickel *et al*., l988b; Rosen *et al*., 1994; Walsh *et al*., 1995), suggesting that it may help reduce illicit opioid use. Finally, buprenorphine's slow dissociation from μ-opioid receptors (Rance and Dickens, l978) not only results in a long duration of action but also diminishes withdrawal signs and symptoms upon its discontinuation (Amass *et al*., 1994; Bickel *et al*., 1997; Cheskin *et al.,* 1994; Fudala *et al.,* 1990; Jasinski *et al*., 1978; Seow *et al.*, 1986), making it particularly useful for opioid detoxification. Such qualities may impact positively on detoxification outcomes by

permitting accelerated buprenorphine detoxifications to be used without inducing significant withdrawal distress.

In designing a buprenorphine detoxification program, three main objectives should be met. First, patient compliance and treatment retention should be maintained. Second, opioid abstinence should be achieved. Third, minimal abstinence symptomology should result from the dose reduction schedule in order to minimize the risk for relapse. The purpose of this study is to determine the clinical utility of BUP/NX as compared to clonidine (an alpha-2 adrenergic agonist) for short-term opiate detoxification with treatment initiated in inpatient settings. Clonidine hydrochloride has been previously shown to be a safe and effective medication for detoxifying individuals from narcotics (Gold *et al*., 1980). Advantages of clonidine include its non-narcotic status and accessibility to primary care providers in both inpatient and outpatient settings. However, side effects such as postural hypotension and sedation (Charney et al., 1981; Gossop, 1988) or unrelieved withdrawal symptoms such as insomnia can lead to early patient attrition and be particularly difficult to manage on an outpatient basis. Although in controlled clinical trials buprenorphine appeared to be more effective than clonidine for alleviating withdrawal symptoms (Nigam et al., 1993; O'Connor et al., 1997), more research is needed comparing the relative effectiveness of these two medications in community treatment settings. In particular, studies are needed in community-based clinics that use the product formulation of buprenorphine (i.e., the BUP/NX tablet) anticipated to be marketed.

How BUP/NX can best be used in a variety of clinical settings to benefit those patients who are not served by the current treatment system remains to be investigated. There are ongoing efforts under NIDA's auspices to introduce buprenorphine for treatment of opiate dependence in physician office-based practice. These protocols are expected to engage patients in treatment for up to a year. Little data have been generated, however, for the shorter-term use of buprenorphine and BUP/NX for detoxification from opiates, a strategy that mirrors much of the opiate detoxification as currently practiced outside of the NTPs. The diversity of clinics in the CTN provides an unparalleled opportunity to conduct such a clinical endeavor. The CTN will benefit directly from the fruits of research while at the same time contribute to a gap in the data on buprenorphine both for labeling purposes and post-marketing surveillance. The CTN leadership had voted as its top priority with highest clinical relevance, BUP/NX for opiate detoxification. This is a "win/win" vote for NIDA and the CTN.

5.0 STUDY OBJECTIVES

The primary objective of this clinical investigation is:

To compare the relative clinical utility of BUP/NX to clonidine in a short-term (13-day) opiate detoxification initiated in an inpatient setting. It is hypothesized that BUP/NX detoxification, compared to clonidine, will be associated with a better treatment response. A treatment responder is anyone who completes the 13-day detoxification and whose last urine specimen collected on day 13 or 14 is negative for opiates.

Other primary objectives are:

To determine the effect of treatment on:

1) abstinence from opiate and other drugs of abuse throughout the detoxification period and during longer term follow-up,
2) withdrawal symptoms,
3) treatment retention,
4) safety,
5) patient satisfaction with the treatment, and
6) extent of ancillary medications dispensed.

Analysis of the data designed to assess the other primary objectives in combination with the primary objective will provide a comprehensive overview of the relative clinical utility (effectiveness) of the two treatment regimens.

6.0 STUDY SPONSOR

Dr. Walter Ling is the study sponsor. This study will be conducted under IND # 34,563 held by Dr. Ling.

7.0 STUDY SITES

The study will be conducted at approximately 6 CTP sites. Patients participating in this study will be housed initially in one of the inpatient settings described in Appendix I and follow the usual inpatient routine. Patients who are discharged prior to completing the 13-day detoxification protocol will continue on their assigned detoxification regimen using the same procedures as if they were still inpatients. Discharge to complete the study by outpatient detoxification could occur because of patient's choice, insurance coverage, or CTP's standard detoxification procedures.

8.0 STUDY DESIGN

A randomized, open-label, parallel groups study design will be used. After screening and baseline assessments, patients will be stratified for gender and randomly assigned in a 2:1 ratio to either a BUP/NX or clonidine 13-day detoxification. Patients will initiate detoxification in the inpatient setting and, as necessary, will continue detoxification as outpatients for the full 13 days. This typically ranges from 5 to 13 days of inpatient detoxification. After the 13 day detoxification, patients will be assessed for outcome measures including relapse and withdrawal symptoms at follow-up visits occurring 1, 3, and 6 months after starting detoxification. Counseling procedures in existence at each CTP will be used throughout the study. Self-help detoxification handbooks will be distributed to all study participants.

9.0 PATIENT SELECTION

A total of 360 male and female patients diagnosed with opiate dependence will be enrolled in the study (240 in the BUP/NX group and 120 in the clonidine group). Entry into this study is open to both men and women and to all racial and ethnic groups. Each of the participating CTP sites will enroll approximately 60 patients. Patients will be recruited by word of mouth, referrals from local narcotic treatment and outreach programs, outpatient and inpatient alcohol and drug abuse clinics, PCPs, local mental health centers and crisis clinics, public service announcements, newspaper advertisements and hospital emergency rooms. Recruitment advertisements will be approved by each site's Institutional Review Board (IRB).

9.1 Inclusion Criteria:

1. Treatment-seeking males and non-pregnant and non-lactating females, 15 years and older, who fulfill DSM-IV criteria for opiate dependence, report experiencing symptoms of opiate withdrawal, are currently physically dependent on opioids, and are need of medical assistance for opioid withdrawal.

2. Systolic blood pressure ≥ 100mm Hg, and pulse ≥ 56 bpm.

3. Good general health or, in case of a medical/psychiatric condition needing ongoing treatment, under the care of a physician willing to continue patient's medical management and cooperate with the study physicians.

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

5. Use of one of the following acceptable methods of birth control by female patients of childbearing potential:

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

9.2 Exclusion criteria:

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

2. Clinically significant abnormalities in ECG.

3. Known allergy or sensitivity to buprenorphine, naloxone, or clonidine.

4. Receiving beta-blockers, calcium channel blockers, tricyclics, digitalis and other medications which may interact adversely with clonidine.

5. Acute severe psychiatric condition in need of immediate treatment, or imminent suicide risk.

6. Dependence on alcohol, benzodiazepines or other depressants, or stimulants, and requiring immediate medical attention.

7. Participation in an investigational drug study, including buprenorphine, within the past 30 days.

8. Methadone or LAAM maintenance or detoxification within 30 days of enrollment.

9. Pending legal action that could prohibit or interfere with participation.

10. Unable to remain in area for duration of active phase of treatment.

11. Females that are pregnant, lactating, or planning to become pregnant.

10.0 INVESTIGATIONAL AGENTS

BUP/NX-combination:

Buprenorphine 2 mg and naloxone 0.5 mg or buprenorphine 8 mg and naloxone 2 mg sublingual tablets are manufactured by Reckitt and Colman Products (Hull, UK) and will be supplied through the National Institute on Drug Abuse and Research Triangle Institute.

Clonidine:

Clonidine (CATAPRES® - clonidine hydrochloride USP) is commercially available and is manufactured by Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT. The clonidine to be used for this study is a 0.1 mg tablet for oral dosing and a transdermal therapeutic system (CATAPRES-TTS® - 1, 0.1 mg per day, for one week).

Ancillary Medications:

Ancillary medications used to treat opiate withdrawal side effects are commercially available and include:

Over the counter medications:
acetaminophen 650 mg

ibuprofen 200 mg
loperimide 2 mg
diphenhydramine 25 mg

Prescription medications:
oxazepam, tablets or capsules 15 mg and 30 mg
lorazepam, tablets 0.5 mg, 1 mg, and 2 mg
phenobarbital tablets, 15, 16 and 30 mg, capsules 16 mg
hydroxyzine hydrochloride tablets, 50 mg
methocarbamol tablets, 500 mg and 750 mg
trimethobenzamide capsules, 250 mg or 100/200 mg suppositories
Donnatal tablets or capsules – atropine sulfate 0.0194 mg, scoplamine hydrobromide 0.0065 mg, hyosyamine hydrobromide or sulfate 0.1037 mg, and phenobarbital 16 mg
zolpidem tartrate tablet, 5 and 10 mg
trazadone hydrochloride tablets 50 mg, 100 mg, 150 mg and 300 mg
doxepin hydrochloride tablets, 50 mg

10.1 Dispensing Investigational Agents

Investigational agents will be dispensed daily according to the appropriate study arm while patients are in the inpatient setting. If patients are released for outpatient detoxification, investigational agents will continue to be dispensed in accordance with the inpatient procedures. Investigational agents will be prescribed, dispensed or administered (furnished) by an individual legally qualified to do so in accordance with state regulations. Patients receiving BUP/NX will be instructed to hold the tablet(s) under their tongue until dissolved. Dissolution of tablets will be monitored as clinically warranted by a nurse, physician or pharmacist at each CTP. Patients receiving oral clonidine will be instructed to swallow all pills and/or to leave their clonidine patch in place until replaced by the nurse, physician, or pharmacist at the study site.

For both in- and outpatient settings, it is recommended that patients be observed for at least several hours on the first day of treatment following the administration of bup/nx or clonidine until vital signs are stable.

Additionally, <u>as clinically indicated</u>, outpatients should not be allowed to drive home by themselves on the first (and sometimes second) day of bup/nx or clonidine treatment.

10.2 Labeling

Investigational agents will be packaged by a central pharmacy and distributed to investigational sites in individual patient cartons. BUP/NX will be packaged in childproof blister packs. This is an open-label study and blinding of investigational agents is not necessary.

10.3 Record of Administration

Accurate recording of all investigational agents dispensed, prescribed or administered will be made.

11.0 STUDY PROCEDURES

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

11.1 Initial Patient Screening

Program staff at each CTP will be thoroughly trained in the protocols in operation at their site, and specifically regarding the inclusion and exclusion criteria detailed in section 9.0. Patients will be recruited through IRB-approved newspaper and poster advertisements, and/or by word-of-mouth. Additionally, any patients calling or walking into the clinic will be advised of the availability to participate in the research protocol. Potential patients contacting the CTP will respond to the CTP's standard screening/intake questionnaire. This screening questionnaire will permit evaluation of the study's inclusion criteria. Potential patients that are identified as meeting the inclusion criteria will be provided basic information about the research protocol and, if interested, provided with an appointment for the purposes of obtaining informed consent and baseline assessments. Any patients deemed ineligible for the research study during the initial patient screening or following baseline assessment will be referred to standard treatment services within the CTP or at another local treatment facility.

11.2 Informed Consent

Prior to the collection of any baseline assessments or initiation of any research procedures, the Study Coordinator (or person assuming this role) at each CTP will obtain informed consent for study participation (see Appendix II for an example Informed Consent Form). Adults, or legally emancipated minors will be provided with a consent form describing the study's purpose, general procedures, risks and benefits along with the patient's role in the study. Additionally, the consent procedure informs patients that descriptive information about them obtained during the baseline assessment on the Basic Data and Locator Questionnaires may be shared with outreach workers at the CTP to facilitate finding patients for follow-up evaluations. The consent form will also specify that neither buprenorphine-naloxone or clonidine has been approved by the FDA for opiate detoxification. The consent form is valid for 14 days in the event the participant requires re-assessment during baseline. (See section 11.3)

**Special Consideration for NW node:* For CTPs requiring a 24-hour period between the receipt of informed consent and signing, baseline assessments or initiation of research procedures should occur following the signing of the informed consent.

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

TABLE 1. TIME AND EVENTS SCHEDULE-CORRECTED COPY

Activity	Screening/ Baseline	Study Interventions (study days)												***		Follow-up (months since study start)		
Time		1	2	3	4	5	6	7	8	9	10	11	12	13	14	1	3	6
Detoxification		X	X	X	X	X	X	X	X	X	X	X	X	X				
Screening Assessments																		
Informed Consent	X																	
Demographics	X																	
DSM-IV Checklist	X																	
Psychiatric eval. **(ASI Lite)**	X																	
Medical History	X																	
Prior Medications	X																	
HIV Risk (HRBS)	X																	
Hepatitis serology	X																	
Safety Assessments																		
Physical exam	X																	
Vital Signs	X	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*			
Hematology	X																	
Blood Chemistry	X																	
Urinalysis	X																	
12-lead ECG	X																	
Pregnancy test	X																	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Efficacy Assessments																		
COWS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ARSW	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ASI Lite	X															X	X	X
SF-36	X															X	X	X
VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
SDR															X			
CSQ														X				
Urine drug screen	X			X				X			X			X		X	X	X
Ancillary medications		X	X	X	X	X	X	X	X	X	X	X	X	X				
Program compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X			

*Blood pressures are monitored in the clonidine group 0 to multiple times daily during treatment according to section 11 of this protocol.
**Brief reporting of SAEs only.
***If subject terminates early, complete all assessments scheduled for days 13 or 14 at final visit.

11.3 Baseline Assessments

Baseline assessments will consist of a comprehensive assessment of addiction severity and withdrawal status, medical and psychiatric status and assessment of HIV risk. The interview will consist of the psychoactive substance abuse disorder sections of the DSM-IV Criteria Checklist (modified from Hudziak et al., 1993) and an abbreviated version of the fifth edition of the ASI known as the ASI Lite (McLellan et al., 1985). Additional questionnaires will also be completed to provide information about demographics and drug history including any concomitant medications received either over the counter or by prescription as well as level of opioid withdrawal being experienced by the patient. Medical status will be determined by medical history, physical exam and laboratory evaluation (including complete blood count, clinical chemistry profiles, serology for Hepatitis B and C, urinalysis, and urine screen for drugs of abuse). The physical examination will include vital signs and ECG for all patients. On or off-site HIV testing and HIV counseling will be encouraged.

Female patients will be required to have a pregnancy test prior to receiving their first dose of investigational agents. Female patients of childbearing potential (including gay women patients who have sex with men) will also be required to practice acceptable birth control (e.g., oral or depo contraceptives, foam, sponges, and condoms). The birth control method will be documented on a CRF. Women who become pregnant will be withdrawn from the study and given immediate access to methadone maintenance services at the CTP or another local treatment provider. Patients refusing methadone maintenance will be referred to another local provider, preferably one providing specialized services for pregnant or post-partum women.

Before entering the in-patient facility, patients will be instructed not to use any heroin or other opiate drugs for at least 6 hours prior to the time scheduled to receive their first dose of study agent and to be in mild withdrawal before taking their first dose. Study coordinators at each study site will take a history from the patient prior to administration of the first dose of study agent to document the time and data of last drug use and verify patient withdrawal status.

Generally patients should only be assessed once to determine if they meet all of the inclusion and none of the exclusion criteria for study participation. However, there may be extenuating circumstances when a patient would become eligible if they could be partially reevaluated on another day. For example, if the only item precluding randomizing the patient was a methadone positive urine test result, the patient could be brought back on the next or subsequent day(s), and another Accutest Screen for opiates, methadone and COWS assessment could be conducted to determine whether they could now be a participant. Another example would be if the patient were eligible except for their reporting having been in methadone/LAAM treatment within the last 30 days. The patient could be brought back at another time when 30 days would have elapsed and another quick test and COWS assessment could be performed provided this was done within 14 days of originally consenting the participant to the study.

In any case, patients should only be reassessed under extraordinary circumstances in which it is obvious that with an additional Accutest Screen for methadone and opiates and a COWS assessment, the individual would likely be eligible to participate and this can be accomplished within 14 days or less from the time of the original consent.

11.4 Randomization And Enrollment

To qualify for the study, patients are required to meet all inclusion/exclusion criteria. A patient will be included in the study after having been examined by the investigator or study physician who verifies that the inclusion criteria are met and no exclusion criteria are present.

Patients will be assigned randomly once it is determined that eligibility criteria have been met**.** Randomization to groups will be performed within each site (CTP). Data management for the Pacific Region Node will create randomization envelopes for each site that will be distributed prior to study initiation.

Approximately 60 patients will be enrolled at each of the participating CTP sites for a total of 360 patients. Patients will be assigned to the BUP/NX and clonidine groups using a 2:1 ratio of random assignment. That is, for every patient assigned to receive clonidine, two patients will be assigned to receive BUP/NX. This 2:1 ratio of assignment should facilitate recruitment into the protocols given that patients will have a 66% chance of being assigned to receive BUP/NX. Moreover, the 2:1 assignment will facilitate acquisition of data in a larger cohort of patients on the use of BUP/NX for short-term opiate detoxification.

11.5 Study Interventions

11.5.1 BUP/NX

To facilitate a comfortable transition onto the BUP/NX combination tablet, patients will be instructed not to use any heroin or other opiate drugs for at least 6 hours prior to receiving their first dose of BUP/NX and to be in mild withdrawal before taking their first dose. Physicians or study coordinators at each study site will take a history from the patient prior to administration of the first dose of buprenorphine to document the time and date of last drug use and verify patient withdrawal status using the COWS and the ARSW. Moreover, a modified, three-day, rapid, buprenorphine induction procedure will be used with all patients in accordance with published guidelines (Amass *et al.,* 2000, in press 2000b). On day 1, patients will receive 2 sublingual tablets that each contains 2 mg of buprenorphine and 0.5 mg of naloxone, comprising a total dose of 4 mg of buprenorphine and 1.0 mg of naloxone. An additional 2 tablets (or 4 mg of buprenorphine and 1.0 mg of naloxone) may be provided if clinically warranted (i.e. if the patient presents with continued withdrawal signs and/or symptoms 1-2 hours following the initial 4 mg dose). Patients receiving BUP/NX will be instructed to hold the tablet(s) under their tongue until dissolved. The following shows the dose and schedule

for the first and remaining BUP/NX administrations over the course of the 13-day detoxification:

Day 1:	4.0 mg buprenorphine – 1.0 mg of naloxone with an additional 4 mg/1 mg dose if needed
Day 2:	8.0 mg buprenorphine – 2.0 mg of naloxone
Day 3:	16.0 mg buprenorphine – 4.0 mg of naloxone
Day 4:	14.0 mg buprenorphine – 3.5 mg of naloxone
Day 5:	12.0 mg buprenorphine – 3.0 mg of naloxone
Day 6:	10.0 mg buprenorphine – 2.5 mg of naloxone
Day 7:	8.0 mg buprenorphine – 2.0 mg of naloxone
Days 8-9:	6.0 mg buprenorphine – 1.5 mg of naloxone
Days 10 - 11:	4.0 mg buprenorphine – 1.0 mg of naloxone
Days 12 - 13:	2.0 mg buprenorphine – 0.5 mg of naloxone

11.5.2 Clonidine

Patients receiving oral clonidine will be instructed to swallow all pills and/or to leave their clonidine patch in place until replaced by medical personnel or until medical personnel directs the patient to change their dosage. The clonidine detoxification protocol was designed to reflect what is being used in clinical practice at a number of the participating CTP sites. Patients will be seen daily, on days of outpatient clinic operations.

In outpatient CTP sites, clonidine detoxification should be started early in the week (Tuesday or Wednesday [see section 11.4]) to insure a steady state level before the weekend with less medical staff. Medical personnel familiar with clonidine need to be available during clonidine treatment for daily patient monitoring, dose adjustment, and prescribing ancillary medication. Medical personnel should be familiar with monitoring vital signs for orthostatic changes and responding to any changes noted. Insure consistency in monitoring by using the same B.P. device at each visit.

Clonidine Dosing Procedure:

Day 1:

Encourage patients to drink lots of fluid. Dehydration exaggerates the hypotensive effects of clonidine. Before administering the test dose of clonidine, ask patients for any history of hypertension or hypotension, fainting or dizziness on rising. Take vital signs noting especially the systolic B.P. Check the EKG to insure the PR interval is not prolonged i.e. > .20 seconds. If the patient has systolic B.P. < 100 mm Hg or heart rate < 56 bpm, do not proceed with the clonidine test dose. Reassess patient if clinically warranted or discontinue the patient from the study.

Be cautious with patients with a history of hypertension or hypotension, fainting or dizziness on rising. Instruct all patients to get up slowly while taking clonidine (e.g. “sit up, swing your feet, and count to 10 before getting up”).

If systolic B.P. is ≥ 100 mm Hg and pulse ≥ 56 bpm, give 0.1 mg oral clonidine test dose (0.05 mg for patients weighing less than 110 lbs,-0.2 mg for patients over 200 lbs). Check B.P. for orthostatic changes after 1 hour. The medical personnel should take B.P. after the patient is sitting for at least 3 minutes, and again after standing for 1 minute (note systolic B.P. and pulse). If systolic B.P. is ≥ 90 mm Hg and the pulse rate is ≥ 50 beats/min, put patient on a schedule of 0.1 mg clonidine q 4-6 hrs but do not exceed 0.6 mg for the first 24 hrs. If the systolic B.P. on recheck is < 90 mg Hg or the pulse rate is < 50 beats/min, instruct the patient to lie down and recheck the vital signs every hour until they return to normal (systolic B.P. ≥ 90 mm Hg and pulse rate is ≥ 50 beats/min). If the patient has symptomatic hypotension or bradycardia (i.e. syncope, dizziness, or chest pain) contact the physician and initiate the appropriate treatment. Treatment may include placing the patient in a recumbent position and beginning hydration with IV fluids.

Check the vital signs before each scheduled dose of clonidine. Skip the dose of clonidine if the systolic B.P. is < 90 mg Hg or the pulse rate is < 50 beats/min. Monitor for symptomatic hypotension, and adjust the dose if necessary. Drowsiness and orthostatic hypotension are common adverse effects of clonidine, requiring that the B.P. be monitored daily; however, these problems usually are not significant. Higher doses generally are needed for management of withdrawal than for treatment of hypertension.

Assuming that the patient tolerates clonidine well on the first day, apply clonidine patches in clinic according to the following weight schedule using TTS-1 patches:

Weight	**Clonidine Patch**
< 110 lbs	1-3 TTS-1
110-200 lbs	2-4 TTS-1
> 200 lbs	2-6 TTS-1

The clonidine patch is a 0.2 mm square that is applied in the same manner as a self-adhesive bandage. It is available in three sizes: 3.5, 7.0, and 10.5 cm^2. In a 24-hour period, these patches deliver an amount of clonidine equivalent to twice-daily dosing with 0.1, 0.2 or 0.3 mg of oral clonidine, respectively. Once the patch is placed on the epidermal surface, clonidine enters the circulatory system through the skin. A rate-limiting membrane within the patch governs the maximum amount absorbed. The patch supplies clonidine for up to 7 days. Only one strength will be used (0.1). Multiple patches can be placed on the patient's upper body, and removed if clinically indicated. (TIP series, number 19 reference).

Day 2:

It takes 2 days for the clonidine patches to achieve a maximum blood concentration; therefore, oral clonidine usually needs to be continued on Day 2. Therefore, oral clonidine may be administered on day 2 as clinically indicated, depending on vital signs and opiate withdrawal symptoms. The clonidine dose may be increased to either 0.2 mg q

6 hrs or 0.1 mg q 3 hrs (but not to exceed 0.8 mg qd) as long as the vital signs sitting and standing are normal. Apply caution, observation and same withholding rules as in Day 1.

Days 3-6

The patch(es) given on Day 1 will provide sustained blood levels of clonidine for up to 7 days. However, if the patient does not tolerate the patches (i.e., they have a rash or persistent hypotension), the patch(es) should be discontinued and oral clonidine administered in its place in doses similar to that given on Day 2, but with adjustments as clinically indicated, through Day 7. Vital signs (sitting and standing) will be checked on every scheduled clinic visit or as instructed by the treating physician.

Day 7

On Day 7, remove all clonidine patches. Evaluate the patient's tolerance of clonidine, vital signs sitting and standing, opiate use during the detoxification, and symptoms of opiate withdrawal to decide whether or not to replace the patches or continue with oral clonidine. A common course is to reduce the dose by one-half for the second week.

Days 8-13

Continue to monitor vital signs for any changes of B.P. and pulse. Discontinue clonidine administration and remove any remaining patches by Day 13.

Day 14

Monitor vital signs for any rebound elevation of B.P.

11.6 Ancillary Medications

All participants will have the option to receive ancillary medications. Dispensing of any medications will be recorded on a CRF. Dispensing of ancillary medications will be at the physician's discretion in accordance with clinical need to assist with the management of withdrawal signs and symptoms during detoxification but should be limited only to those medications listed below. Each type of ancillary medication will be placed into its own childproof bottle, appropriately labeled with the patient's name, date issued, contents and expiration date as well as dosing instructions for the patient. At the start of the detoxification, patients will be instructed on the use of each medication and told they can self-administer the medications in accordance with the instructions provided on the childproof bottle. Refills will be available to all participants during each scheduled clinic visit. Use of ancillary medications will be closely monitored for the duration of the study interventions. The following lists the dose, schedule, and indication for use of ancillary medications:

For anxiety and restlessness:

Days 1-7
lorazepam 1-2 mg q 6 hours prn; NTE 8 mg/24 hour **OR**
oxazepam 15 - 30 mg po q6 hours prn; NTE 120 mg per 24 hours **OR**
phenobarbital 15 - 30 mg. po q6 hours prn; NTE 120 mg per 24 hours **OR**
hydroxyzine hydrochloride 50 mg, po q6 hours prn; NTE 200 mg per 24 hours

Day 8-13

lorazepam 1-2 mg q 6 hours prn; NTE 8 mg/24 hour **OR**
oxazepam 15 - 30 mg. po q6 hours prn; NTE 60 mg per 24 hours **OR**
phenobarbital 15 - 30 mg. po q6 hours prn; NTE 60 mg per 24 hours **OR**
hydroxyzine hydrochloride 50 mg, po q6 hours prn; NTE 200 mg per 24 hours

For bone pain and arthralgias:

Days 1-13

Non-steroidal anti-inflammatory agent, such as ibuprofen (Advil, Motrin and others) 800 mg po q8 hours with food;
NTE 3200 mg in 24 hours **OR**
acetaminophen (Tylenol and others) 650 mg q 4 – 6 hours NTE 3900 mg in 24 hours **OR**
methocarbamol (Robaxin and others) 500-1000 mg po q6 hours prn; NTE 2000 mg per 24 hours

For nausea:

Days 1-13

trimethobenzamide (Tigan) 250 mg po q8 hours prn; NTE 750 mg per 24 hours or 100/200 mg suppositories; NTE 400 mg per 24 hours

For diarrhea:

Days 1-13

loperamide (Immodium) 2 mg, 2 caps followed by 1 cap after each unformed stool: NTE 8 mg per 24 hours. **OR**
Donnatal 1-2 tablets po q 6-8 hours prn; NTE 8 tablets per day

For Insomnia:

Days 1-13

zolpidem tartrate (Ambien) 10 mg, 1 to 3 tabs, po qhs prn **OR**
trazadone hydrochloride 50 mg, 1 to 3 tabs, po qhs prn **OR**
doxepin hydrochloride 50 mg, 1 to 3 tabs, po qhs prn **OR**
diphenhydramine 25 – 50 mg q 4-6 hrs prn; NTE 300 mg q 24 hrs

11.7 Counseling

Since the CTN protocols are designed to occur in "real-life" clinic settings, counseling procedures in existence at each CTP will be followed throughout the study. However, in order to assure that a basic platform of detoxification education is provided to all participants, all CTPs will be provided with self-help detoxification booklets to hand out to all research participants.

11.8 Clinical Assessments During Study Interventions

Adverse events and the use of any concomitant medications occurring since the last dosing will be recorded. VAS, COWS, and ARSW assessments will be performed daily during detoxification. Urine specimens for drug testing will be collected on days 3 or 4, 7 or 8, 10 or 11, and 13 or 14. If the subject terminates early, collect all assessments scheduled for days 13 or 14 at the final study visit.

11.9 Follow-up

Upon completion of the detoxification phase of the study, patients will be scheduled for continued counseling and follow-up assessments at 1, 3, and 6 months following enrollment. Adverse events, concomitant medication use, and a COWS, ARSW, ASI Lite, CSQ, SF-36, SDR assessment and urine drug test will be recorded at the 1-month follow-up visit. ASI Lite, CSQ, SF-36, and SDR assessments and urine drug tests will be performed at 3 and 6 month follow-up visits. Any SAEs that occurred during this period will be reported to the Lead Investigator, NIDA and to the local IRB. Although follow-up data collection should occur at the specified time point, a window of 30 days after the scheduled due date is allowable for data collection. If necessary self reports can also be collected by telephone.

**Special consideration for the Betty Ford Center*: Arrangements will be made so that Betty Ford staff can secure follow-up urine samples in the event the participant's residency is outside the state of California or reasonable distance from the center.

11.10 Post Study Options

Upon completion of the detoxification phase of the study, post study treatment options should be reviewed with the patient in accordance with those available at the CTP or other local providers (e.g. naltrexone aftercare if successfully detoxified from opiates, entry into methadone or LAAM maintenance programs, or other forms of inpatient or outpatient treatment).

11.11 Patient Compensation

Patients will be compensated $25 in scrip for the intake/initial patient screening and for each follow up assessment. Patients completing all three follow up assessments will receive an extra $25 in scrip. Each CTP can determine what type of scrip (e.g., gift certificate for groceries, to KMART, etc.) is most appropriate for their site.

12.0 ASSESSMENT METHODS

12.1 Demographics

Basic demographic information will be collected on the ASI Lite. A Basic Data and Locator Questionnaire will be completed and kept confidential in the patient's records. Data collected on the Basic Data and Locator Questionnaire will be used to facilitate contact with the patient during the research and follow-up. Patients will be asked to provide locator information including their residential street address and a working telephone number, or an address of a relative if they are homeless, as well as the address and telephone number of a non-drug abusing relative or friend who can reach the client in emergencies.

12.2 DSM-IV Checklist

A DSM-IV Criteria Checklist (modified from Hudziak et al., 1993) will be administered to determine the patient's Axis I substance abuse and dependence diagnoses prior to enrollment.

12.3 HIV Risk (HBRS)

HIV risk will be assessed using a 12 item questionnaire adapted from Darke *et al.* (1991) known as the HIV Behavior Risk Survey. HIV risk will be assessed during baseline. HIV testing referral and or counseling will be offered if applicable.

12.4 Vital Signs

Vital signs to be assessed include oral temperature, sitting and standing blood pressure and pulse rate (standing at least 3 minutes). Vital signs will be assessed at baseline for all study patients. Those patients receiving clonidine will have their blood pressure monitored zero to multiple times daily while in-patients and at each clinic visit and while outpatients as described in the clonidine detoxification section of the protocol (section 11).

12.5 Hematology

Blood will be collected in anticoagulant containing vacutainer tubes for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. Laboratories performing these assessments should be either directly regulated by the American College of Pathologists (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. Hematologic tests will be performed at baseline.

12.6 Blood Chemistries

Blood will be collected in non-anticoagulant containing vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, albumin, total protein, calcium, cholesterol, triglycerides, phosphorous, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, lactic dehyrdrogenase (LDH), creatine phosphokinase (CPK), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, and iron. Serology for Hepatitis B and C will also be performed. Laboratories performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. Blood chemistry tests will be performed at baseline.

12.7 Urinalysis

Urine will be collected by clean catch and analyzed for specific gravity, pH, glucose, protein, ketones, occult blood, white blood cells, red blood cells, and epithelial cells. Urinalysis will be performed at baseline.

12.8 ECG

All patients will be administered twelve-lead ECGs at baseline. In order to standardize collection of ECGs across site and ensure ECGs are collected and interpreted in the same manner, the Pacific node will subcontract with Covance Central Diagnostics for the collection and interpretation of ECGs at each participating CTP throughout the CTN. Covance Central Diagnostics will provide equipment, training, toll free transmission, interpretation and hard copy reports using the MTX-2 telephonic transmission device. The portable MTX-2 permits digital data acquisition, onboard storage, and remote transmission and interpretation and yields high quality ECGs. Reports are received within two hours of ECG collection to facilitate faster inclusion/exclusion decisions and patient care.

12.9 Pregnancy Testing

Female patients will be required to have a negative pregnancy test (urine hCG, JANT Laboratories) prior to randomization. Both buprenorphine and clonidine are Pregnancy Category C Drugs. Female patients will also be expected to practice acceptable birth control. Women who become pregnant will be withdrawn from the study and given immediate access to methadone maintenance services at the CTP or another local treatment provider. Patients refusing methadone maintenance will be referred to another local provider, preferably one providing specialized services for pregnant or post-partum women.

12.10 Adverse Events

AEs will be assessed daily during detoxification and at the 1 month follow-up visit by an investigative staff nurse or physician/clinician. Brief assessments for serious AEs will also be done at the 3 and 6 month follow-up visits. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. A study physician will meet with the participant once a week to review the AEs recorded by the nurse and to assess for any additional AEs. The investigator or study physician will assess patients for any medical or psychiatric side effects. Both the nurse and physician will assess AEs by asking the participant "How have you been feeling since I saw you last." The type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF according to the procedures described in section 15.

12.11 Clinical Opiate Withdrawal Scale (COWS)

The COWS is an 11-item interviewer administered questionnaire designed to provide a description of signs and symptoms of opiate withdrawal that can be observed directly in the patient (e.g., sweating, runny nose, etc). The COWS will be completed at each clinic visit during detoxification and the 1 month follow-up visit.

12.12 Adjective Rating Scale for Withdrawal (ARSW)

The ARSW is comprised of 16 signs and symptoms of opioid withdrawal (Bickel et al., 1988a, 1988b; Amass *et al.*, 2000). Patients rate themselves on a scale ranging from 0 (none) to 9 (severe) (maximum cumulative score = 144) on the following items: muscle cramps, depressed or sad, painful joints, excessive yawning, hot or cold flashes, trouble getting to sleep, sick to stomach, irritable, runny nose, poor appetite, weak knees, excessive sneezing, tense and jittery, watery eyes, abdominal cramps, and fitful sleep. The ARSW will be completed at each clinic visit during detoxification and the 1 month follow-up visit.

12.13 Addiction Severity Index (ASI Lite)

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

scores will be calculated according to the procedures described by McGahan *et al.* (1982), Carroll *et al.* (1994). The ASI Lite will be administered before study drug administration and at each of the 1, 3, and 6 month follow-up visits.

12.14 Visual Analog Scales (VAS)

Two VAS will be completed daily during detoxification. The scales consist of 100 point lines anchored with "not at all" on one end and "extremely" on the other.

12.15 Study discharge report (SDR)

The SDR is a brief tracking instrument used to officially record when patients become inactive with respect to the protocol. The SDR will be completed at discharge.

12.16 Client Satisfaction Questionnaire (CSQ)

The Client Satisfaction Questionnaire (CSQ) is a brief, patient-administered questionnaire asking the patient to rate their satisfaction with multiple dimensions of program effectiveness using a four point Likert scale (Attkinsson et al., 1989). The CSQ will be completed by patients at the final study visit (Day 13 or 14).

12.17 SF-36

The SF-36 is a 36-item, patient administered instrument examining health-related quality of life changes as a function of treatment (Ware and Sherbourne, 1992). Each item is rated on a 5 point scale. The SF-36 will be completed at baseline and all follow-up visits.

12.18 Urine Drug Screen

Urine samples are always to be collected before dispensing medications. All urine specimens will be monitored by staff using drug test cups with temperature controlled monitoring. These cups will be provided by the Northwest Toxicology via the Center for Toxicology in Utah, which will serve as the central laboratory contractor for this protocol. Specimens will be shipped to the Center for Toxicology in Utah for subsequent analysis for opioids, methadone, benzoylecognine (a cocaine metabolite), amphetamines, cannabinoids, and benzodiazepines in accordance with the detailed procedures described in the protocol Operations Manual. Urine will be collected at baseline, on days 3 or 4, 7 or 8, 10 or 11, and 13 or 14 during detoxification, and at each follow-up visit. An additional portion will be placed in the backup cup provided by the contractor for storage at the site until the contractor completes analyses and records the data.

Additionally, an FDA-approved one-step test, the Accutest Multi-Drug Screen (for immunoassay of 9 drugs of abuse and TCAs; JANT Pharmacal Corporation) will be used during the baseline/screening phase and at the final study visit for immediate feedback of results for urine drug screening. Following collection of the urine sample into the cup provided by the central contractor, staff will dip this multi-drug screen cassette into that cup and wait for the results. Results are obtained in 3-8 minutes. Once the results

from the Accutest Screen have been recorded on the CRF, the Accutest Screen will be shipped to the central contractor, along with the other specimen of urine collected, for confirmatory analyses by the central contractor.

12.19 Study Compliance

The amount of BUP/NX or clonidine administered daily to each patient will be recorded on a dosage log. For BUP/NX tablets or clonidine given to patients to self-administer on weekends, the daily report of medications used will be provided by the patient and recorded by study staff onto the medication logs at the next scheduled clinic visit.

12.20 Ancillary Medication Tracking

The type of ancillary medication(s) dispensed will be recorded daily during detoxification on the Ancillary Medication Log Form.

13.0 REGULATORY AND REPORTING REQUIREMENTS

13.1 FDA Form 1572

The investigator at each study site will sign a Statement of Investigator (FDA Form 1572) prior to initiating this study.

13.2 IRB Approval

Prior to initiating the study, the investigator at each study site will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for patient recruitment and any educational materials (Self-help detoxification handbooks) given to the patient. Informed consent procedures for minors was explained in section 12.2.

13.3 Informed Consent

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator, sub-investigators, or study physician at each site will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Patients who refuse to participate or who withdraw from the study will be treated without prejudice. The reason for refusal or withdrawal will be noted on a CRF.

13.4 Drug Accountability

Upon receipt of investigational agents (BUP/NX, clonidine, ancillary medications), the investigator/pharmacist is responsible for taking an inventory and providing secure storage. A record of this inventory must be kept and usage must be documented. Any unused or expired BUP/NX, clonidine or ancillary medications shall be returned to McKesson HBOC unless otherwise instructed.

13.5 Outside Monitoring

Data and Safety Monitoring Board (DSMB):

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

This trial is not considered likely to provide evidence of "overwhelming efficacy" of one treatment over another. Accordingly, interim analysis of accumulating efficacy data by treatment assignment is not planned. Rather, in accordance with the Board's SOP, presentation of primary and other efficacy outcome data and other data not intended to evaluate safety will be presented for all treatment groups combined, further broken down by study node and, if feasible, by CTP. No statistical penalty will be taken for this blinded interim analysis of efficacy data which will be conducted for the sole purpose of assessing the acceptability of safety results.

Adverse event data and other data intended for the monitoring of safety will be presented to the DSMB in an unblinded fashion. Since the trial is not considered to be powered to demonstrate statistically significant differences in adverse events or other safety outcomes, p-values will not be calculated for any differences observed unless specifically requested by members of the Board to assist in the evaluation of a potential safety concern. No adjustments will be made for the number of interim analyses in the final report.

Although interim analysis of efficacy data is not planned, the Board may feel that such analysis is necessary to permit proper evaluation of safety data. Should an unscheduled interim analysis of efficacy be necessary, the Board will specify the question, the analysis required, the critical values for a decision and the statistical procedures necessary to control the overall type 1 error at $p<0.05$. A protocol amendment will be included in the DSMB report of the analysis describing necessary changes in the statistical plan that result from the analysis.

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each patient. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to inform the sponsor of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational

medications are properly stored and accounted for, verify that patients' consent for study participation has been properly obtained and documented, confirm that research patients entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.

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

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

The Quality Assurance procedures to be covered at monitoring visits and a checklist of activities is provided in Appendix III.

13.6 Adverse Events Reporting.

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix IV. The occurrence of AEs will be assessed daily during detoxification and at the one month follow-up visit.

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

Each week, a study investigator must review the AE Form completed for the previous week for any events that were reported as continuing. All AEs regardless of severity, will be followed by study investigators until satisfactory resolution. AEs may be reported up to 4 weeks following completion of detoxification.

13.7 Serious Adverse Events

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

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

Walter Ling, M.D., 310-312-0500, ext. 317
Leslie Amass, Ph.D., 310-479-9330, ext. 238
Ann Anderson, M.D., 301-435-0767

Walter Ling, M.D., lwalter@ix.netcom.com
Leslie Amass, Ph.D., lamass@friendsresearch.org
Integrated Substance Abuse Programs (ISAP)
11075 Santa Monica Boulevard,
Suite 200 (Ling), Suite 225 (Amass)
Los Angeles, CA 90025

Ann Anderson, M.D., aanderso@nida.nih.gov
Center for Clinical Trials Network
National Institute on Drug Abuse
6001 Executive Boulevard
Room 4234, MSC 9557
Bethesda, MD 20892-9557

The telephone report is to be followed by receipt of a completed SAE Form with demographic information and a narrative explanation of the event within 2 days. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Therapy Forms, and the Medical History Form from the patient's CRFs. Unexpected serious medical events are also to be reported immediately to the responsible institutional review board according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor.

Dr. Ling, as IND holder, is required by FDA regulations to report SAEs to the FDA in a timely fashion. All AEs that are both serious and unexpected must be reported to the FDA, in writing, within ten working days of notification of the sponsor of the SAE. If the SAE is fatal or life threatening, there is an additional obligation of the sponsor to notify FDA by telephone within 3 working days, with a follow-up written report in 10 working days.

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

In the event that a study patient either withdraws from the study or an investigator decides to discontinue the patient from the study due to a SAE, the patient must have appropriate follow-up medical monitoring. If the patient is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

14.0 ANALYTICAL PLAN

14.1 Statistical Hypotheses

Primary Efficacy Endpoint: It is hypothesized that BUP/NX detoxification, compared to clonidine, will be associated with a better treatment response. A treatment responder is defined as anyone who completes the 13-day detoxification and whose last urine specimen is negative for opiates. By combining treatment retention with opiate abstinence, a composite number is derived that is indicative of both the patients' tolerance to the treatment and the desired outcome of abstinence at the completion of a short-term detoxification procedure. Note that there is no issue concerning the handling of missing data when utilizing this definition of "responder." Patients who fail to either come in or provide a urine sample are, by definition, non-responders.

Other Primary Efficacy Endpoint: Other primary efficacy endpoints were selected to examine the effect of treatment on 1) opiate and other drugs of abuse abstinence throughout the detoxification period and during longer term follow-up, 2) withdrawal symptoms, 3) treatment retention, 4) safety, 5) patient satisfaction with the treatment and 6) extent of ancillary medications dispensed to provide a comprehensive overview of the clinical efficacy and safety of the two treatment regimens.

Hypotheses for the other primary outcome measures include that BUP/NX detoxification, compared to clonidine, will:

1. Increase the number and consecutive duration of opiate and all drug-free urine specimens during detoxification and follow-up.
2. Increase the number of days retained in treatment.
3. Decrease the amount of ancillary medications needed to treat withdrawal symptoms.
4. Lessen the severity of withdrawal symptoms as assessed by COWS, ARSW, and VAS.
5. Lessen the severity of dependence or abuse as assessed by ASI Lite.

6. Improve the quality of life as assessed by the SF-36 questionnaire and satisfaction with treatment (CSQ).

14.2 Outcome Measures

14.2.1 Primary Outcome

One primary outcome measure is the number of treatment responders in each group out of all of the patients randomized to that group (intent-to-treat population).

14.2.2 Other Primary Outcomes

Other Primary outcomes include:

1. The number of urine specimens negative for opiates per patient (a maximum of 4 per patient).
2. The number of consecutive urine specimens negative for opiates per patient (maximum of 4).
3. The number of urine specimens negative for all drugs (opiates, methadone, cocaine, amphetamines, benzodiazepines, and cannabinoids) per patient (a maximum of 4 per patient).
4. The number of days retained in treatment (total days in treatment is the number of days since the start of treatment and the last day of treatment).
5. The frequency of dispensing of ancillary medications, by indication (anxiety or restlessness, bone pain or arthralgias, nausea, diarrhea, or insomnia).
6. The probability of remaining in treatment and being opiate-free at each urine collection.
7. The probability of remaining in treatment and being totally drug-free (negative urine tests for opiates, methadone, cocaine, amphetamines, benzodiazepines, and cannabinoids) at each drug collection.
8. The number and severity of adverse events.
9. The COWS score during treatment and 1-month follow-up.
10. The ARSW score during treatment and 1-month follow-up.
11. The VAS score during treatment.
12. The ASI Lite score during follow-up.
13. The CSQ score at the final visit.
14. The SF-36 score during follow-up.

14.3 Intent-to-Treat and Evaluable Patient Populations

The intent-to-treat population is defined as the patients who are randomized to treatment. The evaluable population is defined as the patients who are properly qualified to participate in the study in accordance with the inclusion and exclusion criteria and who complete the 13-day detoxification procedure.

14.4 Analysis Plan

Baseline characteristics of groups will be generated using demographic data from intake questionnaires as well as the Addiction Severity Index. Information summarized will include gender distribution, age, years of use, route of administration, ethnic distribution, education, income, and ASI composite scores. Appropriate 2-sided *t*-tests or chi-square tests will be used to test for equivalence between groups. Inequalities between groups at baseline will be used as cofactors in analyses of outcome variables if related to outcomes.

Each of the primary and other primary outcome measures will be analyzed for the intent-to-treat population. The primary outcome measure is based on an intent-to-treat principle, and therefore cannot be analyzed in the evaluable population. The other primary outcome measures, however, will be analyzed for the evaluable population in addition to the intent-to-treat population. By examining the other primary outcome measures for the evaluable population, the long-term efficacy in treatment responders can be explored. Comparing results from the intent-to-treat and evaluable population analyses will also provide estimates of the effect of missing data. Major differences in the results, if any, will be further explored. While there is every intent to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency, and some adjustments may be required to meet constraints posed by the structure of the data.

The primary outcome measure, treatment responders, will be compared between groups using the Chi-square statistic. Two-group two-tailed t-tests and analysis of variance (with repeated measures where appropriate) will be used to evaluate group differences in other primary outcomes, including retention, number of negative urines and number of consecutive negative urines, and frequency of ancillary medications dispensed. Survival analysis techniques including log- rank statistics will be used to evaluate treatment response over the duration of treatment and follow-up. Both retention in treatment and retention in treatment with negative urine tests for opiates will be evaluated. Repeated measures such as the ASI, VAS, COWS, ARSW will be evaluated using an appropriate repeated measures test such as generalized estimating equations.

Statistical tests will be two-sided, with alpha set at 0.05. Confidence intervals will be two-sided with a 95% confidence coefficient.

14.5 Descriptive Statistics

Summaries of the characteristics of the patients in each treatment arm at baseline will be prepared for both the intent-to-treat and evaluable populations. The summary will minimally include: gender distribution, age, years of use, route of administration, ethnic distribution, education, income, and ASI composite scores. Another summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatment arms and for major subgroups. The compliance of each group at each assessment day will be summarized.
All adverse events will be reported in tabular form indicating the frequency of each type of event by various demographic characteristics such as gender, ethnicity, age, duration

of addiction, other medical problems both related to and independent of the addiction, and combinations of these characteristics.

14.6 Sample Size Estimate

Sample size and power calculations were made based on the primary outcome measure, treatment response. It was assumed that there would be 20% (maximally) treatment responders in the clonidine group and 30% treatment responders in the BUP/NX group. Using a Chi-Square test power analysis, and assuming a 2:1 buprenorphine:clonidine randomization ratio, an N of 360 is sufficient to detect the 10% difference in number of responders in the two arms with an alpha of 0.05 and a power of 90%. Therefore, the number of patients in the BUP/NX arm is proposed to be 240 and the number in the clonidine arm is to be 120.

14.7 Post Hoc Analyses

During the course of conducting the primary and other primary outcome analyses, the data may suggest other interesting differences in the treatment groups. Post hoc analyses are anticipated to explore these findings.

15.0 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

Data management activities and statistical analytical support will be coordinated by the Pacific Region Node and NIDA.

15.1 Data Collection

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

Paper CRFs must be completed legibly with black ballpoint pen. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. Corrections to paper CRFs must be initialed and dated by the person making the correction. Data entered into electronic CRFs shall be performed by authorized individuals. Corrections to electronic CRFs shall be tracked electronically with time, date, individual making the change, and what was changed. All CRFs should be reviewed by the investigator. Selected CRFs also require the investigator's written signature or electronic signature as appropriate.

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

15.2 Data Accrual, Editing and Control

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

15.3 Data Entry, Processing and Analyses

Data will be entered into the database at each node using the data management system resident within each node. Periodically, during the investigation, data sets will be submitted to the NIDA DTR&D central data repository according to procedures provided during training. NIDA DTR&D central data repository will provide the completed database to the sponsor for data analysis.

15.4 Study Documentation and Records Retention

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

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

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

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must

be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of an NDA.

16.0 CONFIDENTIALITY

16.1 Confidentiality of Data

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

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

16.2 Confidentiality of Patient Records

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

17.0 SIGNATURES

SPONSORS REPRESENTATIVE

Typed Name	**Signature**	**Date**
	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 14.7 of this protocol.

Typed Name	**Signature**	**Date**
_____ Primary Investigator	_____	_____
_____ Subinvestigator	_____	_____
_____ Subinvestigator	_____	_____
_____ Subinvestigator	_____	_____
_____ Subinvestigator	_____	_____

18.0 REFERENCES

Amass, L., Bickel, W.K., Higgins, S.T. and Hughes, J.R. (l994) A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. J Addict Dis 13, 35-47.

Amass, L., Kamien, J.B., Branstetter, S.A., Mikulich, S.K., in press 2000a. A controlled comparison of the buprenorphine-naloxone tablet and methadone for opioid maintenance treatment: Interim results. In: Harris, L.S. (Ed.), Problems of Drug Dependence 1999, NIDA Research Monograph ###. U.S. Government Printing Office, Washington, D.C.

Amass, L. Kamien, J.B. and Mikulich, S.K. Thrice-weekly supervised dosing with the combination buprenorphine-naloxone table is preferred to daily supervised dosing by opioid-dependent humans. Drug and Alcohol Dependence, in press 2000 b.

Amass, L., Kamien, J.B., Mikulich, S.K., 2000. Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. Drug Alcohol Depend. 58: 143-152.

Attkinsson, c., Larsen, D. in collaboration with Hargreaves, W.A., LeVois, M., Nguyen, T., Roberts, B., and Stegner, B.: Client Satisfaction Questionnaire, Univ. of Calif., San Francisco, 1989.

Bickel WK, Stitzer MI, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE (1988a). A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. Clinical Pharmacology and Therapeutics; 43:72-78.

Bickel WK, Stitzer MI, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE (1988b). Buprenorphine: Dose-related blockade of opioid challenge effects in opioid dependent humans. Journal of Pharmacology and Experimental Therapeutics; 247:47-53.

Bickel, W.K., Amass, L., 1995. Buprenorphine treatment of opioid dependence: A review. Exp. Clin. Psychopharm. 3: 477-489.

Bickel, W.K., Amass, L., Higgins, S.T., Badger, G.J. and Esch, R.A. (1997) Effects of adding behavioral treatment to opioid detoxification with buprenorphine. J Consult Clin Psychol, 65(5), 1-81.

Carroll KM, Rounsaville BJ, Gordon LT, *et al.* Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. Arch Gen Psychiatry 1994; 51:177-187.

Charney, D.S., Sternberg, D.E., Kleber, H.D, Heninger, G.R., Redmond, D.E. (1981) The clinical use of clonidine in abrupt withdrawal from methadone: effects on blood pressure and specific signs and symptoms. Arch Gen Psychiatr 38: 273-277.

Cheskin, L.J., Fudala, P.J. and Johnson, R.E. (1994) A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. Drug Alcohol Depend 36(2), 115-21.

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 58th Annual Scientific Meeting of the College on Problems of Drug Dependence, June 22-27, San Juan, Puerto Rico.

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: Harris, L.S. (Ed.), Problems of Drug Dependence 1995, NIDA

Research Monograph no. 162. U.S. Government Printing Office, Washington, D.C., p. 117.
Chiang, C.N., Hawks, R., 1994. Development of a buprenorphine-naloxone combination drug for the treatment of drug addiction. In: Harris, L.S. (Ed.), Problems of Drug Dependence 1993, NIDA Research Monograph no. 141. U.S. Government Printing Office, Washington, D.C., p. 458.
Chutuape, M.A., Johnson, R.E., Strain, E.C., Walsh, S.L., Stitzer, M.L., Block, D.A., Bigelow, G.E., 1999. Controlled clinical trial comparing maintenance treatment efficacy of buprenorphine (bup), levomethadyl acetate (LAAM) and methadone (m). In: Harris, L.S. (Ed.), Problems of Drug Dependence 1998, NIDA Research Monograph no. 179. U.S. Government Printing Office, Washington, D.C., p. 74.
Darke, S, Hall, W., Heather, N., Ward, J., Wodak, A., 1991. The reliability and validity of a scale to measure HIV risk taking behavior among intravenous drug users. AIDS, 5:181-185.
Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychol Med. 1983; 13:595-605.
Fudala, P.J., Jaffe, J.H., Dax, E.M., Johnson, R.E., l990. Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. Clin. Pharmacol. Ther. 47: 525-534.
Fudala PJ, Bridge TP, Herbert S, Chiang CN, Leiderman DB, and the Buprenorphine/Naloxone Collaborative Study Group. A multisite efficacy evaluation of a buprenorphine/naloxone product for opiate dependence treatment. NIDA Research Monograph 179. Rockville: DHHS/NIH/NIDA 1998;105.
Gold, M.S., Pottash, A.C., Sweeney, D.R., Kleber, H.D. (1980) Opiate Withdrawal Using Clonidine. A safe, effective and rapid nonopiate treatment. JAMA 243: 343-346.
Gossup, M. (1988) Clonidine and the treatment of the opiate withdrawal syndrome. Drug and Alcohol Dependence, 21: 253-259.
Hudziak, J., Helzer, J.E., Wetzel, M.W., Kessel, K.B., McGee, B., Janca, A., Przybeck, P., 1993. The use of the DSM-III-R checklist for initial diagnostic assessments. Compr. Psychiatry 34: 375-83.
Huestis, M.A., Umbricht, A., Preston, K.L., and Cone, E.J. (1999) Safety of buprenorphine: No clinicaly relevant cardio-respiratory depression at high IV doses. In: Problems of Drug Dependence, NIDA Research Monograph no. 179 (Harris, L.S., ed.), p. 62. U.S. Government Printing Office, Washington, D.C.
Jasinski DR, Pevnick JS, Griffith JD (1978). Human pharmacology and abuse potential of the analgesic buprenorphine. Archives of General Psychiatry; 35:501-516.
Johnson RE, Jaffe JH, Fudala PJ (1992). A controlled trial of buprenorphine treatment for opioid dependence. Journal of the American Medical Association; 267:2750-2755.
Lange, W.R., Fudala, P.J., Dax, E.M. and Johnson, R.E. (1990) Safety and side-effects of buprenorphine in the clinical management of heroin addiction. Drug Alcohol Depend 26, 19-28.
Ling W, Charuvastra C, Collins JF, Batki S, Brown LS Jr, Kintaudi P, Wesson DR, McNicholas L, Tusel DJ, Malkerneker U, Renner JA Jr, Santos E, Casadonte P, Fye

C, Stine S, Wang RI, Segal D (1998). Buprenorphine maintenance treatment of opiate dependence: A multicenter, randomized clinical trial. Addiction; 93(4):475-86.
Ling W, Rawson RA, Compton MA (1994). Substitution pharmacotherapies for opioid addiction: From methadone to LAAM and buprenorphine. Journal of Psychoactive Drugs; 26(2):119-128.
Ling W, Shoptaw S, Wesson DR, Rawson RA, Compton M, Klett CJ (1995). Treatment Effectiveness Score as an outcome measure in clinical trials. NIDA Research Monograph Series #175, Medication Development for the Treatment of Cocaine Dependence: Issues of Clinical Efficacy Trials. Tai B, Chiang N, Bridge P (eds.). Rockville, MD; U.S. Department of Health and Human Services; 208-220.
Ling W, Wesson DR, Charuvastra C, Klett CJ (1996). A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Archives of General Psychiatry; 53:401-407.
McGahan PL, Griffith JA, Parante R, McLellan AT. Composite scores from the Addiction Severity Index. Washington, DC: National Institute on Drug Abuse Project DA02554 and the Veterans Administration, 1982.
McLellan, A.T., Luborsky, L., Cacciola, J., Griffith, J., Evans, F., Barr, H.L., O'Brien, C.P., 1985. New data from the Addiction Severity Index: Reliability and validity in three centers. J. Nerv. Ment. Dis. 173: 412-423.
Nath RP, Upton RA, Everhart ET, Cheung P, Shwonek P, Jones RT, Mendelson JE (1999). Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. Journal of Clinical Pharmacology; 39(6):619-623.
National Institute on Drug Abuse: Risk Behavior assessment questionnaire: National AIDS Research Project., Community Research Branch, October, 1993.
Nigam, AK, Ray R, Tripathi, BM (1993) Buprernorphine in opiate withdrawal: a comparison with clondine. J Subst. Abuse Treatment 10: 391-394.
O'Connor, P.G., Carroll, KM, Shi, JM, Schottenfeld, RS, Kosten, TR, Rounsaville, BJ (1997) Three methods of opioid detoxification in a primary care setting. Annals of Internal Medicine 127: 526-530.
Rance, M.J. and Dickens, J.N. (1978) The influence of drug-receptor kinetics on the pharmacological and pharmaco-kinetic profiles of buprenorphine. In: Characteristics and Function of Opioids (Van Ree, J.M. and Pereniums, L., eds.), pp.65-66. Elsevier/North-Holland Biomedical Press, Amsterdam.
Rosen, M.I., Wallace, E.A., McMahon, T.J., Pearsall, H.R., Woods, S.W., Price, L.H. and Kosten, T.R. (1994) Buprenorphine: duration of blockade of effects of intramuscular hydromorphone. Drug Alcohol Depend 35, 569-580.
Schuh, K.J., Johanson, C.E., 1999. Pharmacokinetic comparison of the buprenorphine sublingual liquid and tablet. Drug Alcohol Depend. 56: 55-60.
Seow, S.S., Quigley, A.J., Ilett, K.F., Dusci, L.J., Swensen, G., Harrison-Stweart, A. and Rappeport, L. (1986) Buprenorphine: a new maintenance opiate? Med J Aust 144(8), 407-11.
Strain EC, Stitzer ML, Liebson IA, Bigelow GE (1994). Comparison of buprenorphine and methadone in the treatment of opioid dependence. American Journal of Psychiatry; 151(7):1025-130.
Strain, E.C., Stitzer, 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. J. Clin. Psychopharm. 16: 58-67.

Uehlinger C, Deglon J, Livoti S, Petitjean S, Waldvogel D, Ladewig D (1998). Comparison of buprenorphine and methadone in treatment of opioid dependence. Swiss multicenter study. European Addiction Research; 4 Suppl 1:13-18.

Walsh, S.L., Preston, K.L., Bigelow, G.E., Stitzer, M.L., l995. Acute administration of buprenorphine in humans: Partial agonist and blockade effects. J. Pharmacol. Exp. Ther. 274: 361-372.

Walsh, S.L., Preston, K.L., Stitzer, M.L., Cone, E.J., Bigelow, G.E., l994. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clin. Pharmacol Ther. 55: 569-580.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473-83.

Wood WD. An attempt to validate the psychoticism scale of the Brief Symptom Inventory. Br J Med Psychol 1982; 55:367-73.

APPENDIX I: TREATMENT SETTINGS

Pacific Region Node

Betty Ford Center: The Betty Ford Center at Eisenhower is a free-standing Chemical Dependency Recovery Hospital. It opened in October of 1982 on the campus of Eisenhower Medical Center in Rancho Mirage, California. Within the hospital there is an eighty (80) bed Residential Program, an Intensive Outpatient Program with a thirty (30) patient occupancy; and a Family educational component.

The interdisciplinary, medically managed, intensive residential program provides care on a twenty-four (24) hour per day basis, seven (7) days per week, for up to six weeks, depending on patient need. The intensive outpatient program operates five (5) days per week, for four to six (4-6) weeks, again depending on the needs of the patient. The family component is a five day educational program.

The Center accepts patients dependent on alcohol and/or other mood altering chemicals, and is open to all men and women eighteen (18) years of age or older, regardless of race, creed, sex, national origin, religion or sources of payment for care.

APPENDIX II: MODEL INFORMED CONSENT FORM

(*Insert your institution's name here*)

CONSENT[1] TO PARTICIPATE IN RESEARCH

Buprenorphine/Naloxone versus Clonidine For Inpatient Opiate Detoxification

You are asked to participate in a research study conducted by [*insert names and degrees of all investigators*], from the [*insert department affiliation*] at (*name of site*). You have been asked to participate in this study because you are 15 years of age or older, you are dependent on opiates and experience symptoms of withdrawal, and are seeking treatment with a desire to discontinue opiate use. We expect approximately 360 participants nationwide and approximately 60 at this site. Your participation in this study is entirely voluntary. You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.

- **PURPOSE OF THE STUDY**

The purpose of this study is to compare the effectiveness of buprenorphine-naloxone (BUP/NX) to clonidine for short-term opiate detoxification initiated in an in-patient setting. The use of BUP/NX and clonidine for opiate detoxification is still experimental since neither of these medications has been approved by the FDA for opiate detoxification treatment. We want to determine which medication may help you stay in treatment longer, stay off opiates longer, reduce the amount of medications you need during detoxification and better relieve any withdrawal symptoms you might experience. The goal is for you to become detoxified from opiates over a 13-day period.

- **PROCEDURES**

If you volunteer to participate in this study, we would ask you to do the following things:

After you sign this informed consent, and prior to receiving medication, you will be evaluated by study staff to determine if you are eligible to continue in the study. This should take no longer than 24 hours (this is the baseline phase). You will be paid $25.00 in grocery or department store scrip for completing the baseline phase. If it is determined that you are eligible to continue with the study, you will be asked to complete the Detoxification Phase and the Follow-up Phase as described below. Your participation is expected to last no longer than 6 months.

The following schedule gives an overview of your participation in this study:

Baseline Phase (1 day)

Detoxification Phase (13 days)

---

1) This form also serves as the assent and permission form for research participants ages 15-17
Date of Preparation:
IRB #:
Date of Expiration:

Follow-up Phase (at 30 days, 90 days and 180 days)

Baseline Phase

During this phase, which will last between 5 and 24 hours, you will have a physical examination including blood pressure and heart rate measurements. Your doctor and/or study staff will ask you questions about your medical history and about any medications you may currently be taking or have taken in the past. You will be asked questions about your psychiatric and drug use histories, your current withdrawal symptoms and severity and your HIV risk status. You will also have blood drawn (about 4 tablespoons) and provide a urine sample (monitored by a temperature strip). You will have a 12-lead electrocardiograph (ECG), which is a test that measures the electrical activity of your heart by placing sensors on your chest and legs. If you are female, you will be given a pregnancy test and be asked to use an adequate method of birth control to avoid pregnancy while in this study. Examples of effective methods of birth control are oral contraceptives (birth control pills), Norplant, Depo-Provera, condoms and spermicide, cervical caps and spermicide, diaphragms and spermicide, IUDs, complete abstinence, and surgical sterilization.

The study staff will review the results of these tests, and if he/she believes that continued participation in this study may cause you harm, you will not be permitted to continue.

Once the baseline phase is completed, and if it is determined that you are eligible to continue in the study you will be randomly assigned (by chance or toss of a coin) to receive either BUP/NX or clonidine for opiate detoxification for the next 13 days of the study. You are twice as likely to receive BUP/NX as clonidine.

Detoxification Phase

BUP/NX GROUP

Buprenorphine, presently (marketed under the trade name Buprenex) is a medication currently used for the treatment of pain. It has been widely studied over the past twenty years and is expected to soon receive FDA approval for use in treatment of opiate dependence. It is not yet approved by the FDA as a treatment for opiate detoxification. *Naloxone* (marketed under the trade name Narcan) which blocks or reverses the effects of opiates, such as heroin and morphine, is generally used to treat opiate overdose and can cause opiate withdrawal symptoms in opiate addicted persons if taken intravenously (by using IV). BUP/NX is a combination of these two drugs in a 4 to 1 ratio (4 parts buprenorphine to 1 part naloxone) and is the drug that you will be taking if you are assigned to this group. BUP/NX is a sublingual (taken under the tongue) tablet that, if taken properly, is a useful treatment, which can relieve withdrawal signs and symptoms, in people who abuse opiates. However, BUP/NX, if injected, can cause you to immediately experience withdrawal symptoms, such as chills, nausea, vomiting and cramps.

On your first day of receiving BUP/NX, you will be asked to see the study physician and you will be given an opportunity to ask any questions or discuss any concerns you may have about the medication. To facilitate a comfortable transition onto the BUP/NX combination tablet, you will be asked not to use any heroin or other opiate drugs for at least 6 hours prior to receiving your first dose of BUP/NX and to be in mild withdrawal before taking your first dose. You will fill out questionnaires regarding your current physical state (withdrawal symptoms) and study personnel will ask you about the time and type of your last drug use before you are given your first dose of BUP/NX.

On day 1, you will receive 2 sublingual tablets that each contains 2 mg of buprenorphine and 0.5 mg of naloxone, for a total dose of 4 mg of buprenorphine and 1.0 mg of naloxone. An additional 2 tablets (or 4 mg of buprenorphine and 1.0 mg of naloxone) may be given to you if you have continued withdrawal signs and/or symptoms 1-2 hours after your first dose. With each dose of medication given, you will be asked to hold the tablet(s) under your tongue until they are completely dissolved.

For the remaining 13 days you will receive BUP/NX in the following amounts:

Day 2:	8.0 mg buprenorphine – 2.0 mg of naloxone
Day 3:	16.0 mg buprenorphine – 4.0 mg of naloxone
Day 4:	14.0 mg buprenorphine – 3.5 mg of naloxone
Day 5:	12.0 mg buprenorphine – 3.0 mg of naloxone
Day 6:	10.0 mg buprenorphine – 2.5 mg of naloxone
Day 7:	8.0 mg buprenorphine – 2.0 mg of naloxone
Days 8-9:	6.0 mg buprenorphine – 1.5 mg of naloxone
Days 10 - 11:	4.0 mg buprenorphine – 1.0 mg of naloxone
Days 12 - 13:	2.0 mg buprenorphine – 0.5 mg of naloxone

If for any reason, you are discharged from the inpatient service and not able to complete the 13-day detoxification on BUP/NX as an inpatient, you will be asked to continue to participate in the study as an outpatient. You will be asked to come to the site each day for your medication, to have your vital signs checked and to fill out questionnaires, just like you did as an inpatient.

CLONIDINE GROUP

Clonidine hydrochloride (marketed as Catapres) has been previously shown to be a safe and effective medication for detoxifying individuals from opiates although it is not approved by the FDA as an opiate detoxification treatment. Clonidine is non-narcotic and readily available throughout treatment programs across the United States. Clonidine is given for oral dosing (you swallow it) in 0.1mg tablets. It is also given transdermally (as a patch that you place somewhere on your upper body, so that the medication is absorbed through your skin), which gives you 0.1mg per day for one week. During this study you will be given both types of clonidine on some days. If you are assigned to this group you will receive clonidine on the following schedule:

On your first day of receiving clonidine, you will be asked to see the study physician and you will be given an opportunity to ask any questions or discuss any concerns you may have about the medication. Your vital signs will be taken and you will be given a test dose of 0.05 mg of clonidine if you weigh less than 110 pounds or 0.10 mg if you weigh more than 110 pounds but less than 200 pounds, and 0.2 mg if you weigh more than 200 pounds. One hour later, the study staff will again check your heart rate and blood pressure. If it is determined that you are not having any adverse reaction to the medication, then you will be given another 0.10 mg tablet (by mouth) every 4 to 6 hours for the remainder of the first day and you will have between 1 and 6 patches of clonidine placed on your upper body (the exact number is determined by your weight).

For the remaining 13 days you will receive clonidine in the following amounts:
Day 2: You may continue to receive oral clonidine every 4 to 6 hours as needed.
Days 3 to 6: You will stop taking the oral clonidine tablets and continue to wear the patch(es) or, as determined by study staff, you may keep taking oral clonidine tablets and stop wearing the patch(es).
Day 7: Your patch(es) will be replaced, although you may be asked to wear fewer patch(es) than you had for the first 7 days.
Days 8 to 13: Any oral clonidine tablets you are taking will be stopped or any patch(es) you are wearing will be removed and your vital signs will be monitored.
Day 14: Your vital signs will be monitored.

If at any time or on any day the patch(es) fall off, you are asked to let the staff know and these will be replaced if it is safe to do so.

If you are unable, for any reason, to tolerate or wear the clonidine patch(es), you will be given oral clonidine for the remainder of the study.

If for any reason, you are discharged from the inpatient service and not able to complete the 13-day detoxification on clonidine as an inpatient, you will be asked to continue to participate in the study as an outpatient. You will be asked to come to the site each day for your medication, to have your vital signs checked and to fill out questionnaires just like you did as an inpatient.

<u>Both Groups</u>

Each day, study staff will record any adverse (negative) events and the use of any other medications taken since your last dose of study medication. You will be asked to fill out questionnaires each study visit asking about your craving, your withdrawal symptoms and how you feel. Urine samples (monitored by a temperature strip), to test for drugs of abuse, will be collected on days 3 or 4, 7 or 8, 10 or 11, and 13 or 14 (a total of 4 tests). On your first day of treatment, you will be asked to stay at the clinic for several hours after you take your medication so that the study staff can monitor how you are doing. Also, on your first, and possibly second day of treatment, the study staff may require that someone drive you home.

During the entire 13 days of the detoxification phase you may ask the study staff to provide you, if necessary, with medications that may help you relieve anxiety or restlessness, bone pain and aches, nausea, diarrhea and insomnia (inability to sleep). The study allows certain medications to be given to you for these symptoms. The study doctor will decide which of the approved medications you will be given. You will be asked not to take any other medications, other than those prescribed or given to you by the study staff, while in this study.

You will be asked to participate in whatever additional, standard substance abuse treatment services (counseling, groups, etc) that are provided at this site, while you are a participant in this study. *(Please note: Your IRB's may require you to list the exact treatments you will provide at your site that are not part of the research study)* You will also be given a self-help handbook to help you understand what you are experiencing when detoxifying from opiates.

If for any reason you are unable to tolerate or take the medication in the group to which you are randomly (by chance or toss of a coin) assigned, you will not be switched to the other medication, but will be asked to continue to participate in the standard treatment, *as described above that is (if you have described the standard treatment above, otherwise you may have to list the procedures here)* provided at this site or you will be referred for alternate treatment.

Follow-up Phase

Once you complete the treatment phase of the study, you will enter the follow-up phase. You will be asked to continue the standard care, as recommended by the study staff at this site. For the purposes of this study, you will be asked to return on the 30th day, the 90th day and the 180th day after you start the study. At each of these visits you will be asked information about your drug use, your general health, cravings for drugs, withdrawal symptoms, treatment satisfaction and you will be asked to provide a monitored (temperature strip) urine sample for drugs of abuse. Adverse events and other medication use will also be recorded at the 30-day follow-up. A quality of life questionnaire will also be completed at the 180-day follow-up. At each follow-up visit you will be asked to report any health problems such as hospitalizations you may have had.

For each of the follow up visits that you complete, you will be paid $25.00 in grocery or department store scrip. If you complete all three follow-ups you will be paid an additional $25.00 in scrip.

- **POTENTIAL RISKS AND DISCOMFORTS**

BUP/NX GROUP

Continued use of heroin increases the risk of opiate dependence and death. Combining BUP/NX with alcohol or other drugs may be hazardous. Taking BUP/NX within 24 hours of using Methadone or LAAM may cause you to experience withdrawal. A number of deaths have been reported among people who abuse buprenorphine in combination with benzodiazepines, such as Valium or sleeping pills. You are therefore asked not to drink alcohol-containing beverages or take other drugs including benzodiazepines, like Valium or sleeping pills, or narcotic pain relievers, while participating in this study.
THE STUDY MEDICATION MAY IMPAIR MENTAL OR PHYSICAL ABILITIES INVOLVED IN SUCH ACTIVITIES AS DRIVING OR OPERATING MACHINERY AND YOU ARE WARNED TO DO SO WITH CAUTION.

We have found that switching from most opiates (like heroin) to BUP/NX is usually easier if your first dose is no sooner than 6 hours after you last used opiates. If you have used longer acting opiates, like methadone or LAAM, switching to BUP/NX is easier if your first dose is no sooner than 24 hours after you last used. A shorter time between your first buprenorphine dose and any opiate use may result in greater discomfort or opiate withdrawal symptoms such as vomiting and/or nausea.

The effect of combining the BUP/NX with alcohol, or other drugs, is not known. There is a potential risk of increased respiratory depression when benzodiazepines are given together with buprenorphine. In France, there have been reports that several people have died while injecting buprenorphine and benzodiazepines (for example, Valium, diazepam, oxazepam, flunitrazepam (not currently available in the United States), etc.). It appears that these people were injecting higher than normally prescribed doses of benzodiazepines. Although there has been no direct adverse relationship established between the use of buprenorphine and benzodiazepines, you are asked to avoid taking any illicit drugs (especially benzodiazepines) or narcotic pain relievers, and to abstain from drinking alcoholic beverages while participating in this study.

Because BUP/NX must be dissolved under your tongue, it may cause some mild irritation or leave a bad taste in your mouth. As with any medication, there is also the possibility of an allergic reaction. However, since you will be taking the BUP/NX at the site, the study physician and other staff will be available to see how you are reacting to it.

Side effects from BUP/NX may also include headache, constipation, difficulty sleeping, weakness, sleepiness, nausea, vomiting, sweating, and dizziness.

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

Buprenorphine itself may cause physical dependence. It can also cause intoxication and mild respiratory depression. If you stop taking it abruptly, you may experience some opiate withdrawal symptoms, including diarrhea.

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

You may be more sensitive to the effects of opiates when you stop taking the BUP/NX tablet.

The risks of BUP/NX in pregnancy are not known. Women must have a pregnancy test done before the first dose is given, and must agree to use an adequate method of contraception to avoid pregnancy while on BUP/NX.

Clonidine Group

The most common (about 10 percent of people taking the drug) side effects of clonidine (oral or patch) include dry mouth, drowsiness, dizziness, constipation and sedation. **Therefore, if you engage in potentially hazardous activities, such as operating machinery or driving, you are warned to do so with caution.**

Clonidine (oral or patch) may also affect your blood pressure. Generally, clonidine will lower your blood pressure and therefore, when getting up from a sitting or lying position may cause temporary dizziness. You are advised to get up slowly from a lying or sitting position in order to minimize this effect. Drinking adequate or extra amounts of fluids may also help relieve this effect.

In addition, the sedative effect may be increased by the use of alcohol, barbiturates, or other sedating drugs. You are asked to avoid taking any illicit drugs or narcotic pain relievers, barbiturates or other sedatives and to abstain from drinking alcoholic beverages while participating in this study.

Abruptly stopping taking clonidine (oral or patch) may cause your blood pressure to go up and you are cautioned not to discontinue taking the medication without the study physician's advice.

The risks of clonidine (oral or patch) in pregnancy are not known. Women must have a pregnancy test done before the first dose is given, and must agree to use an adequate method of contraception to avoid pregnancy while on clonidine.

The most common side effect of the clonidine patch is a skin rash or irritation. You are asked to notify the study physician promptly if you notice any irritation in the area of the skin where the patch is placed. You may need to have the patch removed if this occurs.

Used (removed) clonidine patches still contain a substantial amount of the drug. Therefore, they must be disposed of properly and kept out of the reach of children. Each used patch should be folded in half with the adhesive sides together and discarded away from children's reach.

BOTH GROUPS

Some discomfort may be associated with the drawing of blood samples. Approximately 60 cc (equivalent to 4 tablespoons or 2 ounces) of blood will be taken during the study. There is a minor risk of bleeding, bruising, or infection at the site of the needle insertion.

You may also experience some inconvenience or you may feel some embarrassment related to providing urine samples and to questioning about your personal habits, lifestyle, and drug or alcohol use, and/or you may experience unanticipated encounters with friends or associates while in the treatment program and/or study.

Loss of confidentiality (people unintentionally finding out personal information about you) is another risk of participating in this study.

Participation in this study may involve risks that are currently unforeseeable.

- **ANTICIPATED BENEFITS TO SUBJECTS**

Based on experience with both Clonidine and BUP/NX in people who are opiate dependent, researchers believe it may be of benefit to you. Of course, because individuals respond differently to treatment, no one can know in advance if it will be helpful in your particular case. The potential benefits may include helping you to stop your use of opiates. The evaluations you receive as part of the study could disclose a medical condition that you might not have been aware of previously.

- **ANTICIPATED BENEFITS TO SOCIETY**

Potential benefits to society from your participation in this study include greater knowledge about opiate dependence treatment, in general, and may help determine how well BUP/NX works, in comparison to Clonidine, in the treatment of opiate dependence.

- **ALTERNATIVES TO PARTICIPATION**

If you decide not to participate in this study, you will be asked to continue in the standard treatment provided at this site. If you choose not to remain at this site, referrals to standard drug treatment programs and detoxification units will be made. Standard treatment options for opiate dependence include methadone and/or LAAM maintenance, naltrexone, or detoxification with methadone, clonidine, and other supplemental medications. Behavioral (non-medication) treatments such as Narcotic's Anonymous, counseling, and other group therapies are also available and referrals will be provided to you.

- **PAYMENT FOR PARTICIPATION**

You will be paid $25.00 in grocery or department store scrip (gift certificates) for completing the baseline phase and for each of the follow-up visits that you complete (at 30, 90 and 180 days) after you terminate or complete the study. If you complete all three follow-ups you will receive an additional $25.00 in scrip. The total payment you may receive from participation in this study is $125.00 in scrip.

- **FINANCIAL OBLIGATION**

Neither you nor your insurance company or any other third party payer will be billed for any drugs, blood or urine tests, EKG test, or any other procedure that is part of this research study. You or your insurance company will, however, be responsible for payment for any treatment or other services received at this site that are not part of the research study.

It is possible that your insurance will not pay for all of the treatments and tests you will receive if you participate in the research. That is because many insurance companies, HMOs, and health benefits plans do not cover experimental treatments. If that happens, you will need to work out payment arrangements with *(insert your facility name here).*

- **EMERGENCY CARE AND COMPENSATION FOR INJURY**

You participate in this research at your own risk. If you are injured as a direct result of research procedures <u>not done primarily for your own benefit</u>, you will receive treatment at no cost. (*Insert your facility name here and any investigator's names and degrees*) does not provide any other form of compensation for injury. You are not waiving any legal claims, rights or remedies because of your participation in this research study.

Should you believe that you have been injured by taking part in this research you should contact one of these researchers right away: (list all of the investigator's names, degrees, phone numbers and addresses here). In case of an emergency in which you are unable to reach (list investigator's names here), please call 911 or go to the nearest emergency room.

- **PRIVACY AND CONFIDENTIALITY**

<u>This study is part of a larger national project in which data will be gathered. The research team will know that you are participating in this study, and investigators conducting the national study may have access to you records. All personal information will be coded and stored in a locked cabinet to protect your confidentiality. The results of this study may be published, but your name or identity will not be revealed in any publications.</u>

To keep information about you confidential, we have obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). This Certificate does not imply approval or disapproval of the project by the Secretary, DHHS. The Confidentiality Certificate will protect the investigators from being forced, even under a court order or subpoena, to release any research data in which you are identified. This protection is not absolute, however. It does not apply to disclosure of medical information in cases of medical necessity, and the Certificate does not protect us from reporting child abuse under State law. Under *(insert your state name here or delete sentence if this does not apply in your state)* law the privilege of confidentiality does not include information about sexual or physical abuse of a child or elder abuse. If a member of the research team has or is given such information, she or he is required to report it to authorities.

Also, because the National Institute on Drug Abuse (NIDA), regulated by the Food and Drug Administration (FDA), sponsors this research staff from NIDA, FDA, and other DHHS agencies may review records that identify you. The (*insert the name of your state Research Advisory Panel if one exists, as well as the name of the IRB this form is submitted to here)* also have access to your records. However, they are bound by rules of confidentiality not to reveal your identity to others.

Other times when information about you may be released without your permission are:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care);
- if required by law (*insert the name of your state here)* law requires that we report suspected cases of child abuse and elder abuse to the proper authorities);
- if we suspect that you are a danger to yourself or others, we may also give this information to the proper authorities. In addition, we may report certain cases of domestic violence.

-we are required to report certain communicable diseases to the county board of health, when we are the first to learn that someone has one of the diseases involved. Examples of these diseases include hepatitis B, hepatitis C, and measles.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

- **PARTICIPATION AND WITHDRAWAL**

Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with *(insert your facility name here*), or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at *(insert your facility name here*).

- **WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR**

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you experience any of the following side effects: your blood pressure becomes too low, you have an allergic response to the study medication you are on, or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigator, [*insert name*], will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

- **CONSEQUENCES OF WITHDRAWAL**

Should you be withdrawn from or drop out of the study, you will not be re-admitted. If you decide to withdraw from the study or are asked to discontinue for any reason, it will not prejudice your care at (*insert name of institution here*). If you decide not to participate or are withdrawn from the study and you also decide to leave the (*insert name of institution here*) you will then be given information about other standard treatment programs for opiate dependence in your area.

- **NEW FINDINGS**

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, which might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

- **IDENTIFICATION OF INVESTIGATORS**

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact [i*dentify all personnel involved in the research as listed in the following subheadings: Principal Investigator, Co-Investigator(s), Participating Personnel. Include the daytime telephone numbers and addresses for all listed individuals, including a night/emergency telephone number.*]

- **RIGHTS OF RESEARCH SUBJECTS**

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

SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Subject's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

_____
Name of Subject

_____
Name of Legal Representative (if applicable)

_____ _____
Signature of Subject or Legal Representative Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject or his/her legal representative, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____
Name of Investigator

_____ _____
Signature of Investigator Date (must be the same as subject's)

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

My signature as witness certified that the subject or his/her legal representative signed this consent form in my presence as his/her voluntary act and deed.

_____
Name of Witness

_____ _____
Signature of Witness Date (must be the same as subject's)

Agreement for Minor to Participate (if applicable)

_____
Name of Participant

_____ _____
Signature of Parent or legal guardian Date

_____
Relationship to participant

APPENDIX III: Proposed QA Monitoring Guidelines and Check List

On-site monitoring of clinical research is conducted to assess the progress of a trial and the accuracy of the data collected. It is the QA staffs' responsibility to monitor both the medical records for study participants and the CRFs for consistency, accuracy, and completeness for adherence to protocol requirements and FDA regulations and guidelines (21 CFR 312, subparts D & E).

The essential QA documents within the Regulatory Study Binder are denoted with an asterisk* <u>Regulatory will monitor all other items within the study binders</u>:

Regulatory Binder Sections:

***Protocol**
Supplemental Protocol
***Consent Forms**
***Case Report Forms**
1572
Curriculum Vitae
Investigator Brochure
***Patient Log**
***Serious Adverse Events**
IRB Correspondence
Regulatory Documents
***Investigational Product Accountability**
Lab Certification
DEA Certification
Signature Logs
***Visitor Log**
Telephone Communications Log
Site-Sponsor Correspondence
***Patient Study Files**
Other Correspondence

PROTOCOL

- Obtain copies of protocol (Regulatory Study binder) and look for correct version and IRB approval dates.
- Establish if enrolled participants meet the proper inclusion/exclusion criteria.
    1. Enrollment criterion:
        a) Information provided on CRF forms - Medical History Forms, Concomitant Medication Forms, Prior Medication Forms, Birth Control/Pregnancy Assessments, etc.
    2. Laboratory Information:
        a) Results – values within correct parameters for enrollment and continuation.
        b) Time periods for testing correctly adhered to (e.g., urines).

CONSENT FORMS

- Look for correct version and IRB approval dates with IRB approval date-stamp.
- Ensure correct informed consent is located within the participant record.

CASE REPORT FORMS

- Indicate where they are located (at study site) in the Regulatory binder.

ADVERSE EVENTS

- These must be properly documented within the CRFs and individual patient charts and indicating the severity (AE or SAE) and also the adequacy of report dates.
- These must also be located in the Regulatory study binder (SAEs).

INVESTIGATIONAL PRODUCT ACCOUNTABILITY (STUDY MEDICATION)

- Study medication receipt forms – Need to be completed and signed by investigator and staff.
- Security for controlled substances - Where and how the medication is being stored.
- Study medication dispensing and return logs - Ensure that investigational products are labeled and dispensed properly according to protocol.

PATIENT LOG

- Adequate documentation log of existence/participation of patients.
- Must be consistent with information (screening#, randomization# patient name code and consent date) within the CRFs and in the individual patient records.

VISITOR LOG

- Sign and date the log in this section to indicate and document the QA visit:
    a) The date of the visit.
    b) Name of the individual who conducted the visit.
    c) A statement of the findings, conclusions and any actions taken to correct deficiencies noted during the visit.
    d) Site director or study coordinator must sign log.

  Please insert a QA monitoring/findings log within this section of the Regulatory Binder

Patient Study Files (Regulatory Binder must indicate where these are located at site)

- The following must be included:
    a) Correct version of the approved informed consent
    b) Medical history obtained – This chart must have proper history to ascertain that the inclusion/exclusion criteria of the protocol are adhered to.
    c) Copies of completed CRFs
    d) SAE information

CHECK LIST

PROTOCOL _____ **P.I**. _____

SITE _____ **AUDITOR** _____

PATIENT I.D. NO. _____

PHASE	ITEM	YES	NO	NA	DATE
Screening	1. Current version of signed consent.				
	2. Signature, date & time prior to enrollment.				
	3. All pages initialed?				
	4. Copy of Informed Consent sent to Central Repository				
Eligibility	5. All pre-enrollment tests documented.				
	6. Lab criteria met.				
	7. Inclusion criterion met.				
	8. Childbearing/lactating restrictions met.				
	9. Patient ruled out for exclusion criteria.				
	10. Waiver/exceptions documented.				
	11. Time Event Sheet completed.				
Randomization	12. Patient randomized according to protocol.				
	13. Time Event Sheet completed.				
Medications	14. Study med dispensed properly (time, duration, route, etc.)				
	15. Time-Event Sheet complete				
	16. Concomitant Meds documented.				
	17. Prescription/med orders in chart.				
	18. Any protocol-prohibited meds given.				
	19. Any protocol discrepancies reported to Site Coordinator, Site Director and/or Node PI.				
AE Reporting	20. Any SAEs				

	21 If yes, were they reported according to requirements (NIDA, FDA, IRB, Etc.)				
Assessment Battery	22. Was examination or instrument administered according to schedule? Note any discrepancies.				
	23. Time Event Sheet completed.				
	24. Depending on how data is collected at each site, either QA will examine data forms on site or it will be done at Node's Data Management Center.				
	25. Missing, incomplete, or out-of-range value will be identified. The RA or Study Coordinator will be notified as soon as possible about potential errors. The RA or Coordinator will respond as soon as possible and resubmit corrected form. QA or DMC will verify that corrections have been made.				
	26. If consistent or systematic errors or an excessive numbers of errors are made on a given instrument, QA or DMC will notify Study Coordinator or Site Director.				
Endpoints	27. Missed visits documented and contact attempts noted.				
	28. If patient has reached any protocol defined endpoints, documentation and follow-up.				
	29. Time-Event Sheet complete.				

APPENDIX IV: Instructions For Evaluating and Reporting Adverse Events

A. GENERAL INSTRUCTIONS

1. The Adverse Events (AE) form must be completed at each study visit.

2. If no AEs occur, check the box marked NONE and sign and date form.

3. Enter only AEs that occur after the patient begins taking the investigational agent.

4. Enter only **one** AE per line.

5. Record the patient's description of the event, including all signs/symptoms reported.

6. Report the severity of the event according to the grading scale below.

7. Report the relatedness of the event to the study medication administration (see section C. below for guidance in determining relatedness).

B. DEFINITIONS – SEVERITY OF EVENTS

1 = Mild: Awareness of symptom, but easily tolerated.

2 = Moderate: Discomfort enough to cause interference with usual activity.

3 = Severe: Incapacitating with inability to work or do usual activity.

4 = Life threatening: At immediate risk of death.

C. DEFINITIONS – RELATEDNESS OF EVENTS

Study physician must review the information and offer an educated opinion about the relatedness of the event to the study drug. Do not use 'UNKNOWN' unless there is absolutely no information available upon which to base an opinion. Do not leave blank.

Use codes provided:

1 = **Definitely** – The adverse event:
- a) Follows a reasonable temporal sequence from drug administration.
- b) Abates upon discontinuation of the drug (de-challenge).
- c) Is confirmed by reappearance of the reaction of repeat exposure (re-challenge).

2 = **Probably** – The adverse event:
- a) Follows a reasonable temporal sequence from drug administration.

b) Abates upon discontinuation of the drug (de-challenge).
c) Cannot be reasonably explained by the known characteristics of the patient's clinical state.

3 = **Possibly** – The adverse event:
a) Follows a reasonable temporal sequence from drug administration.
b) Could have produced by the patient's clinical state or by other modes of therapy administered to the patient.

4 = **Remotely** – The temporal association between the adverse event and the drug is such that the drug is not likely to have had any reasonable association with the observed event. Temporal association is defined as an association between a drug and the observed reaction or event such that the drug was present prior to the reaction or event as defined by history or drug blood level.

5 = **Definitely not** – The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

9 = **Unknown**

APPENDIX V: Clonidine References

Ginzburg, H.M. (1983) Chapter 6. Use Of Clonidine Or Lofexidine To Detoxify From Methadone Maintenance Or Other Opioid Dependencies. J.R. Cooper, F. Altman, B.S. Brown and D. Czechowicz (Eds.), In: Treatment Research Monograph Series, Research on the Treatment of Narcotic Addiction, State of the Art; DHHS Pub # (ADM) 83-1281, pp. 174-224.

Gold, M.S. (1993) Opiate Addiction and the Locus Coeruleus: The Clinical Utility of Clonidine, Naltrexone, Methadone, and Buprenorphine. In: Recent Advances in Addictive Disorders, Vol. 16(1), 61-73.

Kasvikis, Y., Bradley, B., Powell, J., Marks, I., and Gray, J.A. (1991) Postwithdrawal Exposure Treatment to Prevent Relapse in Opiate Addicts: A Pilot Study. In: The International Journal of the Addictions, Vol. 26(11), 1187-1195.

Roehrich, H., Gold, M.S. (1987) Clonidine. In: Advances In Alcohol and Substance Abuse, Vol. 7(1): 1-15.

Spencer, L., Gregory, M. (1989) Clonidine Transdermal Patches for Use in Outpatient Opiate Withdrawal. In: Journal of Substance Abuse Treatment, Vol. 6, pp. 113-117.

Wesson, D.R. (Ed.) Chapter 3. Clinical Detoxification Protocols. In: Detoxification from Alcohol and Other Drugs. Treatment Improvement Protocol (TIP) Series 19. pp. 15-35.

SUMMARY OF CHANGES/CORRECTIONS TO
STUDY #: NIDA-CTN-0001 PROTOCOL

DATE OF CHANGE/CORRECTION	DESCRIPTION OF CHANGE/CORRECTION	PAGE NUMBER
10/16/00	Time and Events Schedule was replaced with a corrected schedule.	15
10/16/00	SAE reporting contact information was modified to replace Ming Shih, Ph.D. with Ann Anderson, M.D. as the SAE reporting contact at NIDA.	30
11/27/00	Line 4 of section 11.5.1 was modified to replace "Study personnel at each study site …" with "Physicians or study coordinators at each study site …"	17