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BUPRENORPHINE/NALOXONE-FACILITATED REHABILITATION FOR OPIOID DEPENDENT ADOLESCENTS/YOUNG ADULTS

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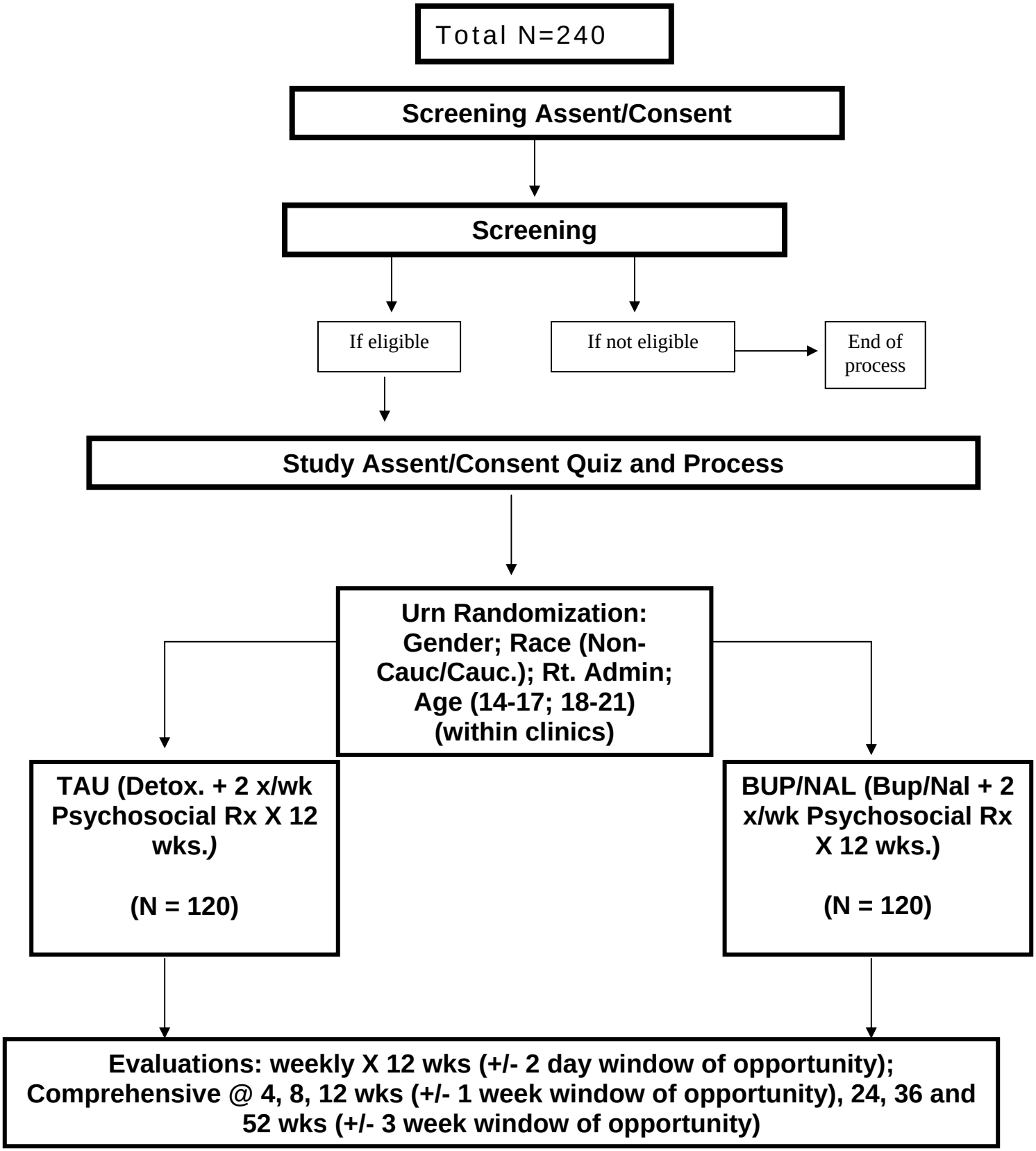
1.0 ABBREVIATIONS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASAP	University of New Mexico Hospitals Addiction and Substance Abuse Programs
AST	aspartate aminotransferase
BUN	blood urea nitrogen
BUP	buprenorphine
BUP/NAL	buprenorphine/naloxone
CBC	complete blood count
CRF	case report form
CTN	NIDA Clinical Trials Network
CCTN	Center for Clinical Trials Network
CTP	community treatment programs
DAP	Duke Addictions Program
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic And Statistical Manual Of Mental Disorders: Fourth Edition
ECG	electrocardiogram
FDA	Food and Drug Administration
GGT	gamma glutamyltranspeptidase
HIV	human immunodeficiency virus
IND	Investigational New Drug
IV	intravenous
IRB	Institutional Review Board
LDH	lactic dehydrogenase
LFT	liver function test
Mg	milligram
NIDA	National Institute on Drug Abuse
NTP	narcotic treatment program
NAL	naloxone
RBS	Risk Behavior Survey
SAE	serious adverse event
SDSS	Substance Dependence Severity Scale
TAU	treatment as usual
VA	Department of Veterans Affairs
YASR	Young Adult Self-Report
YSR	Youth Self Report

2.0 STUDY SCHEMA



3.0 SYNOPSIS

STUDY OBJECTIVES: The aim of this study is to determine if a 12-week course of outpatient buprenorphine/naloxone (Bup/Nal) plus psychosocial treatment results in fewer opioid positive urine tests at 3 monthly evaluation points among opioid dependent adolescents and young adults (ages 14-21) than the usual treatment, which is detoxification plus psychosocial treatment alone. Secondary objectives are to determine if Bup/Nal is associated with longer time to early termination from outpatient psychosocial treatment, less opioid use by self-report, less HIV risk, less non-opioid substance use, better psychosocial functioning, less delinquency, and fewer total problem behaviors during the first 12-week treatment period. The study will also determine if improved outcomes in the Bup/Nal condition are maintained at 24, 36 and 52-week follow-ups.

STUDY DESIGN: After obtaining the appropriate informed assents/consents and completion of screening and baseline measures, 240 persons aged 14-21 seeking treatment for opioid dependence will be randomized 1:1 within six programs located in five Nodes (Delaware Valley, Mid-Atlantic, North Carolina, Southwest, Northern New England) according to an urn schedule stratified on gender, race (Non-Cauc/Cauc), route of administration (injecting opiates/non-injecting opiates), and age (14-17/18-21). Study conditions will be a 12-week course of Bup/Nal combined with 2-times/week psychosocial treatment (BUP/NAL), or detoxification and 2-times/week psychosocial treatments alone (treatment as usual; TAU). Individual and Group Drug Counseling will be the main form of psychosocial treatment provided. Prior to beginning the study, manual-guided training in drug counseling will be provided to clinical staff. Psychosocial treatment may be reduced to once/week or less during months 3-12 if there has been a favorable response (cessation of opioid use; improved adjustment), and depending on individual subject needs.

Subjects in the BUP/NAL condition will receive Bup/Nal in a relatively flexible dosing schedule as determined by a clinical assessment that includes an induction phase of approximately 4 weeks, a stabilization phase of about 4 weeks and a slow dose taper during the last three weeksthat will finish by the end of the 12 week dosing period on day 84. Medication will be administered under observation on a 5-7 day per week schedule. The target stabilization dose will be 12-18 mg Bup/Nal per day with an upper limit of 24 mg/day for the BUP/NAL subjects. Doses will be adjusted or stopped in the event of adverse side effects. TAU subjects will be detoxified with Bup/Nal over the first 7-14 days as determined by clinical assessment in outpatient settings; subjects receiving inpatient detoxification will not be eligible.

After screening is completed, more comprehensive assessments will be done at baseline and at weeks 4, 8, 12, 24, 36 and 52. Assessments at weeks 4, 8, and 12 will have a +/- 1-week window of opportunity, and assessments at weeks 24, 36 and 52 will have a +/- 3-week window of opportunity. They will include a medical and psychiatric history; physical exam; medical assessments (ECG, urine analysis, blood tests), urine drug screens; self-reports of opioid and other drug use; adverse events; alcohol breath test; HIV risk behavior; ratings of overall substance use and adjustment including delinquent/antisocial behavior; information that will allow determination of treatment costs; and non-study treatments received including self-help group participation. Weekly assessments will be obtained during the first 12 weeks, with a -/+ 2-day window of opportunity. They will consist of adverse events; self-reports of times used

opioids and other drugs; urine drug screen and alcohol breath test; appointments kept and urine pregnancy tests for subjects receiving Bup/Nal along with records of its use. A measure of the subject/therapist relationship will be taken at the 4-week assessment and two other measures of treatment process will be taken at baseline and week 12. Timeline follow-back will be used to obtain data on opioid and other drug use, and on adverse events in the case of missed appointments.

A wide range of contact information will be obtained at baseline in order to locate subjects and achieve maximum compliance at the 4, 8, 12, 24, 36 and 52-week follow-ups. The extreme importance of getting follow-up evaluations will be communicated to investigators and staff at the collaborating programs. In addition, subjects will be paid in vouchers to exchange for goods or services upon completion of each assessment. Vouchers will be worth $10 for completing the screening and baseline assessments; $5 for each weekly assessment; $75 for completing each of the 4, 8, 12, 24, 36 and 52 week assessments; and a $75 bonus for completion of all the 4, 8, 12, 24, 36 and 52 week assessments. The bonus voucher will not be offered at the sites of the Southwest Node (ASAP and Ayundantes). Payments will not be made for keeping psychosocial treatment appointments, only for completing the assessments.

The main analyses will focus on outcomes during the first 12 weeks, with follow-ups at 24, 36 and 52 weeks. Hypotheses are that BUP/NAL subjects will have better outcomes on all measures at the 4, 8 and 12 week assessments, and that these differences will be maintained at each of the follow-up points.

STUDY POPULATION**:** Males and females 14-21 years of age who are seeking outpatient treatment, meet DSM-IV criteria for current opioid dependence with physiologic features, and who have none of the study exclusion features.

ELIGIBILITY CRITERIA**:** Subjects must meet DSM-IV-TR criteria for opioid dependence with physiologic features and provide a urine test that is positive for opiates at baseline or after being given 3 additional tries within two weeks of initial screening, and be free of serious medical and psychiatric disorders that in the opinion of the treating physician or program staff might make participation hazardous or impair their ability to provide informed consent. Other exclusions include current alcohol dependence; current abuse or dependence on benzodiazepines or other CNS depressants; a history of overdose involving benzodiazepines or other sedatives within the last 6 months; inability to provide a urine test that is negative for methadone and benzodiazepines during screening even after three repeat tries over a period of two weeks from the time of screening; current use of LAAM; ECG abnormalities that might make participation hazardous; a treatment plan that involves residential or inpatient care within the next 3 months; probability that treatment and/or follow-up appointments will be missed due to impending incarceration or plans to move; pregnancy; lactating; unwillingness to use effective birth control (females only); known sensitivity to buprenorphine; if aged 14-17, parental/guardian consent not obtained; and if 14-17, have a parent/guardian who is mentally impaired so that informed consent cannot be obtained, or is abusing substances to such a degree that it is likely to interfere with the subject's participation in therapy.

STUDY INTERVENTIONS: Bup/Nal will be provided in two dose forms: 2-mg Bup/0.5 mg Nal, and 8-mg Bup/2-mg Nal, by Reckitt Benckiser via NIDA. The mono Bup 0.4 mg product will also be provided and is to be used as necessary at the end of a dose taper. Subjects assigned to BUP/NAL will be stabilized, briefly maintained and then slowly tapered during the last three weeks of the 12-week medication period according to suggested dosing guidelines. Subjects assigned to TAU will be detoxified using Bup/Nal in outpatient settings according to suggested dosing guidelines. In either treatment condition, Bup/Nal will be stopped if the subject misses 3 consecutive days. Medication will not be restarted if the subject is receiving outpatient detoxification in the TAU condition; medication can be restarted if the subject is in the BUP/NAL condition and returns within 7 days. Participants who are being restarted will be given one half the previous dose, observed for 1.5 hours and if the restart dose is well tolerated, he/she will receive a portion or the remainder of the last previous dose as determined by physician judgment at the site. Subjects in the TAU or BUP/NAL groups who have medication stopped will be encouraged to continue with psychosocial treatment. Subjects in either condition who are judged by treatment staff to be not improving (this would include active homicidal, suicidal ideation and/or serious medical or psychiatric conditions) will be referred to another treatment as clinically appropriate and counted as early study terminators, however they will be asked to continue to be contacted for assessments at each follow-up point unless they have requested otherwise.

Subjects will be introduced to their primary counselor at the time they are randomized. Psychosocial treatment will consist of one individual and one group session/week for the first 12 weeks with less frequent appointments in the following weeks/months depending on treatment response and individual subject needs. Individual and group drug counseling will be a modified version of those described in the Individual and Group Drug Counseling Manuals that are available on the NIDA web site. Each is 12-step oriented and similar to the treatments currently used in the collaborating programs. The individual and group counseling manuals have been modified for opioid dependence (available from Mercer & Woody). Each program encourages family sessions that are mainly educational; family treatment services are usually limited to support groups or crisis intervention. Educational materials about opioid dependence and Bup/Nal will be provided in a brochure prepared by NIDA. These materials will be given to all subjects and to the parents/guardians of all subjects who are under 18 and (with the subject's permission) to the parents/guardians of those who are 18-21. Sites will encourage all subjects to attend age-appropriate self-help groups. Records will be kept of attendance at self-help groups, and of attendance of parents/guardians at educational sessions, support groups, therapy sessions and technician visits.

DURATION/SUBJECT FLOW: It is estimated that 2-4 subjects will be enrolled per week across the six sites. Following training of staff in the protocol, use of Bup/Nal, therapy methods and other introductory procedures, the estimated time to enroll 240 subjects is 2.5 years. The entire study, including all follow-up evaluations, will take approximately 4 years to complete if recruitment proceeds at the level of 2-4/week across all nodes.

HUMAN SUBJECTS/SAFETY: Subjects who qualify will be given a brief description of the study and asked to provide assent/informed consent to be screened. Those who qualify based on the screening evaluations will be given a thorough explanation of the study and asked to sign a

more detailed informed consent/assent before medication is dispensed. Each subject will be required to pass a quiz that tests his/her understanding of the protocol prior to study entry. A 90% score will be required to pass and those who fail will be given two chances to retake the exam. Failure to pass on the third occasion will make the subject ineligible to participate.

The signed assent of the subject and consent of a parent or the legal guardian will be required for those 14-17. In the case of subjects whose parents are separated or divorced, parental consent will be required for the parent who has legal custody; if custody is shared, consent will be required from one parent, preferably the one with whom the subject spends the most time. Each parent/guardian who signs the consent will also be required to pass the quiz. Participation of the parent or guardian(s) of subject's aged 18 –21 will be encouraged, but they will be informed of the study only with the subject's permission. All participants will be encouraged to ask questions about any aspect of the study at any time.

Screening assessment will include a medical history and physical examination including vital signs and weight, laboratory studies including liver function, testing for hepatitis B (hepatitis B surface antigen, antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen) and hepatitis C (antibody to hepatitis C core antigen), an ECG, and questions about psychiatric medications and treatment received during the past 30 days. Subjects who have an abnormal ECG that might make participation hazardous will be excluded. Examples of ECG abnormalities that would disqualify a subject from participation unless reviewed by a cardiologist and approved by a site physician are: prolongation of the PR interval; a QRS that is wider than normal for the subject's age; a QTc interval that is longer than 450 ms; or an arrhythmia. Subjects who have any single liver enzyme that is more than five times the top limit of normal (as defined by the lab doing the testing) will be excluded as will those who give a history of using benzodiazepines 15 days or more in the last month, as well as those who are unable to provide a urine test that is negative for benzodiazepine and methadone even after three tries within two weeks following screening, or who have overdosed on benzodiazepines or sedatives during the last 6 months. Subjects who test positive for hepatitis BSAg or hepatitis C will be referred to their primary care provider or a hepatologist but not excluded from participation unless a liver test result is > 5 times the top limit of normal. Local site clinicians should refer any individuals for hepatitis B vaccine if indicated based on screening results. Subjects who fail screening may be re-screened after 28 days from the time screening began if the failure is judged by the Site P.I. to reflect a transient condition that may resolve.

The ECG will be repeated at 4 and 12 weeks for all subjects. Subjects in the BUP/NAL condition who develop clinically significant ECG abnormalities (such as those listed above) at the four week evaluation will have the medication slowly tapered unless continuation of medication is judged appropriate by a study physician at the site after consultation with a cardiologist. If a dose taper, there will be a repeat ECG at the end of the taper followed by referral to a primary care provider or cardiologist. Liver enzymes will be repeated every 4 weeks for the first 12 weeks. Subjects who have a single liver enzyme that increases to more than five times the top limit of normal will be referred to their primary care provider or a hepatologist for evaluation. The baseline medical evaluation will be repeated at 12 weeks. Subjects who report using benzodiazepines 15 or more times in the past 28 days while receiving Bup/Nal or who are clinically judged to be intoxicated with benzodiazepines, alcohol or other sedatives on more than

one occasion will be placed on a slow dose taper and encouraged to continue with psychosocial treatment. Counseling and withholding of medication on the day it occurs will manage a single episode of sedative intoxication. Study staff will evaluate all subjects weekly during the first 12 weeks to record drug and alcohol use and adverse events (AEs). Timeline follow back methods will be used to ask about AEs in the case of missed appointments. AEs and Serious Adverse Events (SAEs) will be reviewed and evaluated by study medical personnel at the site, reported to the local PI, the local IRB, the lead investigator and IRB as applicable, and to NIDA within the timeframes specified by the CTN and as per FDA and local requirements. Consultation with the L.I. will be encouraged in cases where it is uncertain if the event is an AE or SAE.

Women of childbearing age who are not pregnant and wish to participate will be required to use an acceptable method of birth control as outlined in protocol section 9.2. Women will be given a urine pregnancy test at screening and weekly while on BUP/NAL. Women at the North Carolina site will be given a serum pregnancy test at screening and will have weekly urine pregnancy tests while on BUP/NAL. Those who become pregnant while on Bup/Nal will be slowly tapered from the medication and referred to the most appropriate treatment available.

A medication log will be maintained throughout the study for any non-study medications that the participant may take. This will also include medications that the participant may be prescribed for an illness/AE.

OUTCOME ASSESSMENTS: A comprehensive set of outcome measures will be administered at baseline and at 4, 8, 12, 24, 36 and 52 weeks. Briefer measures to assess drug and alcohol use and adverse events will be obtained weekly during the first 12 weeks. Time Line Follow-Back methods will be used to obtain self-report data on drug use from the time of the last evaluation in the case of missed appointments, and to obtain these data at the 24, 36 and 52-week follow-ups. Weekly assessments will have a +/- 2-day window of opportunity. Assessments at weeks 4, 8 and 12 will have a +/- 1-week window of opportunity, and assessments at weeks 24, 36 and 52 will have a +/- 3-week window of opportunity.

CLINICAL SIGNIFICANCE: Current treatments for opioid dependent adolescents and young adults are often unavailable and when found, clinicians report that the outcome leaves much to be desired. This study hopes to improve this situation by making Bup/Nal available and combining it with psychosocial treatment while also providing some of the first data on the efficacy, acceptability and safety of Bup/Nal when used with subjects in this age group. Based on current and past experience with buprenorphine, a moderate to strong effect on opioid use during the 12-week treatment episode is expected, as well as a strong/very strong effect on participation in psychosocial treatment. Moderate effects are expected on improvements in HIV risk, non-opioid substance use, psychosocial function, delinquent behavior and total problem behaviors. We hypothesize that the advantages seen during the first 12 weeks of treatment with Bup/Nal will also be detectable at each follow-up point.

These findings should provide new information that is especially important in view of the increasing prevalence of opioid dependence, the high rates of morbidity and mortality associated with untreated opioid dependence, and the relative absence of effective treatment options for this group of younger subjects. This study will introduce the use of Bup/Nal to each of the

participating sites and, if safe and effective, is likely to be adopted and used to supplement current treatment approaches. The data should also provide useful information to guide future studies, especially those aimed to determine the optimal duration and most effective dosage of Bup/Nal treatment for opioid dependent subjects who are 14-21 years of age.

4.0 BACKGROUND AND RATIONALE

4.1 Epidemiology: Recent epidemiological data show a trend for increased heroin use among all age groups since 1992 (Substance Abuse and Mental Health Administration, 1997) and an increase in the prevalence of use (141,000 new users in 1995). Heroin-related emergency room visits comprised 14 percent of all drug-related episodes in 1995 and rose 64 percent between 1988 and 1994 (Substance Abuse and Mental Health Administration, 1996). Age of first use has declined (Substance Abuse and Mental Health Administration, 1997) and use of heroin by American adolescents is at its highest level since the 1960's (Arrestee Drug Abuse Monitoring Program, 1998). A recent Monitoring the Future Study (MTFS) (Buchanan, 1998) reported lifetime prevalence rates of heroin use among 8th, 10th and 12th graders as 2.3%, 2.3%, and 2.0%, respectively. These percentages are likely underestimates as the MTFS only surveys youth attending school; it does not capture many at highest risk such as dropouts or those in juvenile detention centers. An example of this trend is seen in the following graph, which shows DAWN data of emergency room mentions for heroin between 1995 and 1999 for persons aged 12-17 and 18-25 (Drug Abuse Network Warning Network, 1999):

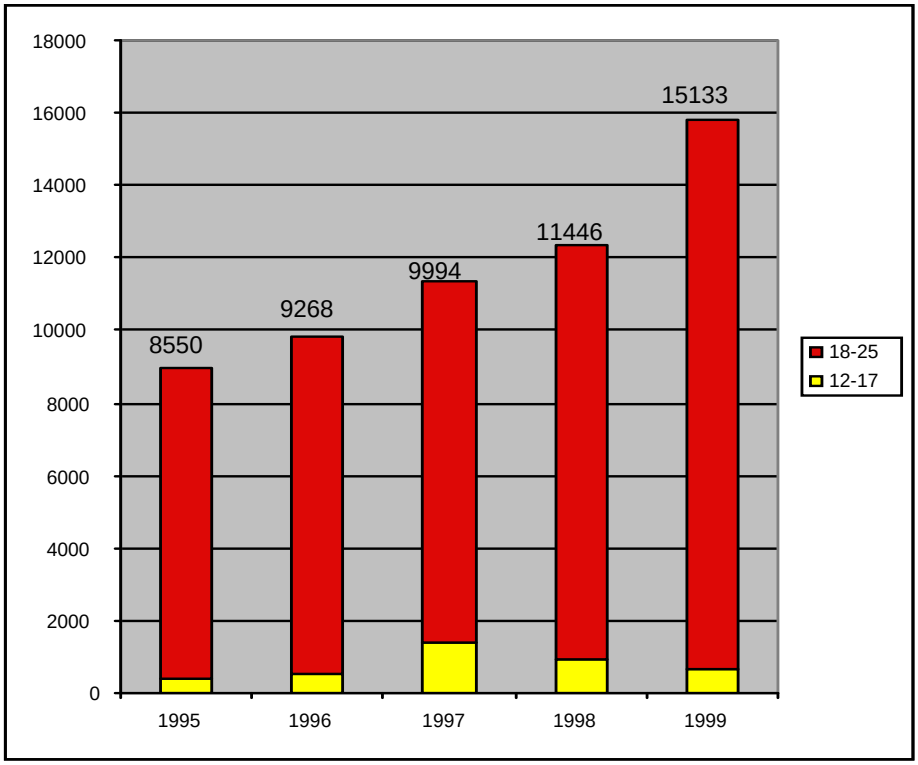


Figure 1 - DAWN Mentions of Heroin by Age Group 1995-99

An even higher prevalence of heroin use appears to exist on the East Coast. For example, data from the 1998 National Institute of Justice Drug Use Forecasting program (DUF), now the Arrestee Drug Abuse Monitoring Program (ADAM), show that in Philadelphia, Washington and New York City arrestees have some of the highest percentages of 15 to 20 year olds who tested positive for opioids. Reflecting these trends, subjects enrolled in the NIDA/VA private practice Bup/Nal study were 10 years younger on average and had nearly a decade less history of heroin use compared to subjects entering methadone maintenance (Ling, personal communication, 2000). Many of these subjects had opioid dependence with physiological features, were middle class, held steady jobs and were not interested in methadone maintenance.

At the local level, the Philadelphia County Medical Examiner's office recorded 151 opioid-related deaths during the first six months of 2000 and 19 of these were for individuals 21 or under. The Wilmington Medical Examiner recorded 40 opioid-related deaths in 1999 and 58 in 2000. Among these, 9 individuals were under age 21 in 1999 and 13 in 2000. These deaths are a likely consequence of the increased purity of heroin (National Institute on Drug Abuse, 1997) and the use of Oxycontin, which comes in strengths as high as 80 mg/tablet. Three drug treatment facilities that are part of the Delaware Valley Node have been treating 100 to 200 adolescents and young adults with opioid dependence each year for the last 2-3 years and these types of subjects are also being seen in the participating sites in Baltimore and North Carolina.

In addition to the mortality and social dysfunction associated with opioid dependence, these young people are at significant risk for infection with hepatitis B, C, and HIV.

4.2 Overview of Treatment for Heroin Addicted Adolescents/Young Adults: Interviews with staff from methadone maintenance and drug free residential programs where young subjects with short addiction histories are applying for treatment indicates a general, though not absolute, unwillingness to place them on maintenance. The result is that these patients are usually detoxified, followed by referral to drug free outpatient rehabilitation. Detoxification often requires pharmacotherapy and rehabilitation usually involves a 12-step approach using a combination of individual and group therapy. Family therapy also occurs and it is usually a combination of education about addiction, support, and crisis intervention and attempts to reduce negative affects that interfere with the goals of treatment. Few outpatient programs provide intensive family therapy because it is rarely covered by public or private insurance in substance abuse treatment programs. Detoxification is completed over 3-10 days in inpatient or outpatient settings and outpatient therapy is intended to last 12 months but opioid dependent subjects rarely stay in treatment for even 3 months. Long-term pharmacotherapy is usually limited to treatment of co-occurring psychiatric disorders. Residential treatment is very limited and difficult to access in many regions of the country, and outpatient treatment is often funded for only one individual and one group counseling session/week.

Most opioid dependent adolescents do not stay in the outpatient treatment that is offered. One unpublished study found that only 8% of opiate dependent outpatients completed a three-month course of treatment in a large urban clinic (Forman, R., 2001). A local example of this dropout problem is seen in CTN study #002. This study randomized opioid dependent subjects (mainly adults over 21) to a two-week detoxification using either Bup/Nal or clonidine. Preliminary results indicate that Bup/Nal subjects completed detoxification at a significantly higher rate than clonidine subjects though urine test results and the overall efficacy of Bup/Nal as compared to clonidine are not yet available (Amass, personal communication, 2002).

In addition to the problems of early dropout, infectious diseases are of special concern because intravenous use and unprotected sex are common among young, addicted patients (Crome et al, 1998; Hopfer, 1998). Most literature on treatment outcome for patients 21 and under is three decades old; consequently, there are no data on the prevalence of important new risks such as sharing injection equipment, unprotected sex, and other behaviors that increase the risk for HIV and hepatitis.

4.3 Agonist Maintenance: Literature from the 1970's suggests that treatment with an opioid agonist may be helpful for many opioid dependent adolescents and young adults. These patients, like adults, are reported to have high relapse rates and are at great risk for the very serious and even fatal complications associated with opioid dependence (Lloyd et al, 1974; Bright, personal communication, 2001). In one study, adolescent addicts on methadone maintenance had a lower termination rate than older patients and a generally progressive decline in illicit drug use related to the number of months in treatment (Nightingale et al, 1970). Increased school attendance was reported in another study (Millman and Nyswander, 1970), as were reductions in positive urine tests and arrests (Lloyd et al, 1974). Methadone doses ranged from 10 to 80 mg per day

(Vandervort, 1970; Nightingale et al, 1970; Millman and Nyswander, 1970; Schoof and Stanczak, 1972; DeAngelis and Lehmann, 1973; Lloyd et al, 1974; Crome et al, 1998).

Though results from this limited number of studies have been positive, regulations for persons under 18 have restricted the use of methadone maintenance even more than in adults. Patients under 18 have been required to have two documented unsuccessful drug-free treatments before admission to maintenance and a parent, legal guardian, or responsible adult must complete and sign FDA form 2635: "Consent to Treatment with an Approved Narcotic Drug". LAAM has been prohibited in persons under 18 and a recent advisory from FDA states that LAAM has been associated with fatal cardiac arrhythmias and should be used only as a second line treatment (FDA Physician's Alert, 2001).

4.4 Buprenorphine and Buprenorphine/Naloxone: Buprenorphine is a mu opioid partial agonist that has promise for treating opioid dependence. It has a high safety profile and its tight binding and slow dissociation from opioid receptors give it a long duration of action and are thought to account for its relatively mild withdrawal (Martin et al, 1976; Hambrook & Rance, 1976; Lewis, 1978; Jasinski et al, 1978). Early investigations showed that it could substitute for morphine, suppress withdrawal, and decrease heroin self-administration (Jasinski, 1978; Mello and Mendelson, 1980; Mello et al., 1982). Extensive research in the U.S., including large-scale controlled trials involving approximately 1000 subjects, have shown that buprenorphine is safe and effective for treating opioid dependence in adults (Johnson et al., 1992, Schottenfeld et al., 1994, Strain et al, 1996, Ling et al., 1998, Johnson et al, 2000). Its safety and effectiveness for pain control have been established for children aged 2 to 12 years as seen in data from a pharmacokinetic study, several controlled clinical trials, and post-marketing studies and case series (PDR, 2001).

The less intense withdrawal associated with buprenorphine could be especially important for adolescents and young adults who have often been addicted for only a few months or years and wish to use this medication to ease transition to a drug free state. Buprenorphine is also likely to improve compliance with psychosocial treatment, which could be an important advantage since compliance has consistently been associated with better outcome. Another unrelated but potentially important finding supporting buprenorphine's potential value in persons 14-21 is that it appears to be associated with no decrease in caloric intake, which could be important for subjects who are still developing physically (Jasinski et al, 1978).

Recent epidemiological data have emerged supporting the concept that buprenorphine, at least in adults, has a greater margin of safety than full mu agonists such as methadone. In France more than 75,000 patients have been treated with buprenorphine (not combined with naloxone), mainly by private physicians and with no special restrictions on use. Although there have been reports of abuse, overdose deaths have occurred at lower rates than with methadone, which is more tightly regulated. The relatively few buprenorphine-related deaths appear to have been associated with abuse of other drugs, especially benzodiazepines (Auriacombe, 2001). While these data suggest the need for caution, the risks associated with buprenorphine appear small in comparison to the risks associated with untreated and inadequately treated opioid dependence, specifically: HIV, hepatitis B & C, criminal involvement, social and academic disruption, and death due to drug overdose.

Most of the controlled studies of buprenorphine have used the liquid preparation, but more recently a sublingual Bup/Nal tablet in a 4:1 combination has been developed. Studies of this tablet have shown that its bioavailability approaches 70% or more of the liquid (Ling et al., unpublished data, 2001). Most importantly, the available evidence indicates that the combination deters intravenous use and that it can be safely dispensed to adults outside the methadone clinic setting (Mendelson et al., 1996, Fudala et al., 1998; Walsh, unpublished data, 2001). The Bup/Nal combination may reduce these two risks associated with agonist treatment, further increasing its appeal of this medication as an adjunct in treating these young adults.

4.5 Recent Safety Data on Subjects 21 and Under: Sixty-one subjects 21 and under have participated in the recent NIDA/VA buprenorphine office based practice study (Walsh, unpublished data, 2001). SAEs and AEs were collected and classified using COSTART terms. Though the study was open to subjects 15 and older, only three were 17 and under (one each at 15, 16, and 17 years); the other 58 were 18-21. There were eight SAEs among these 61 subjects; only one was judged "probably related to study medication, others were judged "unrelated". These eight SAEs were: seizure and post-ictal confusion (age 16; unrelated), admitted for in subject detoxification (2 subjects aged 18, one 19; the 19 year-old was judged "probably related"); viral gastroenteritis (age 19; unrelated); spontaneous pneumothorax (age 21; unrelated), pregnancy (age 21; unrelated), and fracture pelvis (age 21; unrelated).

In addition there were thirteen AEs judged "definitely related": asthenia (1), constipation (1), dry mouth (6), gastroenteritis (1), headache (1), nausea (1) and withdrawal syndrome (2).

Eighty three AEs were judged "probably related": constipation (30), depression (4), dizziness (2), drug dependence (1), headache (1), impotence (2), insomnia (1), lacrimation (1), nausea (13), nausea & vomiting (2), back pain (1), somnolence (15), sweating (2), tremor (1), vomiting (1), weight gain (1), and withdrawal syndrome (3).

One hundred and fifty-five AEs were judged "possibly related", the most common being: anxiety (14), constipation (11), peripheral edema (14), headache (41), and insomnia (14). Two hundred thirty six AEs were "unrelated" for a total of 487 including the 8 SAEs.

Dr. Nicholas Lintzeris, a medical officer from the Turning Point Alcohol and Drug Centre in Fitzroy, Victoria, Australia treated 58 subjects in study using buprenorphine sublingual tablets for detoxification and maintenance. Only six subjects were 21 and under and among these there were no SAEs and five AEs. Among these AE reports there were 2 instances of withdrawal, 2 of sedation, and one of a headache; 2 subjects reported no AEs. All subjects were heroin dependent with no major medical or psychiatric problems or recent methadone treatment. Doses of buprenorphine were 6 mg on day 1 and 8-10 mg on days 2-4. Subsequent doses were not reported (Personal communication via e-mail, 2001).

Another study reported that adolescents with hepatitis B or C who were treated with buprenorphine might experience increases in liver enzymes (Petry et al, 2000). The increases were small (about 15%) and it was unclear if they resulted from buprenorphine or hepatitis since most subjects had hepatitis C, which is known to result in chronic infection. However this report

indicates that opioid dependent adolescents receiving buprenorphine should be tested for hepatitis B and C, monitored, and compared to those receiving psychosocial treatment alone, to collect data that can be used to determine if there is evidence that buprenorphine is associated with liver damage.

4.6 Conclusion: The number of opioid dependent adolescents and young adults is increasing. Despite this increase, there are few programs that treat these subjects and those that do typically offer detoxification and brief residential care followed by outpatient counseling with encouragement to participate in self-help groups. Clinical reports indicate that dropout and relapse rates are very high with all of the associated risks including HIV infection, hepatitis and overdose death. Methadone maintenance is generally unavailable for these patients due to their short addiction histories and existing regulations. Consequently, opioid dependent young people have very few prospects for treatment or recovery. Research with adults indicates that Bup/Nal in combination with psychosocial treatment can improve treatment outcome for young people addicted to opioids. The Bup/Nal combination has been studied in over 1000 adults and found to be safe and effective. There is limited experience with Bup/Nal in adolescents and young adults but the available data indicate it is likely to be safe and effective for this age group as well.

We propose to compare the effectiveness of a 12-week course of Bup/Nal plus 2 sessions/week of psychosocial treatment, with the more usual approach of detoxification plus 2 sessions/week of psychosocial treatment. The study will be conducted at six programs located in five CTN Nodes. Psychosocial treatments will be equal in frequency and approximately equal in style and content. All subjects will receive the usual encouragement to participate in age-appropriate self-help groups. This study should yield important new information on the practical issues of acceptability, efficacy, cost and safety of a 12-week course of Bup/Nal as compared to treatment as usual for subjects in this age range. In addition, the follow-up evaluations will provide new and valuable information on the outcomes of opioid addicted young people over a 52-week period.

5.0 STUDY OBJECTIVES

The primary objective is to determine if a 12-week course of outpatient buprenorphine/naloxone plus psychosocial treatment (BUP/NAL) results in fewer opioid positive urine tests among opioid dependent adolescents and young adults (ages 14-21) than the usual treatment, which is detoxification plus psychosocial treatment alone (TAU). Secondary objectives are to determine if the BUP/NAL condition is associated with longer time to early termination from the assigned outpatient treatment condition, less opioid use by self-report, less HIV risk, less non-opioid substance use, better psychosocial functioning, less delinquency, and fewer total problem behaviors during the first 12 weeks. The study will also determine if the expected improved outcomes in the BUP/NAL condition during the first 12 weeks are maintained at the 24, 36 and 52-week follow-up evaluations.

The primary outcome measure will be opioid use, as measured by urine drug tests, at the 4, 8 and 12-week evaluations. The primary hypothesis is that, over this period, opioid use will be significantly lower in the BUP/NAL group than in the TAU group. It is also hypothesized that the secondary outcomes of longer time to early termination from the assigned outpatient

treatment, self-reported opioid use, HIV risk, non-opioid substance use, psychosocial functioning, delinquency, and total problem behaviors will favor BUP/NAL over TAU and that these differences will remain significant at 24, 36 and 52 week follow-ups.

6.0 STUDY SPONSOR

NIDA is the study sponsor and holds the IND for this study, which is IND#64,578.

7.0 STUDY SITES

7.1 Overview: Six programs that are medically staffed, operate in areas where opioid dependence is a problem among younger patients, and that feel comfortable using a medication with agonist properties for patients in this age range will participate. One is in the Delaware Valley Node (Brandywine Counseling); a second in the Mid-Atlantic Node (Mountain Manor); a third in the North Carolina Node (Duke Addictions Program); the fourth and fifth programs arelocated in the Southwest Node (University of New Mexico Hospitals Addiction and Substance Abuse Programs [ASAP] and Ayudantes, a community program near Santa Fe); the sixth is Mercy Hospital Recovery Center, located in Portland, Maine. Each program has seen increases in the number of young people seeking treatment for opioid dependence during the last two years. In addition, each program has medical staff in place to implement the protocol, and views Bup/Nal as a promising medication that may improve participation in psychosocial treatment and outcome. Each program has agreed to use Bup/Nal in a 7-14 day outpatient detoxification procedure for subjects assigned to TAU and whose treatment plan involves outpatient detoxification. In fact, the programs see the use of Bup/Nal for outpatient detoxification as an asset, especially when compared to clonidine.

Each program uses a flexible, 12-step approach to treatment that consists of 12-step oriented individual and group therapy with encouragement to participate in age-appropriate self-help groups. The individual and group drug counseling manuals by Mercer, Woody and Daley that were used in the NIDA cocaine psychotherapy study and that are on the NIDA web site describe a treatment approach that is similar to those used in each program. These manuals have been modified for treating opioid dependence and will be used to guide therapy during the study. Family treatment services are offered in the programs but discussions with staff indicate that they are primarily educational and crisis-oriented, and not long term or complex (e.g. structural family therapy as described by Minuchin and others). The aim of the family interventions used in this study will be to educate the parents/legal guardians about opioid addiction, obtain their support for participation in treatment, reduce negative affects that may be interfering with the goals of treatment, and respond to crises.

The individual and group drug counseling manuals will be reviewed with staff at each site as part of the training program prior to beginning the study. Two-treatment sessions, consisting of one individual and one group session, will be scheduled each week for the first 3 months for all participants at each site. The frequency of therapies may be reduced to one session/week after 12 weeks depending on compliance, subject progress, and individual needs. The drug counseling manuals and training program should provide a reasonable degree of standardization in the psychosocial treatments across sites and also improve the treatments that are used by making

them more systematic. All sites will encourage subjects to attend age-appropriate self-help groups, as is done in the usual course of treatment. Family educational sessions, attendance of family members at support groups and other family interventions will be recorded in the same way that we will record attendance at self-help group meetings.

These three steps: using manuals to guide treatments at the collaborating sites; reviewing the manuals during pre-study training; and having a similar number of treatment sessions should provide a reasonable and practical level of standardization in the psychosocial treatments across sites. We will document the number of therapy sessions kept during the study, attendance at self-help groups, receipt of non-study treatments, clinic contacts, and attendance by family members at educational or therapy sessions and family support groups. As a further check on the comparability of treatment across sites, we will measure the helping alliance between the subject and his/her therapist(s) using the Haq-II (Luborsky et al, 1997) at 4 weeks, and the degree to which subjects adopt 12-step principles using the Addiction Recovery Scale (ARS; Mercer et al, 1993) at baseline and 12 weeks. These measures should provide an opportunity to control for differences in the therapist/subject relationship and the degree to which the subject's adoption of 12-step concepts mediate outcome.

Subjects who are judged by staff to be not improving will be offered other treatment options as clinically indicated and counted as early terminators from the study. Efforts will be made to complete all follow-up assessments on these subjects unless they have instructed research staff otherwise.

7.2 Recruitment: We are cautiously optimistic that recruitment will be sufficient to enroll 240 subjects in 2.5 years after study start-up procedures are completed. Each collaborating site reports the presence of opioid dependent subjects in this age range with few meaningful treatments available, thus we expect to be able to recruit from a pool of untreated patients. Recruitment can be increased through referrals from other agencies, advertisements, and by "word of mouth." We anticipate that the latter method will be the most effective based on our experience with the CTN #0002 protocol. Within a few weeks of starting protocol #0002, the investigators had a waiting list of over 30 patients, some coming from as far as Philadelphia to the Trenton site where the study was conducted for a chance to receive a two-week outpatient detoxification with Bup/Nal or clonidine. Though the #0002 study was recruiting mainly adults, we think that the rapid development of a waiting list reflects the high level of interest in Bup/Nal among opioid dependent patients, and also demonstrates the gap between treatment demand and availability, at least in the Philadelphia area. Though there are fewer young opioid dependent patients than adults, treatment services are even less available for this younger group. In addition, as the epidemiological data cited earlier show, the use of opioids by young people is on an upward trend and anecdotal reports from treatment providers indicate that this trend continues. Thus we think it reasonable to expect that we will be able to tap an unmet need and enroll adequate numbers within a reasonable time.

7.3 Retention and Follow-up: During staff pre-study training, the importance of getting follow-up data will be strongly emphasized. We will obtain extensive locator information at study intake so as to have multiple sources to locate subjects for follow-up. It will include the subject's name; address and phone number; e-mail and beeper numbers; others living at the

primary address; address the subject expects to be if planning to move within the local area; three contacts who might know where the subject can be located if not at the primary address; best times to contact the subject; name of probation/parole officer if applicable; and any additional information that might be useful including employer and school attended. A locator form that contains this information and has been used in other projects is in the Appendix.
For follow-up appointments the research assistant (RA) will begin notifying subjects (phone, mail, outreach visits) two weeks before the window for their scheduled assessment. If not located at the primary address, the RA will use the alternative locator information. Follow-up appointments may be conducted at the clinic site or alternate sites such as the subject's home or a public location. If the subject is contacted but the appointment is missed, the RA will repeat this procedure until the appointment is kept or until the corresponding window of opportunity has closed, at which time the subject will be considered to have missed the follow-up.

In addition, the brief weekly assessments and comprehensive assessments at weeks 4, 8, 12, 24, 36 and 52, combined with vouchers worth $5 and $75 respectively, plus a bonus voucher worth $75 for completing the comprehensive measures should encourage compliance with the assessments (the bonus voucher will not be offered at the sites of the Southwest Node). We have chosen to not reimburse more than $5 for the weekly assessments, as we are concerned that higher payments may be implicitly coercive to attend psychosocial treatment, which is one of the outcome measures. Weekly assessments will have a +/- 2-day window of opportunity. Assessments at weeks 4, 8 and 12 will have a +/- 1-week window of opportunity, and assessments at weeks 24, 36 and 52 will have a +/- 3-week window of opportunity.

For different reasons we have limited the urine test data that will be used to measure the primary outcome to the tests done at study intake and the 4, 8, 12, 24, 36 and 52 week follow-ups rather than on a random basis as is done in adult studies comparing different agonist treatments. We realize that random callbacks and more frequent urine tests are optimal, however we anticipate that there will be major differences in compliance with psychosocial treatment and that these differences will result in such an imbalance of missing weekly urine data that they will be impossible to interpret, thus resulting in much wasted time and effort. However, we will do weekly urine and alcohol breath testing as an additional safety measure to identify subjects who are at risk for adverse events resulting from interactions between buprenorphine, benzodiazepines, alcohol or other sedative drugs. For purposes of data collection, we will put a special focus on getting all assessments, especially the ones at 4, 8, 12, 24, 36 and 52 weeks. In addition, we will ask subjects if they used opioids in the last 3 days at each of these assessments and then compare their answers to the urine test results as a validity check on self-reported use. Urine specimens will also be tested for adulteration.

Though few data are available on the relationship between reimbursement, time intervals and compliance with follow-up in this age group, adolescent studies at the University of Pittsburgh reimbursed adolescents $125 for one year follow-ups and had 91% compliance (Howard Moss, personal communication 2001). Similar procedures for the NIDA cocaine/psychotherapy study achieved a follow-up of 81% at 9 months with adults. The procedures we describe here have consistently obtained 85% or more follow-up rates at 3-6 month intervals for opioid dependent adults participating in HIV studies. These participants are often homeless or move frequently and can be especially difficult to locate. We anticipate that most of the adolescents and young

adults in this study will be living with parents or relatives and thus may be more easily contacted for follow-up appointments.

7.4 Emergencies: Each site has standing procedures for responding to emergencies, as will be described below. In addition to site-specific procedures, study personnel will adhere to the following:

- As part of the study orientation and informed assent/consent process, participants and their parent or guardian (when applicable) will be provided with brochures describing the study in detail including possible side effects associated with Bup/Nal. Emergency procedures and 24-hour emergency telephone numbers will be included with these materials.
- During hours when no medical personnel are on duty, on call medical personnel will be scheduled so they can respond to emergencies that might arise.
- In addition to onsite and on call medical personnel, the protocol team (Woody, Poole, Forman, McNicholas) will be on call by phone cell-phone or e-mail to provide consultation.

7.5 Study Sites:

Delaware Valley Node:

Brandywine Counseling Center

Newark, Delaware 19702

Background Information – Brandywine Counseling - Brookhill is a not for profit substance abuse treatment facility located in Newark, Delaware, 40-minutes from the CTN offices. The Brookhill location is owned and operated by the parent organization, Brandywine Counseling, Inc (BCI). BCI treats urban opioid dependent subjects at several sites and currently has a census of approximately 1000 men and women - most being on methadone maintenance. In the past year, BCI treated approximately 100 opioid dependent subjects that were 14-21, most of whom had been addicted for only 1-3 years. The physicians at BCI are reluctant to put subjects under age 21 on methadone due to their short addiction histories and as a consequence, are very interested in the Bup/Nal study.

Treatment As Usual – The most common approach used by BCI for patients under 21 with a short history of opioid dependence is outpatient clonidine detoxification followed by naltrexone and 12-step focused drug counseling. The failure rate from detoxification is high and few patients ever take the first dose of naltrexone. Those who take it usually drop out within a month (Allshouse, personal communication, 2001); less than 10% are placed on methadone. Staff reports that many of the patients who fail treatment return several years later, still addicted, and are then placed on methadone. BCI dispenses methadone 7 days/week and can easily administer Bup/Nal on a daily basis. Individual and group counseling services are available daily.

Psychosocial treatment is oriented toward the 12 steps and involves a combination of individual, group and supportive/educational family counseling. Individual counseling sessions are daily during detoxification, decreasing to 2-3 times/week and then to once/week or less if stable

remission is achieved. Scheduling subjects for psychosocial treatment twice/week will present no problem as it is within the usual range of standard treatment. Treatment is planned to continue for 6-12 months but most subjects drop out well before that time.

Emergency Medical Procedures – Upon determining that a subject may require emergency care, a member of the nursing or medical staff conducts an initial assessment of the subject's needs. If a determination is made that medical care is required, 911 emergency services are called and an ambulance is dispatched. A member of the nursing staff monitors the subject until an ambulance arrives. Subjects requiring emergency medical services are transferred by ambulance to Christiana Care Health Systems, 4755 Stanton Ogletown Road, Newark, Delaware 19807 (phone: 302-733-1000). For emergencies that occur in off duty hours, a clinic physician can be reached by telephone and his/her number will be given to all study participants.

Mid-Atlantic Node

Mountain Manor Treatment Center
Baltimore, MD

Background - Mountain Manor Treatment Center - Baltimore (MMTC) is a JCAHO accredited community based substance abuse treatment provider in urban Baltimore, operated by Maryland Treatment Centers, Inc. The Baltimore center began serving substance-abusing adolescents in 1989. The adolescent substance abuse outpatient programs are part of the expanding MMTC continuum of care for drug-involved and dual diagnosis adolescents at the Baltimore site, which now also includes a residential program, intensive outpatient, day treatment, special education day school, and a mental health clinic. These programs serve both adolescents up to age 18, and young adults up to age 21.

The outpatient program at MMTC provides both high intensity [intensive outpatient (IOP)/partial hospitalization (PHP) – American Society of Addiction Medicine (ASAM) Level II] and low intensity [outpatient (OP) – ASAM Level I] outpatient services to adolescents, with approximately 450 outpatient admissions per year. In the IOP program, patients attend 3-hour sessions up to 4 evenings per week, with flexible dosing of 1-4 sessions depending on need. In the PHP program, patients attend 6-hour sessions up to 5 times per week. Low intensity group and individual outpatient sessions (usually ~1/wk) are scheduled throughout the week including weekends. A mental health clinic for dual diagnosis outpatients meets for 2-3 sessions weekly.

Approximately half of the outpatients are referred from the community, including a large proportion from the Department of Juvenile Justice; others are stepped down from MMTC's residential program. The programs treat a significant proportion of opioid dependent patients. Data from the residential program showed a 29% rate of opioid dependence, which translates to approximately 150 opioid dependent residential admissions per year. The outpatient program treats approximately 5-10 opioid dependent patients at any given time and up to 60 annually.

Based on a Center for Substance Abuse Treatment (CSAT) funded study, we have found that opioid dependent patients at MMTC have higher severity of drug use and psychosocial impairment; are notoriously hard to engage in outpatient treatment; and drop out of treatment and

relapse early. Many cannot tolerate residential confinement and either refuse detoxification or leave prematurely. Clinical staff has long recognized these difficulties in outpatient management of these high-severity, treatment refractory opioid dependent patients, especially after they have failed several attempts at residential detoxification.

Treatment As Usual - Current services at MMTC (IOP/PHP or OP level of care) include substance abuse education; 12-step based group and individual counseling; relapse prevention groups and refusal skills training; HIV and sexual risk behavior education; urine drug screening to monitor progress/relapse; and family education groups. In addition, counselors provide sessions to address situational stressors, family issues and problem solving needs. They also serve as case managers, facilitating communication between the patients and their families and schools, the juvenile justice system, primary care and mental health providers, and other involved stakeholders. Ongoing psychiatric care is provided for dual diagnosis patients. Although patients from the community are typically admitted to the IOP level of care, individual patient needs permit flexible movement along the continuum of care available at MMTC ranging from residential to OP treatment.

Detoxification Procedures - Currently, many of MMTC's patients with relatively short histories of opioid dependence receive detoxification at the MMTC residential program using clonidine and other medications. Other patients enter the MMTC system directly at the outpatient level, having received ambulatory detoxification at a local adult hospital-based program, using a 3-4 day course of sublingual buprenorphine. For outpatients who relapse, ambulatory clonidine detoxification has also been used. Patient interviews show that many would prefer detoxification with buprenorphine to clonidine, and also that many have refused the center's detoxification services altogether because buprenorphine has not been available. Patients will be medicated 5 days per week—Monday through Friday, and 4 days/week in the case of holidays, and take home doses will be given out for Saturday and Sunday except for holidays where additional take-homes will be provided.

Emergency Medical Procedures - The facility has 24-hour onsite nursing coverage and medical personnel (physicians and/or physician assistants) available on-site during business hours and Saturdays. Emergencies are managed by on-site evaluation and referral to the emergency department at St Agnes Hospital, located 5 minutes from MMTC. Physician on-call coverage is available 24 hours, 7 days, and program physicians are available by pager by first calling the operator at Mountain Manor. This emergency phone number will be given to all study participants.

North Carolina Node

The Duke Addictions Program (DAP)
Durham, N.C.

Background: The Duke Addictions Program (DAP) was established in 1986 to provide comprehensive outpatient treatment to persons with substance use disorders and their families. Since that time the program has expanded and now operates intensive outpatient programs for adults and adolescents with specialty services for women, and substance abusers who are

pregnant, HIV infected, and mentally ill. DAP also provides an Executive Intervention Program designed to support corporate agencies and families by discretely facilitating treatment services for members of corporate, government, health care and church based organizations. DAP's multi-disciplinary staff is supervised by a board certified Addiction Medicine psychiatrist and includes social workers, licensed therapists, and certified substance abuse counselors and supervisors.

Treatment as Usual: DAP provides a holistic, systems and community centered approach offering non shame based care and integration of a wide range of established and alternative interventions. These core and special services include ambulatory detoxification; individual, group and family therapy; multi-family therapy; family retreat programs; relapse prevention; psychiatric management; expressive therapies; educational programs; structured orientation to self-help support groups such as Alcoholics Anonymous and Narcotics Anonymous; and ongoing evaluation services. Treatment typically consists of extended care patient and family involvement based on individualized treatment goals and objectives.

Experienced therapists provide treatment for adolescents/young adults. The 12-step oriented drug counseling approach as outlined in the individual and group counseling manuals is similar to interventions that are part of the usual treatment at Duke thus both the intensity and style of treatment proposed for this study fit into the overall program. DAP has family counseling available addressing early recovery issues, crisis management, and relapse prevention. There is a parent support group and a multi-family counseling group where lectures are given and families communicate with one another about common issues of concern and the recovery process.

The DAP has not been treating adolescents with opioid dependence but will begin an adolescent opioid dependence treatment component for this study including outpatient detoxification using Bup/Nal. Medication will be dispensed five days/week or 4 days a week in the case of holidays. The schedule for medication dispensing will be explained to the subject and the parents/guardians where relevant, and the need to take medication as prescribed will be emphasized.

Detoxification Procedures: Patients needing detoxification are referred to other providers and then back to the DAP. The most common referral for detoxification is to the adolescent inpatient unit at the University of North Carolina, however an outpatient detoxification arm using Bup/Nal will be added for this study.

Emergency Procedures: The nurse practitioner or physician treats non-life-threatening events at the clinical site. Life-threatening emergencies are triaged via 911 to the Duke Emergency Services. Nurses or physicians initiate CPR and other emergency procedures on site if required before the 911 emergency services arrive. Subjects aged 14-17 who experience serious adverse events including suicidal or homicidal ideation/behavior will have their parents/legal guardians notified. Emergencies that occur outside normal working hours are managed through the emergency room at Duke Emergency Services. All subjects enrolled in the study will be given the pager numbers of the site P.I. and study liaison to contact if immediate assistance is needed outside normal clinic hours.

Southwest Node

Ayudantes, Northern Clinics
Española**, NM**

Background: Ayudantes (Spanish for "helpers") was incorporated as a nonprofit agency in 1979. Funded by state, federal and local government and managed care contracts, it operates three clinics in Northern New Mexico, in the communities of Española, Las Vegas, and Santa Fe, all of which lie near Interstate 25 - a primary north-south drug distribution artery. Española in particular, and surrounding Rio Arriba County, have received national attention for (and substantial federal funding to address) very high levels of multi-generational heroin dependence. The cultural identity of Hispanic communities in the area of the Española site and other areas of the north is much more rooted in old Spain, whereas in the south of the state identification is closer to Mexico. Monolingual Spanish-speaking families are common.

The three Northern Clinics of Ayudantes together served 582 patients in 2001, 65% of who presented for treatment of heroin dependence, with 25% using cocaine (including crack) and/or methamphetamine. Of these 582, approximately 125 were treated in the methadone program at the Española site with an additional 30 receiving residential drug-free treatment. The methadone clinic at Española treats 60-65 patients at any one time and is open six days/week and closed on Sunday. Staff includes B.A. and M.A. level counselors, counselors, part time psychiatrists a Medical Director, a nurse, and office support staff.

Psychosocial treatment is provided through psycho-educational groups (including anger management), women's groups (including parenting), and coordination with NA/AA groups; individual cognitive-behavioral therapy; and supportive services which consist of general case management facilitating access to education, employment, etc. Every patient is assigned a primary clinician who is responsible for coordination of treatment. The individual and group drug counseling approach that will be used in this project appears to fit well into the 12-step oriented and relapse prevention approaches that are part of standard clinic operating procedures.

Emergency Procedures: The nurse or physician treats non-life-threatening events at the clinical site. Life-threatening emergencies are triaged via 911 to the local hospitals in the three communities served. All staff is required to obtain CPR and First Aid certification. Nurses or physicians initiate CPR and other emergency procedures on site if required before the 911 emergency services arrive. Subjects aged 14-17 who experience serious adverse events including suicidal or homicidal ideation/behavior have their parents/legal guardians notified. Emergency medical evaluations after clinic hours are available at Española Hospital. Emergency psychosocial consultation is available on site via a counselor who is on call 24/7.

All subjects enrolled in the study will be given written instructions about how to contact the available emergency services. The pager numbers of the P.I. and Clinical Director will be available to these emergency services if additional consultation is needed.

**University of New Mexico Hospitals Addiction and Substance Abuse Programs (ASAP)
Albuquerque, N.M.**

Background: ASAP is the largest and longest running outpatient drug dependence treatment program in New Mexico. Established by UNM in 1977, its public programs have served over 60,000 clients, a majority of whom represent ethnic minority groups. ASAP serves at least 1,500 unique clients per year (about 60% with illicit drugs as the primary presenting problem, and most of the rest with concomitant alcohol and other drug problems; approximately 360 are in the methadone maintenance program. Consistently, just over half of treated clients are Hispanic, with proportionate representation of Asian and Black (4-5%), and Native Americans (5-6%). Women comprise about one third of those receiving services at ASAP. ASAP has extensive experience with clinical research, including randomized trials of psychosocial and pharmacotherapeutic interventions. ASAP staff and programs have been participating in NIH-funded clinical trials for 15 years and several of the counselors on staff have participated in manualized protocols.

Treatment as Usual: ASAP's clinical staff include licensed health professionals including physicians, nurses, psychologists, social workers, pharmacists and counselors, plus a similar number of support staff. All clinical staff is required to hold a New Mexico license to practice in their respective disciplines. Treatment staff has expertise in a wide range of evidence-based approaches including cognitive-behavioral strategies, coping skill training, motivational interviewing, 12-step facilitation, marital and family therapy, psychoeducation and supportive/expressive psychotherapy. A strength of ASAP is in the range of services and approaches offered within a single facility. Specialized units provide intake and triage, ambulatory detoxification, intensive outpatient rehabilitation, outpatient behavioral and pharmacotherapies including methadone maintenance, and specialized programs for women and for adolescents. ASAP's on-site facilities also include a dispensing pharmacy, a cashier office through which research reimbursements can be made, and full-time security staff.

All individuals in this study will receive medication as part of the dispensing procedures in the methadone program. The basic treatment model consists of weekly group and individual therapy, plus a weekly family group. The 12-step oriented individual and group drug counseling that is proposed for this study is consistent with approaches that are normally used in these programs.

Detoxification Procedures: Outpatient medical detoxification for all substances of abuse is provided. Patients are usually seen daily (Mon-Fri) by a nurse, physician or P.A. and case manager. While completing detoxification, patients begin outpatient therapy with an orientation group and assignment to individual and group therapy. Clonidine is commonly used for opioid detoxification, although methadone is sometimes used for extended detoxification. Patients on this study who are assigned to TAU will receive their Bup/Nal 6 days/week in the methadone program, as described above.

Emergency Procedures: The nurse practitioner or physician evaluates and treats non-life-threatening events at the clinical site. Life-threatening emergencies are sent via 911 to the University of New Mexico Hospital Emergency Department. Psychiatric emergencies are dealt with by referral to the University of New Mexico Psychiatric Center Emergency Service, or by direct admission of patients to inpatient units of that facility. Staff initiates CPR and other emergency procedures on site if required before the 911 emergency services arrive. Subjects

aged 14-17 who are experiencing serious adverse events including suicidal or homicidal ideation/behavior will have their parents/legal guardians notified. All subjects enrolled in the study will be given the pager numbers of the site P.I. and Medical Director to contact if immediate assistance is needed outside normal clinic hours. Subjects will also have access to the UNM hospital emergency Department that will also be able to reach clinic physicians.

Northern New England Node:

Mercy Hospital Recovery Center
Westbrook, Maine 04092

Background Information – Mercy Hospital – A JCAHO accredited behavioral health program, The Recovery Center is the largest substance abuse treatment center in Maine and has been serving the community for over 20 years. Located in Westbrook, Maine, Mercy Recovery Center is a member of Catholic Health East, a faith based healthcare organization. The Recovery Center offers inpatient and outpatient services for more than 5,000 patients per year. Mercy treats the entire spectrum of addictions from alcohol to all types of drugs utilizing a continuum of care approach based upon ASAM Patient Placement Criteria. Services provided by The Recovery Center include: Inpatient detoxification, Partial Hospitalization, Day and Evening Intensive Outpatient services, Family programs and Level 1 individual, group and continuing care services.

Treatment As Usual – The most common approach used by the Recovery Center for patients under 21 with a short history of opioid dependence is a 2-4-day inpatient detoxification utilizing Suboxone. Following inpatient detoxification, patients are generally referred to Partial Hospitalization for a 5 to 10 day length of stay. The partial program meets 6 days per week for 6 hours per day. Services include Motivational Enhancement, Cognitive Behavioral Skills groups, 12-step facilitation, individual counseling and weekly multi-family educational and therapy groups. Patients are followed by their admitting physician for on-going medication management services which are integrated across the programmatic continuum of care.

Following the stabilization period in Partial Hospitalization, patients are stepped down to Intensive Outpatient services. Programs for intensive outpatient are available in the day or evening. Service design allows continuity in treatment planning and group modalities building upon goals and objectives identified in preceding levels of care. Lengths of stay for the intensive outpatient programs range from 2 to 4 weeks in duration. Participants attend treatment 4 to 6 times per week, and participate in the weekend multi-family program. Patients participating in treatment with on going medication services contract to remain in the Level 1 continuing care groups for duration of 1 year. Mercy does not currently treat patients under the age of 18.

As noted above, psychosocial treatment is oriented toward the 12 steps and involves a combination of individual, group and supportive/educational family counseling. Though Suboxone (bup/nal) is being used as part of treatment as usual, the program physician has reached his 30 patient limit and thus there is a waiting list for this treatment. Patients in this study will not be counted against this 30 patient limit because it is done under an IND.

Detoxification Procedures –Detoxification procedures happen predominantly on the inpatient unit; however, roughly 45% of patients admitted to the Partial Hospitalization program, do so as direct admits. In both cases, Suboxone is the medication of choice both from patients and program physicians. As noted above, patients choosing to utilize Suboxone detoxification and assisted treatment have been required to contract for 12-month involvement in psychosocial treatment. Detoxification services include education on HIV/ Hepatitis C and risk reduction, motivational strategies, goal groups, 12-step introduction, family sessions and case management services to facilitate discharge planning.

Emergency Medical Procedures – Upon determining that a subject may require emergency care during daytime hours, clinical staff have access to program physicians via on-call systems. Patients' conditions are assessed and the capacity exists to move them up in levels of care, such as Level IV Detoxification or to Mercy Hospital's emergency room, via ambulance. Mercy Hospital's emergency department is located at 144 State Street, Portland Maine, 04101. During evening and overnight hours, patients may call and have their calls connected directly to a physician to assess and make recommendations. Patients may be instructed to go to their nearest emergency room, come to the treatment facility for admission, or to call 911.

8.0 OVERVIEW OF STUDY DESIGN

Potential candidates will have a brief explanation of the study and be asked to provide their assent/informed consent for screening when they apply for treatment. Those who qualify after having completed screening will be given a complete explanation of the study, asked to sign an assent/informed consent for the study itself, and complete any remaining items in the baseline assessment. Subjects will be randomized in a 1:1 schedule within each program using an urn randomization stratified according to gender, route of administration (IV/non-IV) age (14-17/18-21), and ethnicity (Caucasian/Non-Caucasian) to BUP/NAL or TAU. A total of 240 subjects will enter the study with approximately equal numbers at each site. In case one or more nodes are recruiting more slowly than expected, subjects will be added to other nodes so that the total number of participants reaches 240.

Subjects in the BUP/NAL group will receive 12 weeks of Bup/Nal using a relatively flexible dosing schedule that includes an induction phase of approximately 4 weeks, a stabilization phase of approximately 4 weeks with a target dose of 12-18 mg Bup/Nal per day and an upper limit of 24 mg/day, and a slow taper during the last 4 weeks. Subjects in the TAU condition will be detoxified in an outpatient setting at the participating site using Bup/Nal over 7-14 days according to a flexible dosing schedule with a maximum dose of 14 mg/day.

Study medication will be administered under observation at each site. Subjects will be asked to hold the Bup/Nal under their tongue until it is completely dissolved, which usually takes 2-10 minutes. Stabilization will have occurred when the subject is having few or no signs of opioid withdrawal, sedation, or other side effects during the 24-hour dosing period as determined by a clinical evaluation. Doses will be adjusted or stopped in the event of excessive sedation or other adverse effects. Subjects in each group will be scheduled for two sessions/week of psychosocial treatment, one of which will be individual drug counseling, and the second group therapy using the approaches described above. Additional sessions may be provided if clinically indicated.

Each week during the first 12 weeks we will document compliance with psychosocial treatment, medication use, obtain a self-report of times used opioids and other drugs during that week, administer a sedation scale, perform a urine drug screen and breath test, and obtain a report of side effects or other adverse events. Time Line Follow-Back procedures will be used to obtain self-report data on opioid and other drug (alcohol, benzodiazepines, cocaine, marijuana) use and adverse events. Comprehensive assessments will be repeated at 4, 8, 12, 24, 36 and 52 weeks (see Table 1). Time Line Follow-Back will be used at the 24, 36 and 52-week assessments to obtain data about opioid and other drug use during each week of the preceding 28 days.

TAU subjects receiving outpatient detoxification will have medication discontinued if they miss 3 consecutive days, as will BUP/NAL subjects. However BUP/NAL subjects will have the option of restarting medication if they return within 7 days; medication will be stopped if they miss 7 days. Subjects receiving Bup/Nal will have a dose taper if they report using benzodiazepines 15 or more days in the last month, or if they are clinically assessed as being intoxicated with sedatives on more than one occasion. Sedative intoxication will be determined using DSM-IV-TR criteria that include significant impairment such as unsteady gait, slurred speech and difficulty with coordination. Subjects who are discontinued from Bup/Nal will be encouraged to continue with psychosocial treatment.

The primary outcome will be opioid positive urine test results at the 4, 8 and 12-week assessments. Secondary outcomes are time to dropout from outpatient psychosocial treatment with dropout defined as having no treatment sessions in the assigned condition lasting 30 minutes or longer for two consecutive weeks; self-reported opioid use; HIV risk behavior; overall substance use; psychosocial functioning; delinquency; and total problem behaviors during the first 12 weeks. The study will also determine if the expected improved outcomes in the Bup/Nal condition during the first 12 weeks are maintained at 24, 36 and 52-week follow-ups.

Subjects will be asked if they have used opioids during the last 3 days at the 4, 8, 12, 24, 36 and 52-week assessments. Comparing it with the urine test data will check the validity of their self-report. Such a comparison was made in the NIDA cocaine/psychotherapy study and self-reports were found to be valid (Crits-Christoph, 1997).

Hypotheses are that:

1. Subjects assigned to BUP/NAL will have less opioid use and better outcomes on all other variables at the 4, 8 and 12-week assessments.

2. Gains favoring BUP/NAL will be maintained at the 24, 36 and 52-week follow-ups.

9.0 SUBJECT SELECTION

We will enroll 240 consenting male and non-pregnant/non-lactating females between the ages of 14 and 21. Subjects must meet DSM-IV-TR criteria for opioid dependence with physiologic features and must be free of serious medical or psychiatric disorders that would make

participation hazardous. Judgments about suitability for the study will be made on the basis of clinical examinations and laboratory tests. Current use and features signifying physiologic dependence (as defined in DSM-IV-TR) will be documented by the medical history and will include presence of signs and symptoms of opioid use and withdrawal and an opioid positive urine test. . Subjects will be accepted provided they are not acutely suicidal, homicidal, psychotic or otherwise seriously impaired or incapable of giving informed consent.

Subjects will be recruited mainly from among those applying for treatment but also by word of mouth and referral from local drug treatment and outreach programs, primary care providers, mental health clinics, and crisis centers. If advertisements are necessary they will be approved by the Penn IRB and by the local IRB's, as applicable. Subjects must meet all inclusion and none of the exclusion criteria listed below:

9.1: Inclusion Criteria:

- 14-21 years at study entry. This would include any individual who is 21 years of age but has not yet reached their 22nd birthday at the time of randomization.
- Be seeking outpatient treatment and meet DSM-IV-TR criteria for opioid dependence with physiologic features as determined by history and clinical evaluation.
- Be judged competent to provide informed consent/assent by treatment staff
- If 18-21, provide written informed consent and pass the informed consent quiz
- If 14-17, provide written assent to participate and have a parent or legal guardian who will provide written informed consent; both subject and parent/legal guardian must pass the informed consent quiz.
- Patients receiving medications for other psychiatric or medical disorders are allowed in the study provided the medications are being prescribed by a physician for a legitimate psychiatric or medical disorder and are being taken within the recommended dose range. For example, in the case of psychotropic medications, patients taking tricyclics (amitriptyline, desipramine, imipramine, etc.); other non-SSRI antidepressants (desyrel, buproprion, others); mood stabilizers (lithium, valproic acid, carbamazepine, for example), stimulants (methylphenidate, adderal, for example), or antipsychotics (risperdal, olanzapine, for example) may enter provided the above conditions are met. Patients who are receiving other medications must have the consent of the treating physician to participate and it must be documented in the clinical record, either after speaking with the physician in person or by telephone, or by a note from that physician.

9.2: Exclusion Criteria - Subjects must not:

- Have a medical condition that in the opinion of the program physician and staff makes continued participation unlikely or hazardous. Exclusions include endocarditis, severe hepatic damage as indicated by any liver enzyme tests (ALT, AST, GGT, LDH, bilirubin) > 5-times the top limit of normal, renal failure, advanced HIV disease (multiple opportunistic infections, wasting syndrome) and an abnormal ECG as seen by prolongation of the PR interval greater than 200 ms; a QRS that is wider than normal for the subject's age (>119 ms); a QTc interval that is longer than 450 ms; or an arrhythmia. Subjects with values

greater than these cutoffs may participate if judged not clinically significant by the Site P.I. after review by a cardiologist.
- Have a psychiatric disorder that in the opinion of the program physician and staff renders the subject unable to give informed consent or makes participation hazardous. Exclusions include homicidal or suicidal ideation that requires immediate attention, acute schizophrenia, mania, hallucinations, delusions, or cognitive impairment that renders the subject incapable of providing informed consent.
- Report using benzodiazepines for more than 15 days in the last 28 days; history of overdose involving benzodiazepines or other sedatives within the last 6 months; be unable to provide a urine test that is negative for benzodiazepines at screening evaluation even after three tries (after screening) within 28 days from the date of screening; or have current abuse or dependence on benzodiazepines, alcohol or other sedatives as determined by a clinical evaluation.
-
- Be unable to provide a urine test at the screening assessment that is negative for methadone even after three tries (after screening) within 28 days from the date of screening.
- Be taking LAAM (licit or illicit), or naltrexone at the time of screening
- Be expecting to leave the geographic area prior to study completion or have pending legal action that is likely to result in incarceration and that would prohibit continued participation.
- Have a treatment plan that involves > 7 days of inpatient detoxification or > 7 days of residential or inpatient substance abuse treatment.
- Be planning overnight admission to a hospital for medical or surgical treatment during the first 3 months of the study.
- Be planning to receive other opioid agonist treatment during the first 12 weeks of the study.
- Be nursing or pregnant
- Be unable/unwilling to use a medically acceptable method of birth control such as oral contraceptive, barrier with spermicide (diaphragm or condom), levonorgestrel implant, intra-uterine contraceptive system, medroxyprogesterone acetate injection, surgical sterilization, contraceptive ring or patch, or abstinence.
- Have known sensitivity to buprenorphine or naloxone.
- Aged 14-17 and consent from the parent/legal guardian not obtained
- If aged 14-17, have a parent/guardian who clinical staff judge to be mentally impaired to such a degree that informed consent cannot be obtained, or is abusing substances to such a degree that it is likely to interfere with the subject's participation in the study

10.0 INVESTIGATIONAL AGENTS

10.1 Buprenorphine/naloxone: Reckitt Benckiser via NIDA will provide Buprenorphine 2 mg/Naloxone 0.5 mg, and Buprenorphine 8 mg/Naloxone 2 mg sublingual tablets. Doses of Bup 0.4 mg will also be provided for 1-2 days if clinically indicated at the end of the Bup/Nal taper. The FDA has approved the buprenorphine/naloxone product under the name Suboxone and the mono buprenorphine product under the name Subutex. However, the 0.4 mg buprenorphine dosage form has not been approved for use in the United States. Both Subutex and Suboxone received approval for treatment of opioid dependence in adults. Based on the expected abuse potential of buprenorphine, it has been placed in Schedule III of the Controlled Substances Act.

10.2 Licenses: Approval of the protocol by the appropriate IRB(s) and a current DEA registration by the medical staff who are responsible for dispensing controlled substances must be completed prior to shipping Bup/Nal. Medication will be shipped by a NIDA research pharmacy to the participating programs. Medication will be prescribed, dispensed and administered by legally qualified persons in accordance with federal and state regulations.

*10.3 Medication Replacement***:** There will be no replacement of prescribed or dispensed medication.

*10.4 Buprenorphine Accountability***:** Medication use will be recorded at each clinic visit. The research pharmacy, site physician and other individuals responsible for medication security at the site will maintain accurate and current records of all dispensed and returned medication. Returned medication will be accurately labeled, kept separately until the end of the study, available for audits, and not be re-used.

10.5 Buprenorphine Dispensing: Done by nurses, a study physician, or pharmacists in accord with state and federal regulations.

10.6 Buprenorphine Labeling: Take-home medication will be provided in childproof containers and labeled as follows:

Buprenorphine (0.4 mg) or Buprenorphine/Naloxone combination tablets (2mg/0.5mg and 8mg/2mg)
KEEP OUT OF REACH OF CHILDREN
In case of emergency, please call: (number to be determined)
Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use

Medication will be packaged by the NIDA research pharmacy and distributed to the appropriate pharmacies/dispensing sites.

10.7 Non-opioid medications: may be used for relief of withdrawal symptoms according to the standard of care in the clinic. Any medications that the participant takes in addition to the study medication should be recorded as a concomitant medication.

11.0 STUDY PROCEDURES

11.1 Initial Subject Screening: Staff at each program will be trained in the protocol including a review of the manualized psychosocial treatments. Subjects who give a history of current opioid dependence with physiologic features, who demonstrate signs of opioid withdrawal and appear to meet other eligibility criteria will be asked to provide a signed assent/consent to be screened for eligibility at the time they apply for treatment. A logbook will be kept in each clinic and a note made describing the reasons a patient declines to be screened or enter the study. No identifying information of any type will be kept in this logbook, only a note as to why a person who was asked to participate declined the offer. Those who are screened and considered eligible will be given a full explanation of the study and, if they continue to express interest in participating, asked to sign the informed consent/assent for the study itself.

11.2 Informed Consent: Will include an explanation about the use of random assignment, the treatment conditions, pharmacology of Bup/Nal, recommendations to comply with medication and psychosocial treatment, importance of keeping all scheduled appointments and assessments, conditions under which medication will be stopped, reimbursements for completing the assessments, and the times at which assessments will be needed. Similar explanations will be provided to subjects/guardians as applicable. Subjects/parents/legal guardians who remain interested will complete the informed consent/assent, the quiz and all baseline assessments. The signed assent of the subject and consent of a parent, or the legal guardian(s) will be required for those 14-17 (see Appendix for consents and assents).

Prospective subjects who staff believe have reading difficulties will be asked to read the first two lines of the consent form and the first two questions of the quiz. Those who are able to read will be considered literate and able to proceed without additional assistance. Those who have difficulty reading will have the consent form and quiz read to them by the research assistant and discussed so as to make sure they understand.

In the case of subjects whose parents are separated or divorced, parental consent will be required for the parent who has legal custody; if custody is shared, consent will be required from one parent, preferably the one with whom the subject spends the most time. Each parent/guardian who signs the consent will be required to pass the quiz. The parent or guardian(s) of those 18 or over will be informed of the subject's wish to participate but only with his/her permission. Subjects and parents/legal guardians will be encouraged to ask questions about any aspect of the study. Verification that individuals identified as parents or legal guardians for subjects who are 14-17 years of age are as they represent themselves will be done by inspection of the subject's birth certificate or legal papers designating the identity of the legal guardian(s).

The consent/assent procedure will inform subjects that descriptive information may be shared with research staff to help locate them for follow-up evaluations. The consent/assent will also provide details about responsible use of medication and the conditions under which subjects may be discharged from the study. The consent/assent will specify that the FDA has approved Bup/Nal for treatment of opioid dependence for person's aged 16 and over. This assessment/intake/consent/assent procedure will take several days, which is normal for subjects applying for treatment thus we do not anticipate that participation in the study will delay the start of treatment.

11.3 Administering Bup/Nal: The history, physical examination presence of signs and symptoms of opioid withdrawal and an opioid positive urine test will confirm the presence of current opioid dependence with physiologic features. Laboratory tests that are abnormal may be repeated to confirm/deny abnormality depending on the judgment of the Site P.I. and/or reviewed with the L.I. (Woody), his backup (during vacations or other times when he cannot be reached) or the NIDA Medical Safety Officer to determine if the subject meets study entrance/continuation criteria. Subjects will be instructed not to use heroin or other opioids for at least 6 hours and to be in mild withdrawal prior to receiving the first dose of Bup/Nal. Study personnel will take a history prior to administering the first dose to document the time and date of last opioid use and verify that the subject is experiencing withdrawal. Subjects will be told to hold the study

medication under their tongue until the tablet is dissolved. An explanation of dosing will be provided so the subject understands that the medication will be inactivated if swallowed and that it is likely to cause opioid withdrawal if dissolved and injected.

Bup/Nal will be administered under direct observation and the first dose will be 2-mg/0.5 mg. The study nurse or physician will observe subjects for 1.5-2 hours and give a second dose if clinically appropriate; most subjects are expected to receive an additional 2 to 6 mg (expressed as Bup). Subjects will return on day 2 and will receive the total dose given on day 1 (unless overmedicated or having some other adverse event, in which case it will be reduced). They will be observed for 1.5-2 hours and the dose will be adjusted upward as needed by 2-6 mg using the same methods as on day 1. On day 3 the subject will be given a single dose, which will be the total dose given on day 2 (unless overmedicated in which case the dose will be reduced), observed for 1.5-2 hours and may have an additional upward dose adjustment as needed according to clinical judgment. Subjects experiencing disabling side effects after any dose will have it adjusted until stabilization is achieved. Stabilization will have been achieved when the study physician judges that the subject has few or no signs and symptoms of sedation, withdrawal or other medication-related adverse events during the 24-hour dosing interval. BUP/NAL subjects can have further upward dose adjustments aimed to suppress opioid use up to a maximum of 24 mg/day. TAU subjects will begin a dose taper after reaching a maximum of 14 mg on a schedule that will end by day 14.

The target dose for BUP/NAL subjects will be 12-18 mg Bup/Nal per day since most adolescents on a recently-completed NIDA/VA study have been stabilized on 16 mg/day (Bright, personal communication, 2001), though lower doses are allowed if found clinically appropriate by clinical staff. The target dose for TAU subjects who are receiving outpatient detoxification will be 8-10 mg/day, then tapering to zero within 7-14 days. In both conditions, dosing will be flexible, consistent with clinical practice where efforts are made to have the subject feel comfortable without sedation or other side effects. TAU subjects must begin a dose taper by day 5 and end by day 14. Dose taper for BUP/NAL subjects will be started in the second week of month three and completed over the next 3 weeks, unless done prematurely for any of the reasons described above. Subjects may receive 0.4 – 0.8 mg of Bup (without Nal) during the last few days of dose taper if clinically indicated. Sample detoxification and dose taper schedules are as follows (see next page):

TABLE 1: SAMPLE DETOXIFICATION SCHEDULES FOR TAU SUBJECTS

Day	7-Day Detox.	10-Day Detox.	12 Day Detox	14-Day Detox.
1	6	6	6	6
2	8	8	8	8
3	8	10	10	12
4	6	8	12	14
5	4	6	10	14
6	2	6	8	12
7	0.8*	4	8	12

8		2	6	10
9		2	4	8
10		0.8*	2	6
11			0.8*	4
12			0.4*	2
13				0.8*
14				0.4*

*****Buprenorphine alone

TABLE 2: SAMPLE DOSE TAPER SCHEDULES FOR BUP/NAL SUBJECTS

Day	**Starting dose 8 mg**	**Starting dose 12 mg**	**Starting dose 16 mg**	**Starting dose 20 mg**	**Starting dose 24 mg**
1	6	10	14	18	22
2	6	10	14	16	20
3	6	10	12	14	18
4	6	8	12	14	16
5	6	8	10	12	14
6	6	8	10	12	12
7	4	8	8	10	10
8	4	6	8	10	10
9	4	6	8	8	8
10	4	6	6	8	8
11	4	6	6	6	6
12	4	4	6	6	6
13	2	4	4	4	4
14	2	4	4	4	4
15	2	4	4	4	4
16	2	2	4	4	4
17	2	2	2	2	2
18	0.8*	2	2	2	2
19	0.8*	0.8*	0.8*	0.8*	0.8*
20	0.4*	0.8*	0.8*	0.8*	0.8*
21	0.4*	0.4*	0.4*	0.4*	0.4*

*Buprenorphine alone.

We expect that the initial stabilization for BUP/NAL subjects will take 3-7 days. Medication will be dispensed on an observed basis and between 5 and 7 days/week at the beginning of the study, depending on the site. Subjects in all programs may qualify for up to two take home doses in addition to those they would normally receive at the participating clinic if they have been in treatment for at least two weeks, have provided one or more drug free urine tests following initial stabilization, and are considered appropriate for take home dosing by the Site P.I. and other treatment staff. Take home doses should be ordered such that the patient receives no more than 3 take-homes at any one time unless an emergency or holiday schedule requires otherwise. Appropriateness will include compliance with psychosocial treatment, absence of illegal or

antisocial behavior, and a clinical judgment that medication will be taken as prescribed. These protocol-specific take-home schedules can be modified by the local P.I. if clinically indicated for emergencies such as serious illness, severe adverse weather conditions, etc.

Study medication will be stopped if subjects miss 3 or more consecutive days and will not be restarted if the subject is receiving outpatient detoxification in TAU, however it can be restarted for BUP/NAL subjects if they return within 7 days. Participants who are being restarted will be given one half the previous dose, observed for 1.5 hours and if the restart dose is well tolerated, he/she will receive a portion of or the remainder of the last previous dose as judged appropriate by a study physician at the site. BUP/NAL subjects who miss 7 or more consecutive days will not be eligible to restart Bup/Nal but will be encouraged to continue with psychosocial treatment. Subjects who are receiving Bup/Nal and report using benzodiazepines15 or more days in the last month will have a slow dose taper but will be encouraged to continue with psychosocial treatment. Subjects receiving Bup/Nal who are clinically judged to meet DSM-IV-TR criteria for sedative intoxication will be managed by withholding Bup/Nal for that day and increased counseling. The second instance of sedative intoxication will result in a slow dose taper with encouragement to continue with psychosocial treatment.

Efforts will be made to involve parents/legal guardian(s) to facilitate compliance for all subjects, including those 18 and over unless their participation is judged clinically inappropriate. Examples of inappropriateness would be parents who have active substance use disorders that are likely to interfere with treatment, those who have other psychiatric disorders that render them unreliable or unable to give informed consent for subjects aged 14-17, or situations where so much tension exists that parental involvement is likely to discourage compliance or be otherwise counterproductive.

11.4 Subject Flow and Length of Study:

Week 1:After documenting eligibility, getting informed consent/assent, and completing baseline assessments, subjects will be randomized and begin the study on a Monday, Tuesday or Wednesday. These first three days of the week are chosen because subjects starting Bup/Nal must be seen daily for the first 3 days and these observations will be difficult or impossible to conduct if extended into the weekend. Baseline measures that are not state dependent may be done during the first 2-3 days if more convenient (see baseline measures as outlined in the schedule of assessments). Medication will be administered as described above.

All subjects will be introduced to their counselor and begin psychosocial treatment and weekly evaluations. Stabilizing subjects on medication and managing withdrawal and other psychiatric symptoms will be done in accordance with local standards of care.

Week 2: BUP/NAL subjects continue medication and psychosocial treatment. TAU subjects finish detoxification and continue psychosocial treatment. Non-opioid medications may be used to suppress continuing opioid withdrawal in accordance with local standard of care for TAU subjects but may not be needed in BUP/NAL subjects since the Bup is likely to suppress withdrawal. The research assistant will remind subjects of the pending 4-week evaluation.

Weeks 3 - 4: Psychosocial treatment continues for both groups with a focus on encouraging and maintaining abstinence and continuing in treatment. Those in TAU may have persistent withdrawal symptoms and their management will be a focus of drug counseling. Those in BUP/NAL may require further dose adjustments. Ancillary, non-opioid medications may be used for relief of psychiatric symptoms as clinically indicated in either group, according to local program policies. Weekly evaluations continue and 4-week evaluation is completed.

Weeks 4-8: Psychosocial treatment continues with a focus on encouraging and maintaining abstinence, forming more healthy social networks, and continuing to attend psychosocial treatment. Further dose adjustments can be made for BUP/NAL subjects if necessary. Subjects will be reminded of the 8-week evaluation during week 6. Bup/Nal subjects are reminded toward the end of the first 8 weeks that dose taper begins during week 10; the 8 -week evaluations are completed.

Weeks 9-12: Subjects continue in psychosocial treatment. Subjects reminded of 12- week evaluation during week 10. Dose taper begins for BUP/NAL subjects at the beginning of week 10 and 12-week evaluation completed.

11.5 Missed visits and termination: BUP/NAL subjects who miss 3 or more consecutive doses will have medication stopped but can be restarted if they report to the clinic within 7 days of their last dose, as described above. Those who miss 7 or more consecutive days of Bup/Nal will not have medication restarted but will be encouraged to continue with psychosocial treatment. TAU subjects receiving outpatient detoxification who miss 3 days will have Bup/Nal stopped and not be eligible to have it restarted. Subjects who have no treatment sessions lasting 30 minutes or more for two or more consecutive weeks will be counted as study dropouts. Subjects will be informed of these rules in the assent/consent and at the beginning of treatment. The following windows of opportunity exist for assessments: weekly assessments— +/- 2 days; assessments at weeks 4, 8 and 12— +/- 1 week; and assessments at weeks 24, 36, and 51— +/- 3 weeks.

Subjects may be administratively discharged for serious behavioral problems (threats, diverting or selling drugs, assault, loitering, having weapons in the clinic), according to policies of their program. Efforts will be made to assess subjects at all follow-up points, even if dropped out, administratively discharged, or transferred. Sites other than the clinic may be used to conduct these visits especially if the subject has been administratively discharged. The reason for leaving the study will be noted on the End of Study/Termination case report form.

Subjects who tell study personnel that they have changed their mind and do not want to be contacted for follow-up will not be contacted and their data from that point on will be counted as missing. We do not expect to have many subjects in this category, as this type problem has been uncommon in past studies.

11.6 Safety Precautions: Safety assessments will include physical examinations at screening and 12 weeks; laboratory tests including liver enzymes at weeks 4, 8, and 12; an ECG at screening and at 4 and 12 weeks; urine drug screens; alcohol breath test; monitoring of sedation produced by alcohol, benzodiazepines or other drugs; and regular evaluations of adverse events.

Pregnancy tests will be performed weekly for women on Bup/Nal. The ECGs will be done as a precaution; no prolongation of the QT interval or other ECG abnormalities have been attributable to Bup or Bup/Nal in studies done up to this point.

Adverse events will be noted on the Adverse Event Form. The site physician and/or study nurse will evaluate the intensity, seriousness, and causal relationship of the event to the study medication or treatment condition. This evaluation may require additional laboratory tests or other evaluations if judged necessary in the opinion of study medical personnel at the site, the L.I. (Woody) or NIDA Medical Safety Officer.

SAEs are to be reported (e-mail, fax, phone call) within 24 hours of becoming aware of the event to the Site P.I., L.I. (George Woody, M.D.), and the NIDA medical safety officer as per CTN and FDA guidelines. A follow-up report is to be submitted to the same individuals within five working days unless the SAE was resolved at the time of the initial report. Each site will report to their IRB(s) as indicated in the local IRB procedures for reporting SAEs. All SAEs will be followed up until resolution, and all SAEs will be reported whether or not considered study-related. All study staff are responsible to recognize and report AEs/SAEs upon awareness. If an adverse event occurs, appropriate evaluation and management will be done and may include, in addition to medical treatment, additional laboratory tests, other medical evaluations, a reduction in dose, temporary cessation of medication, or early termination of the trial. Any subject who receives at least one dose of study medication will be included in the safety evaluation.

12. 0 MEASURES

Comprehensive evaluations will be done at screening/baseline and at 4, 8, 12, 24, 36 and 52 weeks. During the first 12 weeks, efforts will be made to obtain weekly self-reports of the number of times opioids and other drugs and alcohol were used each week. Time Line Follow-Back (TLFB) will be used to obtain weekly self-reports for use of opioids, other drugs, and also to obtain these data at the 24, 36 and 52-week follow-ups. The following windows of opportunity exist for assessments: weekly assessments— +/- 2 days, assessments at weeks 4, 8 and 12— +/- 1 week, and assessments at weeks 24, 36 and 52— +/- 3 weeks.

Urinalyses for drugs of abuse will test for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, methamphetamine, morphine (hydrocodone, hydromorphone), oxycodone, phencyclidine (PCP), and tetrahydrocannabinol (THC). The urinalyses for drugs of abuse will be performed on site utilizing the SureStep drug screen card (which tests for all drugs noted above except Oxycodone but does include a test for tricyclic antidepressants) and the Rapid One OXY on-site urine drug screen for Oxycodone. Women will have urine pregnancy testing at screening (except DAP, which will perform a serum pregnancy test at screening as per the requirements of the Duke IRB) and weekly urine pregnancy tests while on Bup/Nal. Alcohol levels will be tested with a breath test. A summary of study measures is:

12.1 Demographics: the CTN Baseline Demographics Form which includes assessment of alcohol and drug use in the past 30 days and lifetime, presence/absence of overdose involving benzodiazepines or other sedatives within the last 6 months and additional locator information.

12.2 Diagnosis: The opioid sections of the Substance Dependence Severity Scale (SDSS) Lite will be used to document opioid dependence with physiologic features (tolerance or withdrawal) and verified by the site clinician. Further evidence for current dependence on opioids will be the history and admitting medical evaluation.

12.3 Health Status:

- Medical history and physical examination at screening and 12 weeks
- CBC with differential and platelets, glucose, BUN, electrolytes, UA at screening and 12 weeks
- Liver panel (AST, ALT, GGT, LDH, and Bilirubin) at screening and weeks 4, 8 and 12.
- Hepatitis B and C at screening and 12 weeks. Note- Hepatitis B and C results are not required prior to randomization.
- ECG at screening and 4 and 12 weeks
- Pregnancy test at screening and weekly if on Bup/Nal

12.4 Inclusion/Exclusion Form to verify that subjects qualify for the study

12.5 Drug Use:

- Urine drug test at screening, weekly for the first 12 weeks and at 24, 36 and 52 weeks
- Alcohol breath/saliva at screening, weekly for the first 12 weeks and at weeks 24, 36 and 52
- Sedation Scale at baseline and weekly for the first 12 weeks.
- Self-report of times used opioids and other drugs at screening, baseline, weekly for the first 12 weeks and at 24, 36 and 52 weeks.

12.6 Adverse Events:

- Weekly during the first 12 weeks and at weeks 24, 36 and 52

12.7 Compliance:

- Records/reports of number and type of psychosocial therapy appointments kept from baseline until end of study or early termination.
- Weekly record of Bup/Nal use.

12.8 Service Received/Therapy Process

- *Non-study Medical Services* (NMS: Polsky, Glick, 2002). This form is a 6-item self-report which asks about medical services that the participant may receive that are not a part of the outpatient program. It looks at therapy appointments, visits to medical offices, hospitalizations and emergency room visits and is to be completed at baseline, weeks 4, 8, 12, 24, 36 and 52.
- *The Helping Alliance II Questionnaire (Haq-II)* at month 1. Measures the therapeutic alliance and takes 5-10 minutes to complete. There are 19 items that the subject rates on a scale of 1-6 from “strongly disagree” to “strongly agree”. An example is the statement “I feel I can depend upon the therapist”. Since subjects may have a group and an individual therapist, the subject will be asked to rate each therapist on the Haq-II at the 4-week evaluation. The Haq-II has been used with success and demonstrates good convergent validity with the California Psychotherapy Alliance Scale (CALPAS) total score (Luborsky et al, 1996).
- *The Addiction Recovery Scale* (ARS; Mercer, Carpenter & Barber, 1993) This scale is a 40-item measure that was used in the NIDA Cocaine/Psychotherapy Study to evaluate mediators of outcome in drug counseling. Items are based on the 12-step approach to recovery ("I know that recovery from addiction is a lifelong process," "When I experience craving, I go to a 12-step meeting," "I haven't gotten around to getting a sponsor," "I rely on my higher power to help me stay clean." The internal consistency reliability (Cronbach's alpha) of the total of the

40-items was found to be 0.82 using baseline data from the main clinical trial in the Cocaine/Psychotherapy Study. This scale will be completed at baseline and week 12.

- *Short Opiate Withdrawal Scale* (SOWS; Gossup, 1990): This 10-item self-report scale is easy to understand and was found to provide a reliable and valid means of measuring the signs and symptoms of withdrawal among persons with opioid dependence. It will be administered to both groups during weeks 1 through 12 and will provide information about Bup/Nal withdrawal symptoms.

12.9 HIV Risk Behavior:

Risk Behavior Survey (RBS) at baseline, 4, 8, 12, 24, 36 and 52 weeks. The RBS is an interviewer administered measure used in all CTN studies and assesses behaviors (sharing injection equipment, unprotected sex) that put one at risk for HIV and other infections such as hepatitis. It takes 5-10 minutes (Booth, 2001).

12.10 Time and Crime: This is a self-report instrument that was developed by Dan Polsky, Ph.D. and obtains information necessary to measure the economic outcomes of the study that are not asked on other instruments. Questions on time spent commuting to treatment come from the Client DATCAP, an instrument intended to collect and organize detailed information on resources used in service delivery and their associated dollar cost (Salome et al, 2003). Questions on Education and Employment are typical of questions in employment surveys of adolescence such as "The Women's Employment Survey and the National Longitudinal Survey of Youth". Questions on crime and legal activity come from the Addition Severity Index, version 5 (McLellan et al, 1992). It takes 5-10 minutes and will be done at baseline and at 4, 8, 12, 24, 36 and 52 weeks.

12.11 Substance Use and Overall Adjustment:

- *Young Adult Self-Report (YASR) and Youth Self-Report (YSR)* (Achenback and Edelbrock, 1991) are questionnaires that have been widely used with young adults and adolescents. The YASR is used with young adults aged 18-30; the YSR for individuals 11-18 who are still in school. Each measure both competencies and internalizing and externalizing problems among individuals in their specified age groups. They are easy to administer, well accepted, and supported by an enormous body of research demonstrating validity and reliability. Problem scales include scores for withdrawal, somatic complaints, anxiety and depression, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior, self-destructive behavior, and total problem behaviors. Each takes about 40 minutes and will be administered at baseline, 12, 24, 36 and 52 weeks. These instruments are copyrighted and a use license has been obtained for this study.
- *EuroQol (EQ-5D)* at baseline, and at 4, 8, 12, 24, 36 and 52 weeks. The EQ-5D is a self-administered, standardized instrument used as a measure of health outcome and comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has three levels (some, moderate, extreme problems), generating a total of 243 theoretically possible health states. One item records self-rated health status on a graduated (0-100) visual analogue scale. The EQ-5D is ideally suited for use in clinics and face-to-face interviews. It is only two pages, cognitively simple, and takes only a few minutes to complete. (EuroQol Group, 1990; Kind et al, 1999).
- *End of Study/Termination:* This form will be completed at 52 weeks or after the subject terminates early. It will collect data on length of time in the study or reason for early termination.

- *Medication Experience (Participant and Staff)*: These are three-item questionnaires that assess the participants experience with the medication Bup/Nal from the participant perspective and one from the staff perspective. These forms are to be completed at the end of the drug treatment phase (end of the 7-14 day Bup/Nal detoxification or the end of the 12 week Bup/Nal) or when the participant terminates early. The staff version of this form should be completed after seeking input from the treatment team.
- *Substance Dependence Severity Scale*: The (SDSS) Lite, along with the baseline assessments, will be used to document opioid dependence with physiologic features (tolerance and withdrawal) and the absence of exclusionary substance dependence diagnoses (benzodiazepine, alcohol, and other sedatives) at screening. The opioid dependence subscale will be repeated at week 12 and at weeks 24, 36 and 52.

After informed consent is obtained, the entire testing battery, not including vital signs, blood draws and the ECG will take approximately 2.5 hours at baseline and 1.5 hours at 1, 2, 3, 6, 9, and 12 months. Weekly assessments will take about 15 minutes. Table 3 summarizes these assessments: (see next page)

TABLE 3: MEASURES

Instrument/Time	P0	P1	P2												P3	P4	P5
	Screen	*B/L*	*Treatment*												*M 6 +/- 3 weeks*	*M 9 +/- 3 weeks*	*M 12 +/- 3 weeks*
	--	--	W1	W2 +/- 2 days	W3 +/- 2 days	W4 +/- 1 week	W5 +/- 2 days	W6 +/- 2 days	W7 +/- 2 days	W8 +/- 1 week	W9 +/- 2 days	W10 +/- 2 days	W11 +/- 2 days	W12 +/- 1 week	--	--	--
Adverse Events			*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
ARS		*												*			
Blood Chemistry	*													*			
Breathalyzer	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
CBC Lab	*													*			
Compliance - Therapy			*	*	*	*	*	*	*	*	*	*	*	*			
Demographics	*																
Dosing Logs			*	*	**	**	**	**	**	**	**	**	**	**			
ECG	*					*								*			
End of Study/Termination																	
EQ-5D		*				*				*				*	*	*	*
HAQ-P						*											
Hepatitis B&C	*													*			
Inclusion/Exclusion	*																
Liver Enzymes	*					*				*				*			
Med Experience PT			*	*	*	*	*	*	*	*	*	*	*	*			
Med Experience Staff			*	*	*	*	*	*	*	*	*	*	*	*			
Medical History	*													*			
Non-Study Medical Svr		*				*				*				*	*	*	*
Physical Exam	*													*			
Pregnancy Test (F only)	*	*	*	*	**	**	**	**	**	**	**	**	**	**			
Prior/Con Medication	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Random/Study Enroll		*															
RBS		*				*				*				*	*	*	*
SDSS Lite	*													*	*	*	*
Sedation Scale		*	*	*	**	**	**	**	**	**	**	**	**	**			
Serious Adverse Events		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
SAE Addendum		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
SOWS			*	*	**	**	**	**	**	**	**	**	**	**			
Time & Crime		*				*				*				*	*	*	*
Timeline (Monthly)															*	*	*
Timeline (Weekly)(D&A)			*	*	*	*	*	*	*	*	*	*	*	*			
Urine Analysis Results	*													*			
Urine Drug Screen	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Vital Signs	*	*	*	*	**	**	**	**	**	**	**	**	**	*	*	*	*
YASR (18-21)		*												*	*	*	*
YSR (14-18)		*												*	*	*	*

* Both Groups
** Bup/Nal Group
P=phase
M=month
W=week

13.0 REGULATORY AND REPORTING REQUIREMENTS

13.1 FDA Form 1572: The Principal Investigator and all persons who will be assisting in the conduct of the study will be listed on FDA Form 1572. The site investigator will sign the Statement of Investigator (FDA Form 1572) prior to beginning the study**.** The FDA Form 1572 must be updated should any of the information change.

13.2 IRB Approval: Written IRB approval will be obtained from the appropriate IRBs before the study begins. Should changes to the protocol and/or informed consent become necessary after the study begins, amendments will be submitted in writing by the investigator for IRB approval. No advertising for subject recruitment will be done without IRB approval of the content of the advertisements.

13.3 Informed Consent: The potential study candidate or parent/legal guardian will be given a brief explanation of the study and a copy of the IRB-approved screening consent/assent. If agreement to be screened is obtained, screening measures will be completed. If the subject meets admission criteria a copy of the study consent/assent form will be given to him/her and if applicable, to the parent/legal guardian. The RA and study physician at each site will explain all aspects of the study in lay language and answer the subject's questions. The P.I., Co-P.I. and Project Director will be available by phone, cell-phone or e-mail for additional information/explanation if necessary. If the subject wishes to participate, he/she will be asked to sign the informed consent/assent; no study procedure other than the baseline evaluation will be performed prior to signing. Subjects who do not wish to participate or who agree but later withdraw from the study will be treated in the collaborating program in the usual manner without prejudice. The research assistant will keep a log of all subjects approached for the study and note reasons for refusal to enter; reasons for early termination will be noted on the End Study Report.

13.4 Drug Accountability: Upon receipt of study medication from the NIDA research pharmacy, the program pharmacist/nurse will be responsible for taking an inventory and providing secure storage. A record of the inventory must be kept and usage documented at the research pharmacy and the local site from which medication is dispensed. Any unused or expired medication will be destroyed according to procedures outlined in the Operations Manual.

13.5 Outside Monitoring

Data and Safety Monitoring Board (DSMB): An independent Data and Safety Monitoring Board (DSMB) will examine accumulating data to assure that the risks and benefits of participation remain acceptable and that the results of the trial will be scientifically valid. This DSMB is formed by NIDA and serves that function for all CTN protocols.

Clinical Monitors: All investigators and study sites will allow the L.I. or his designate, NIDA and /or their representatives and representatives from their own Node and IRB's to audit the participating programs and source documents. Monitoring visits provide an opportunity to evaluate the progress of the study, the quality of the data, compliance with the protocol, and potential problems. Monitors will check to make sure that data are accurate and in agreement with source documents. They will verify that study medications are properly stored and accounted for, that consent/assent forms have been properly obtained and the process documented, that participants entered into the study meet inclusion criteria, and that all essential documents required by good clinical practice guidelines are appropriately completed and filed.

Lead Node QA Monitor or Lead Node QA Representative will conduct a site initiation visit prior to beginning the study. They will assure that proper study-related documentation exists, that all relevant training has been completed, and that the appropriate infrastructure and facilities are in place. Lead Node monitors may revisit a clinical site as needed at any time during the course of the study.

Visits by Node QA monitors will be coordinated and scheduled at specified intervals, more frequently at the beginning of the study. The monitors will verify that procedures are being conducted according to the protocol and GCP guidelines. At the end of the study, monitors will advise on storage of records and return of unused medication.

13.6 Adverse Event Monitoring (AEs): All AEs occurring during the course of the study must be collected, documented, and reported to the Lead Node, Site P.I. local IRB(s), and the NIDA Medical Safety Officer at intervals stipulated by the CTN but at least annually. The occurrence of AEs will be assessed at baseline and weekly during the first 12 weeks and again at the 24, 36 and 52-week follow-ups. Timeline follow-back methods will be used to query about AEs in case of missed appointments.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the study, whether or not it is considered medication-related or clinically significant. An unexpected AE is one that is not described with respect to nature, severity, or frequency in the Investigator Brochure. For this study, AEs will include events reported by the subject or observed by clinic or study staff. A new illness, symptom, sign, or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions that were present prior to study entry and do not worsen are not considered AEs. All AEs must be recorded on the AE form and classified as mild, moderate or severe, and as definitely, possibly or not related to study medication. The AE Form will also be used to record follow-up information for unresolved events previously reported and study investigators will follow all AEs until a resolution. All AEs will be assessed to determine if they meet criteria for a SAE. Local investigators will be encouraged to consult with the Lead Node or NIDA if they are uncertain whether or how to classify an event.

13.7 Serious Adverse Events (SAEs): A serious adverse event is defined as any event that is fatal; immediately life-threatening; requires intervention to prevent serious injury; is permanent or substantially disabling; requires or prolongs inpatient hospitalization; or a congenital anomaly. Subjects will be systematically evaluated for SAEs at each clinic visit per CTN and FDA requirements. Any event that a study investigator, the NIDA Safety Monitor or the NIDA Data Safety and Monitoring Board (DSMB) judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution is also classified as a SAE. Examples are allergic reactions, hypotension that requires clinical intervention, elevation of one or more liver enzymes to greater than five times the top limit of normal, lengthening of the QT interval or other cardiac abnormality, hospitalization for any reason, and study-related accidents. Any SAE, whether or not related to the study, must be reported within 24-hours of the time it becomes known to study personnel by telephone, e-mail or fax to the L.I., Project Director, or their alternate; and to the NIDA/CTN Medical Safety Officer that is responsible for monitoring the study. Contact numbers for these individuals are in the operations manual.

The initial SAE report is to be followed by submission of a final SAE Form within five working days. Attached to the SAE Form should be photocopies of any relevant information, including physical examination(s) and laboratory results. Consultation with the Lead Node is encouraged if there is uncertainty about whether an event should be classified as an AE or SAE. All SAEs must be followed-up until resolution. A follow-up report is required unless the SAE was resolved in the initial report.

NIDA, as IND holder, is required by FDA regulations to report SAEs to the FDA in a timely fashion. If the SAE is fatal or life threatening, the Sponsor must notify the FDA by telephone within 3 working days, with a follow-up written report in 10 working days. All other reportable SAEs must be reported to the FDA in writing within 10 working days from the date the Sponsor was notified of the SAE.

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. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA so that the Sponsor can comply with these regulations.

In the event that a subject withdraws from the study or an investigator decides to discontinue him/her due to a SAE, the subject must have appropriate follow-up monitoring. The outcome of SAEs must be reported through NIDA to the DSMB.

13.8 Record Retention: Government regulations require that the investigator retain all study documentation pertaining to the conduct of a clinical trial for a minimum of 5 years after discontinuation of the IND or 7 years after the last publication.

14. HUMAN SUBJECTS

14.1 Safety and Side Effects: Buprenorphine has been studied in children aged 2-12 for pain control and has been found safe and effective. It also has been shown to have a favorable safety profile among adults, as described earlier. It has been administered to several hundred opioid addicts aged 21 and under for detoxification with no known serious adverse events and a significant reduction in discharges against medical advice (Bright, personal communication, 2000; Mulligan, personal communication, 2000). Bup/Nal has been administered to at least 67 subjects 14-21 for longer periods of time with no known SAEs definitely attributed to it. The known risks of taking Bup/Nal for persons of any age are small, especially when compared to the risks of untreated opioid dependence. The close monitoring that will be provided should provide adequate safeguards to quickly identify and respond to adverse events if they occur.

A description of possible side effects attributable to Bup/Nal is detailed in the consent form and will be reviewed with the subject and his/her parents/guardians prior to beginning the study, as described earlier. Possible side effects include sedation; physical dependence; precipitation of withdrawal in opioid dependent individuals; and overdose if taken with high doses of benzodiazepines, alcohol or other sedatives. Each of these potential problems will be explained

in the consent and reviewed verbally and in writing with the subject and (if applicable) the parents/guardian(s). Precautions against entering subjects who are abusing benzodiazepines or other sedative type drugs or of continuing subjects on Bup/Nal who develop benzodiazepine, alcohol or other sedative drug dependence have been described earlier in this protocol.

LAAM, a medication that has been approved for maintenance treatment of opioid dependence, has recently been reported to cause toursades de pointes and deaths in a very small number of subjects. This finding led to its being taken off the market in Europe and a warning that it should be used only as a second tier medication in the U.S. No cardiac abnormalities have been attributed to Bup or Bup/Nal in studies done to date but because problems have occurred with LAAM, ECGs will be done at baseline and at 4 and 12 weeks. Subjects with an abnormal ECG will be excluded unless approved for participation by the site physician or LI after review by a cardiologist. Examples of ECG findings that could exclude subjects and require evaluation by a cardiologist are: prolongation of the PR interval (> 200 ms); a QRS that is wider than normal for the subject's age (> 119 ms); a QTc interval that is longer than 450 ms; or an arrhythmia. Subjects with an abnormal ECG will be referred to their primary care provider or a cardiologist for evaluation. Subjects who develop an abnormal ECG that is clinically significant and judged by a site physician in consultation with a cardiologist to be a potential problem while on Bup/Nal will be slowly detoxified and referred to their primary care provider or a cardiologist for further evaluation.

Below is a summary of the monitoring plans described in the protocol for each area of clinical concern.

Data Collected	Schedule of Assessments		Limits for Safety	Actions Taken
	Pre-Randomization	**Post-randomization**		
Cardiac Data (EKG)				
The PR interval	Screening	Wks 4 & 12	Prolongation > 200 ms	Consult; exclude and/or slow taper off Bup
QRS	Screening	Wks 4 & 12	Wider than normal for age (> 119 ms)	Consult & allow if not clinically signif;or, exclude and/or slow taper off Bup
QT	Screening	Wks 4 & 12	Longer than 450 ms	Consult & allow if not clinically signif; or, exclude and/or slow taper off Bup
Arrhythmia	Screening	Wks 4 & 12		Consult & allow if not clinically signif; or, exclude and/or slow taper off Bup
Benzodiazepine Usage Data				
Self Report	Screening via Demographics	Weekly for first 12 wks via TLFB	15 or more times in past 28 days	Exclude (if at screening) or slow taper off Bup
Urine test	Screening	Weekly for first 12 wks	Positive for Benzodiazepine	Exclude if unable to provide neg. urine after 3 tries within 14 days after screening; slow taper off Bup if occurs twice
Sedation Scale	Screening	Weekly for first 12 wks	Judged to be intoxicated	Exclude (if at screening); hold Bup; slow taper off Bup if occurs twice.
Pregnancy Data				
Pregnancy Test	Screening	Weekly (if on Bup/Nal) for first 12 wks	Positive for pregnancy	Exclude (if at baseline) or low dose taper off Bup
Liver Panel				
Test of liver enzymes	Screening	Wks 4, 8 & 12	Single liver enzyme 5X top limit	Exclude and refer to primary care provider or hepatologist (if at screening); refer to primary provider, or hepatologist (if in study)
Test for Hepatitis B or C	Screening		Positive result	Refer to primary care provider or hepatologist

Note: Subjects who fail screening may be re-screened in 28 days after start date of initial screening if site physician judges that exclusionary finding(s) likely reflect a transient condition.

14.2 Reporting Abuse and Neglect: Reporting abuse or neglect to social agencies for those under 18, or for the elderly, is required by most states. Participants may report abuse or neglect during the baseline interview or at any time during treatment, and they must know that the participating CTPs are obligated to report such cases, as described in the consent form. Similarly, participants

who are evaluated as suicidal or homicidal must understand that the CTP is obligated to take emergency action which may involve communicating this information to a third party or even involuntary commitment to a psychiatric treatment facility. This information will be included in the consent form as well.

14.3 Confidentiality: Research records will be protected by a Certificate of Confidentiality issued by the National Institute on Drug Abuse, which protects the investigator from releasing information where the participant is identified by name, even under court order or subpoena. This protection applies to all situations except mandatory reporting requirements, as described above. Data obtained by research staff, including urine or breath test for drugs of abuse or alcohol, will not be shared with clinical staff and will be protected by the Certificate of Confidentiality.

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

14.5 Subject Reimbursement: Follow-up data are extremely important since differential dropout from treatment is expected. Vouchers with cash equivalents to purchase recreational or necessary items such as CD's, clothes, a Walkman, food or clothing will be used to reimburse subjects. Each site will choose what cash equivalent reimbursement is most appropriate for their subjects. The cash equivalents have been chosen to be not so high as to create implicit coercion to participate, yet high enough to strongly encourage compliance with the assessments. These amounts will have to be approved by each IRB; we are proposing:

- $10 voucher for completing screening and baseline evaluations
- $75 vouchers for the 4, 8, 12, 24, 36 and 52-week evaluations with a bonus of a $75 voucher if all assessments are completed (maximum = $525). The bonus voucher will not be offered at the sites in the Southwest Node (ASAP and Ayundantes.
- $5 vouchers for weekly assessments during the first 12 weeks, except those at 4, 8 and 12 weeks when the monthly assessments are done (maximum = $45)
- The maximum a subject can earn if all assessments are completed is $570 over 52 weeks.

Subjects will be reminded of assessment appointments at the time they attend clinic, or by using the locator information that was described earlier.

All subjects will be issued an ID card stating that they are participating in a federally funded study of Bup/Nal and a phone number to call in case of emergency.

15.0 ANALYTIC PLAN

15.1 Primary and Secondary Outcomes and Hypotheses: The primary outcome measure will be the presence of opioid use, as measured by urine test, at 4, 8 and 12 weeks of treatment. The

primary hypothesis is that, over this period, opioid use will be significantly lower in the BUP/NAL group than in the TAU group.

There are seven secondary outcomes, all of which refer to the first 12 weeks of the treatment period:

1. Time to early termination from psychosocial treatment, defined to occur at the first time no psychosocial treatment lasting 30 minutes or longer (individual, group, or family) in the assigned condition has been met for two consecutive weeks.
2. Self-reported opioid use, as measured by the TLFB
3. HIV risk, as measured by the RBS
4. Self-reported substance use, other than opioid use, as measured by the TLFB
5. Psychosocial functioning, as measured by that dimension of the YASR or YSR
6. Delinquency, as measured by that dimension of the YASR or YSR
7. Total problem behaviors, as measured by the YASR or YSR

The secondary hypotheses are that the Bup/Nal group will have better outcomes in each of these seven domains than will the TAU group. The extent to which the expected improvements in these domains in the Bup/Nal group, relative to the TAU group, are maintained over 24, 36 and 52 weeks will also be examined. Here, it is expected that the Bup/Nal group will continue to show an advantage over the TAU group.

15.2 Pre-analysis: Prior to performing analyses addressing the primary and secondary hypotheses, standard data screening/cleaning procedures (Tabachnik and Fidell, 2000) will be applied. These procedures will (1) screen the data for data-entry errors, (2) check for outliers, and (3) assess the extent and pattern of missing data. Descriptive statistics will be calculated for all response variables and for principal explanatory and demographic variables. These will include means, standard deviations, and 5-number summaries for continuous variables, and proportions for categorical variables.

An important set of analyses will compare the characteristics of TAU across the sites. These comparisons will include measures of subject attitude and beliefs about treatment received (e.g. total score on the Haq-II, and ARI), and measures of treatment received (e.g. number of appointments of 30 minutes or more for group or individual therapy made by subjects, obtained from the weekly reports). Measures that appear to differ significantly across the sites will be considered for inclusion as covariates in the main analyses. It is possible that such differences will not fully capture unexpected differences in TAU across the sites. To allow for such differences, we will include a term for site (in the role of a blocking factor) in our analyses, and will test for a site by treatment interaction in each analysis. If a significant site by treatment interaction is found, the results for that analysis will be described in terms of effects within the three sites, while the overall effect will be reported for analyses in which no significant interaction is found.

15.3 Randomization: The study participants will be randomly assigned to one of the two treatment groups using urn randomization, as described above in the Study Design section. Because of the size of the sample, and the use of the urn randomization, no baseline differences between the treatment and control groups are expected, and the primary analysis of the outcome

variable will make no adjustment for baseline differences between the two groups. Secondary analyses will be performed to identify baseline variables on which the groups may differ. Any significant differences between the groups will be included as covariates in the outcome analysis to test group differences based on outcome measures adjusted for baseline non-equivalencies. This analysis will be regarded as supportive of the primary analysis, and is in conformity with the ICH guidance on statistical principles, section 5.7 (DHHS, 1998). Analyses associated with the primary and secondary outcomes will follow an "intention to treat" rule in which subjects' treatment group assignment is the one to which they were initially assigned.

15.4 Subject Population: The analysis of the primary and secondary outcomes will be based on all subjects randomly assigned to the BUP/NAL and TAU groups; follow-up is planned for all subjects regardless of their intervention or drop out status. Sensitivity analyses will be conducted to compare the tests of hypotheses using all assigned subjects versus all subjects who have not terminated early at three months. No subset analysis is planned, although it may be necessary depending on the results of the overall analyses.

15.5 Analysis Plan: In all analyses, the assumptions underlying the application of all statistical methods that are used will be examined, principally through the use of standardized residuals, influence diagnostics, and graphical displays.

Overall Analytic Plan: The objective of this study is to "determine if a 12 week course of outpatient buprenorphine/naloxone (Bup/Nal) plus psychosocial treatment results in fewer opioid positive urine tests at 4, 8 and 12 week evaluation points among opioid dependent adolescents and young adults (ages 14-21) than usual treatment which is detoxification plus psychosocial treatment alone." As stated earlier in the protocol, " A generalized estimating equation (GEE) model will be used to compare the log-odds of opioid use between the two treatment groups. It is expected that the principal group effect will be that Bup/Nal (12 week) group will show a significantly lower odds of use at the end of 4 4weeks, and that this difference will remain through the 8 and 12 week follow-up points."

Primary Efficacy Outcome: As described above, the primary response will be the three indicators of opioid use during the initial 12 weeks. A generalized estimating equations (GEE) model (Diggle, Liang, and Zeger, 1994) will be used to compare the log-odds of opioid use between the two treatment groups. The GEE approach only makes assumptions with respect to the mean and variance of the data, rather than to the full distribution. This provides a "robust" approach, but usually at the cost of larger sample sizes. Based on the work of Lipsitz et al (1994), the sample size in this study will be more than adequate for the method to be valid. The explanatory variables will be group and time, and an interaction term will be used to test for differential trends over the 12 weeks. It is expected that the principal group effect will be that the BUP/NAL group will show a significantly lower odds of use at the end of the first 4 weeks, and that this difference will remain through the remaining 8 weeks. It is also expected that the BUP/NAL group will continue to improve relative to the TAU group over the 12-week medication period, and the interaction term will test for this.

Secondary Efficacy Outcomes**:** The time to early termination from psychosocial treatment will be compared using Cox regression models. Subjects are scheduled to have two sessions of

psychosocial treatment each week, which provides a reasonably continuous time scale for the analyses. The main explanatory variable will be treatment group. The main assumption for these models, that the hazard rates for the two groups are proportional, will be examined using time-varying explanatory variables (Collett, 1994).

The weekly reports and TLFB will provide reports on daily use of opioids and other illicit drugs across the first 12 weeks. These reports will be used to construct repeated measures of use for each of the six two-week periods (viz. number of days used in each period). The treatment groups will be compared, separately for opioids and other substances, using GEE models similar to that of the primary response.

Most of the remaining secondary hypotheses, dealing with HIV risk, psychosocial functioning, and delinquency, will use measures gathered at the 4, 8, and 12 week assessments, and will be tested using GEE models. As usual, the main explanatory variables will be treatment group and time and their interaction. In each case, the response will be continuous, and is likely to be skewed towards scores representing poorer outcomes. Although GEE models do not assume that the response is normally distributed, it is usually helpful to reduce such skewness by transformation of the response. The final secondary measure, problem behaviors, is obtained as a single measure for the entire three-month period, and will be analyzed using an analysis of covariance model.

Post-Treatment Outcomes**:** The extent to which the expected benefits of Bup/Nal persist after the treatment period will be examined by considering the secondary measures, at follow-up assessments at 24, 36 and 52 weeks after the start of the treatment period. In addition to treatment group, variables indicating extent of compliance with psychosocial treatment will also be included as explanatory variables in these models. This will allow investigation of whether variation in compliance is associated with longer-term treatment outcome.

15.6 Other Analytic Issues:

Design Effects: Given the multi-site nature of this study, design effects might be expected to result from intra-class correlation of the measures. Thus, indicators of the clinical sites will be included as random effects in secondary analyses of the primary and secondary outcome measures. As the sites are reasonably similar, the biggest effect of such clustering is likely to be a change in standard errors, which would be unlikely to alter the main conclusions of the study's analyses.

Sampling Bias: In previous studies of adults given buprenorphine, high enrollment has been reported. Thus, enrolled subjects are expected to be similar to the clinic populations from they have been sampled, so the results of the study should be generalizable to those populations.

Missing Data: The primary analysis, and most of the remaining secondary analyses, will use the monthly assessments, where it is expected that rates of attendance will be much higher than for the weekly appointments in the TAU group. It is likely that there will be missed monthly assessments, with a greater number expected in the TAU group. It is possible that, in such a situation, analyses that ignore the missing data may yield significantly biased results. Although

there is no formal procedure that will completely address this problem, two methods have been developed, selection models and pattern mixture models. Selection models try to simultaneously model the dropout process and the observed data. Pattern mixture models (Little, 1993) compare the treatment-outcome relationships between the main patterns of missing data. As pointed out by Hedeker and Gibbons (1997), selection models (e.g. Kenward (1998); Rotznitzky, Robins, and Scharfstein (1999) may be most useful when the dropout process is well understood, and the variables that influence it are known to be measured. In the present study, little is known about the dropout process in the adolescent/young-adult population, and pattern mixture models will be used to examine the effects of missing data on the conclusions of the analyses.

To implement these models, subjects are grouped on the basis of their pattern of missing data (with amalgamations of rarely occurring patterns to keep the number of pattern-groups at a manageable level). This grouping defines a nominal variable, which is then used as a predictor in the analyses. For longitudinal data, subjects are usually grouped according to the visit after which they dropped out. As in the primary analysis, and most of the secondary analyses, this will involve a small number of time points, the number of patterns to be considered in this study will be small. The regression coefficients associated with this nominal variable, and its interactions with the other predictors, quantify how response-predictor relationships differ across the different patterns of dropout. Overall effects for the explanatory variables may then be found by averaging over the patterns (Little, 1993).

As mentioned above, there is no method that will completely deal with the problem of missing data. Pattern mixture models provide a formal framework, but much of their implementation proceeds in an exploratory manner. Kenward (1998) gives an example of this interplay between formal models and exploratory data analyses in the context of selection models. An example of a pattern-mixture application to a GEE model in longitudinal data with dropout is given by Park and Lee (1999).

It is likely that, in addition to the missing data caused by missed visits, there will be a small amount of other data missing due to skipped items or skipped forms. For analyses involving such omissions, we will use EM-algorithm-based single-imputation methods, as described in Schafer (1997, Chapter 3).

15.7 Sample Size Calculation: Power estimates are for the primary hypothesis, at a 5% significance level. Initially, there will be 120 subjects in each of the two treatment groups. The primary response will be tested using a three time-point GEE model. The power estimates for this model are based on Pan (2001). Certain assumptions need to be made on the expected numbers of time points per subject, and on the "true" and "working" correlation structure among the repeated measurements. For the correlations, a conservative assumption is that both working and true correlations are compound symmetric; as this situation requires more subjects than the others considered by Pan. In the absence of pilot data, it is assumed for the present study that the required correlation parameter is 0.5.

Pan's calculations can accommodate subjects with different numbers of observations, thus allowing for the effect of dropout. They cannot, however, allow for differential dropout rates over the two treatment groups. The expected rate for the TAU group is therefore used for both

groups, although this will lead to an underestimate of the power available. For these calculations, we assume that we will lose 50% of the TAU group to follow-up by the three-month visit. We view this as an overestimate of the rate of loss. For simplicity, assume also that this occurs linearly, with about 20% dropout between assessments, as the power estimates were not sensitive to changes in the pattern of dropout leading to 50% total loss.

Under these assumptions, the smallest treatment effect that can be detected with 80% power is about a 20% difference in the probabilities of use over the groups (corresponding to an odds ratios of about 2.5). As an example, the sample size of 240 provides 84% power for rates of use of 20% in the Bup/Nal group and 39% in the TAU group. Pan does not provide formulae for the testing of an interaction effect, as might be needed if there were a large site by treatment interaction. It is clear that the smallest detectable difference between the groups would be larger in such a case. As an extreme case, assuming we test the treatment effect separately in each site, and have about 80 subjects available, our smallest detectable difference would increase to about 30-35%.

15.8 Interim Analysis

Rationale for An Interim Analysis: Buprenorphine has been approved for treatment of opioid dependence and can be used to treat those aged 16 and above. This study proposes to use this treatment in adolescents aged 14 to 21. Buprenorphine has not been approved for use in those below 16 years of age, so this study is being conducted under an IND, and will require an interim analysis.

As described in page 11 of the protocol, “Current treatments for opioid dependent adolescents and young adults are often unavailable and when found, clinicians report that the outcomes leave much to be desired. The investigators hope to improve this situation by making Bup/Nal available and combining it with psychosocial treatment while also providing some of the first data on efficacy and safety of Bup/Nal when used with subjects in this age group”. Therefore, a formal interim evaluation of treatment efficacy may demonstrate earlier that Buprenorphine is effective in this population.

Administrative Considerations: A statistical test of the primary hypothesis will be performed when approximately half of the stated sample size has been enrolled in the study for at least three months.

Methodological Details

- Primary Endpoint
    - Urine tests for opiates obtained at 4, 8 and 12 weeks post randomization.
- The Statistical Hypotheses

- H_0: The proportion of urines negative for opioids obtained from participants exposed to the 12-week buprenorphine maintenance arm will be the same as the proportion obtained from the participants exposed to the 7 – 14 day Buprenorphine detoxification.
- $H_{1:}$ The proportion of urines negative for opiates obtained from participants exposed to the 12-week buprenorphine maintenance arm will be different from the proportion obtained from the participants exposed to the 7 – 14 day Buprenorphine detoxification.

- The Statistical Tests
  - The difference in the proportion of participants with clean urines across the two treatment groups (pooled across the 4, 8 and 12 week points in time.) is greater than zero. Within the context of the GEE model, this translates to a test that the parameter for the treatment group effect is greater than zero.

- Interim Type I error Rate
  - We suggest that this be determined by the O'Brien-Fleming procedure (see O'Brien, Peter C. and Fleming, Thomas R. *A Multiple Testing Procedure for Clinical Trials*. Biometrics, 35, 1979, 549-556. Also, see the formulas presented on pages 29 and 30 of Group Sequential Methods with Applications to Clinical Trials, by Christopher Jennison and Bruce Turnbull. 2000. Chapman and Hall/CRC. Boca Raton). Accordingly, if the overall alpha level were to be .05, then for one interim look, for a two-sided test, the interim alpha level would be .00517566. On the final look, the alpha level would be .048.

- Required Sample Sizes per Group.
  - The sample size requirements were computed for 80% power, with an alpha of .05. With the use of the O'Brien-Fleming corrections for Type I error rates, the required sample size is slightly higher. These calculations are proportional to those computed for a given effect size and variance estimate by factors that increase with K (the number of interim looks). For power of .80, and overall alpha of .05, the required sample size per group is 1.008 times the original estimate, or (1.008*120) = 120.96, or 121. Then, the total, recomputed sample size is 242 rather than 240.

15.9 Post Hoc Analyses: Post hoc analysis will further examine the association of treatment processes and outcomes. The measures of treatment processes will be obtained from the HAQ-II, and the ARS. Proportion of opiate free urines, and the secondary outcome measures, at weeks 24, 36 and 52 will be regressed on the measures of treatment process from the previous time points. The indicator of treatment randomization will be entered into these equations first to permit an estimation of the degree to which service utilization and other aspects of the treatment process explain the outcomes, over and above the receipt of treatment.

16.0 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

16.1 Data collection: Data will be collected on a secure web based system developed by the Delaware Valley Node. Paper CRFs will be prepared by the Delaware Valley Node and made available at the study sites and in most instances should only be used only if there is a technical problem with the web based system. These forms should then be entered into the web-based system once the technical problem is resolved. Some CRFs will be collected on paper and later entered into the web-based system. Forms that are to be completed first on the paper CRF and later entered into the web based system will be designated in the Study Operations Manual.

The Node Investigator will be responsible for maintaining accurate, complete and up-to-date records, and for maintaining any source documentation related to the study in accordance with the standards for Good Clinical Practice and the Food and Drug Administration.

Paper CRFs must be completed legibly with black ballpoint pen. Striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry should be used to make corrections. Corrections to paper CRFs must be initialed and dated by the person making the correction. The Principal Investigator must retain a copy of all original CRFs.

16.2 Data Accrual, Editing and Control: Data will be collected and entered directly into the web-based system. This system will provide an audit trail of data entry and on-line QA functions. Once the data have been entered a data query document will be produced and forwarded to the participating node if inconsistencies or questions arise. The collaborating nodes will be responsible for distributing these queries to appropriate personnel for timely resolution. Sites will resolve data inconsistencies and errors with the Delaware Valley Data Management Center.

16.3 Data Backup: All data entered into the data entry system is stored in SQL Database Server tables. The data on the SQL database server is replicated to a backup server in real-time. In addition the data are also backed up daily on tape. Two sets of tapes are maintained with one set being stored off-site.

16.4 Data Entry, Processing and Analyses: Data from the web-based system will be submitted to the NIDA central data repository according to specified procedures.

16.5 Study documentation and Records Retention: Study documentation must include all case report forms, data correction forms, electronic data files, workbooks, source documents, monitoring logs, drug accountability 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 subject consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, subject diaries and progress notes, ultrasound photographs, hospital charts or

pharmacy records and any other reports or records of any procedure performed in accordance with the protocol.

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

CTN/NIDA policy requires that the investigator retain all study documentation pertaining to the conduct of a clinical trial for a minimum of 5 years after discontinuation of the IND or 7 years after the publication of the last paperr.

17.0 CONFIDENTIALITY

The Delaware Valley Node has a Confidentiality Certificate that will protect research data from non-research oriented external demands such as subpoenas or court orders. NIDA or any regulatory agency may consult and/or copy study documents in order to verify case report form data.

Abuse and neglect reporting to social agencies for persons under 18 and for the elderly is required by most states. Participants may report abuse and neglect during the baseline interview or at any time during therapy, and they must know that the participating CTPs are obligated to report such cases to the appropriate social agency. Similarly, participants who are clinically evaluated as suicidal or homicidal must understand that the CTP is obligated to take emergency action which may involve communicating information to a third party or even involuntary commitment to a psychiatric facility. Many states require reporting of specific communicable diseases such as hepatitis, tuberculosis, syphilis or AIDS. We do not anticipate having more than a few subjects with AIDS due to their young age and the fact that younger subjects tend to have a longer period of time between HIV infection and development of AIDS. The protection from the Confidentiality Certificate will apply to all situations except these mandatory reporting requirements, which may vary according to local IRB and state requirements. Data obtained by research staff, including urine drug tests and or breath test for alcohol, will not be shared with clinical staff and will be protected by the Certificate of Confidentiality.

Information furnished to the investigator by NIDA and/or Reckitt Benckiser will be maintained in confidence. However this information can be divulged to the IRB, Ethical Review Committee, or similar or expert committee; affiliated institution; and research employees but only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

18.0 QUALITY ASSURANCE

The main goal of quality assurance is to protect the rights /safety of human subjects and make certain that the study results are credible. To these ends, there will be a 100% review of all informed consents and documentation of informed consent process, 100% review of the research data obtained from the first 10 subjects recruited at each site followed by a minimum 10% random sampling of these documents every 8 weeks until the end of the study.

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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 13.7 of this protocol.

Typed Name	**Signature**	**Date**
_____	_____	_____
Principal Investigator		
_____	_____	_____
Co-Principal Investigator		