
NIDA-CTN-0030

**A Two-Phase Randomized Controlled Clinical Trial of
Buprenorphine/Naloxone Treatment Plus Individual Drug
Counseling for Opioid Analgesic Dependence**

**NATIONAL INSTITUTE ON DRUG ABUSE
CLINICAL TRIALS NETWORK**

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List of Abbreviations

<u>Abbreviation</u>	<u>Definition</u>
AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT/SGPT	Alanine aminotransferase
ASI	Addiction Severity Index
AST/SGOT	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
BUN	Blood urea nitrogen
BUP	Buprenorphine
BUP/NX	Buprenorphine/naloxone
CAB	Common Assessment Battery
CAP	College of American Pathologists
CBC	Complete blood count
CCC	Clinical Coordinating Center
CIDI	Composite International Diagnostic Interview
C _{max}	Maximum concentration
COWS	Clinical Opiate Withdrawal Scale
CPA	Continuing Protocol Application
CPK	Creatine phosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CTN	NIDA Clinical Trials Network
CTP	Community treatment program

<u>Abbreviation</u>	<u>Definition</u>
DATA	Drug Addiction Treatment Act
DHHS	Department of Health and Human Services
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th Edition
EMM	Enhanced Medical Management
ESR	End of Study Report
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GGT	Gamma glutamyltranspeptidase
HIV	Human immunodeficiency virus
IDC	Individual Drug Counseling
IRB	Institutional Review Board
LDH	Lactic dehydrogenase
LFT	Liver function test
LI	Lead Investigator
LN	Lead Node
mg	Milligram
ML	Maximum likelihood
MPA	Multiple Project Assurance
NIDA	National Institute on Drug Abuse
NTP	Narcotic treatment program
NX	Naloxone
OHRP	Office of Human Research Protection
OTP	Opioid Treatment Programs
RA	Research Assistant
REML	Restricted maximum likelihood

<u>Abbreviation</u>	<u>Definition</u>
SAE	Serious adverse event
SD	Standard deviation
SMM	Standard Medical Management
VAS	Visual Analog Scales
WNL	Within normal limits

1.0 Study Synopsis and Schema

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1-1	<i>Study Design</i>
1-9	<i>Study Population</i>
1-11	<i>Study Intervention</i>
1-15	<i>Study Timetable</i>

1.1 Study Objectives

The **primary objective** of this study is to determine whether the addition of individual drug counseling to the prescription of buprenorphine/naloxone (BUP/NX) along with Standard Medical Management (SMM) for subjects dependent on prescription opioid analgesics improves outcome both during a) an initial four-week treatment with taper and b) a 12-week stabilization treatment for those who do not respond successfully to the initial treatment with taper.

This two-phase **outpatient** study (see study schema below) will include participants meeting DSM-IV criteria for opioid analgesic dependence (i.e., physical dependence is not sufficient for study participation) who do not require ongoing opioid therapy for pain. Participants will undergo an initial four-week BUP/NX outpatient treatment with taper, and will be randomized to SMM or Enhanced Medical Management (EMM), which consists of SMM plus twice weekly individual outpatient drug counseling. After the initial treatment with taper, participants who are thus far successful will be followed for eight weeks to assess success or failure (see definitions below). Initial treatment failures will be eligible for treatment in Phase 2. Phase 2 consists of a 12-week outpatient stabilization treatment with BUP/NX, plus random assignment to SMM or EMM, followed by a four-week taper and eight weeks of follow-up.

The **overall research question** for the study is: What benefit does EMM offer over SMM a) in a short-term treatment paradigm (a four-week BUP/NX treatment with taper) and b) in a longer-term treatment paradigm (12 weeks of a stabilization dose of BUP/NX) for subjects who have not responded successfully to the initial short-term BUP/NX treatment with taper?

1.2 Study Design

Participants [Phase 1 will enroll a sufficient number of participants to obtain a Phase 2 (n=324)] seeking treatment for prescription opioid dependence will be enrolled in this two-phase, randomized, multi-center study after screening and baseline assessments. It is expected that approximately 900 potential participants will be screened to attain the targeted enrollment.

1.2.1 PHASE 1

1.2.1.1 Research Questions - Phase 1

The **primary research question** for **Phase 1** is whether **EMM** is superior to **SMM** in the context of a four-week initial BUP/NX treatment period for this population.

There are two **secondary research questions**.

1. What percentage of this subject population responds successfully (as defined below) to a four-week initial taper of BUP/NX, plus brief medical counseling visits (i.e., SMM), either with or without drug counseling?
2. Are there subject characteristics that predict the likelihood of success in Phase 1?

The following characteristics will be examined:

- a. pain status
- b. reason for initial use of opioids
- c. sociodemographic characteristics (sex, race, age)
- d. severity of withdrawal symptoms
- e. severity of craving
- f. presence of current or past heroin use
- g. presence of other substance use disorders
- h. presence of other psychiatric disorders
- i. level of depression
- j. number of previous treatment experiences

1.2.1.2 Hypothesis - Phase 1

Phase 1 Main Hypothesis: There will be a higher rate of successful response to an initial 4-week BUP/NX treatment with taper among subjects receiving EMM (i.e., SMM plus individual drug counseling) than among subjects receiving BUP/NX and SMM alone.

1.2.1.3 Primary Outcome Measure for Phase 1

The **primary outcome measure** for **Phase 1** will be binary, i.e., “success” or “failure.”

“Success” in Phase 1 will be operationalized as follows: a participant is a “success” if all of the following criteria are satisfied during the four-week treatment with taper and eight weeks of follow-up:

1. Use of opioids on 4 or fewer days per month (beginning after the end of Week 2) as evidenced by self-report.
2. Urine screen for opioids are never positive on 2 consecutive weeks (beginning after the end of Week 2).
3. Completion of the four-week medication regimen and eight-week follow-up period (including Week 6 and Week 8 SMM or EMM booster visits) without participating in other formal substance abuse treatment (e.g., methadone maintenance, drug counseling; self-help groups such as Narcotics Anonymous and treatment for other issues such as medical or psychiatric problems do not count here).
4. Absence of needle use.
5. Absence of no more than one urine sample after (beginning after the end of Week 2).

All participants found not to meet any of the success criteria listed above at any time during Phase 1 will not be required to complete all visits in Phase 1 prior to entering Phase 2. Rather, these participants will be offered the opportunity to participate in Phase 2 when the participant is identified as a failure. However, failures can elect to remain in Phase 1 through Week 12 follow-up and can make the transition to Phase 2 at any time up until the conclusion of Phase 1.

1.2.1.4 Phase 1 Study Design

All participants will be administered BUP/NX in a 1-day induction regimen, which begins the 4-week BUP/NX treatment phase. Participants will also be randomly assigned to either SMM or EMM (both described below). Randomization will be stratified within site with respect to chronic pain and lifetime heroin use to decrease the likelihood of meaningful imbalances between the treatment groups with respect to the potentially important factors ‘chronic pain’ and ‘lifetime heroin use.’ Participants will be seen twice during the first week of treatment.

The following induction algorithm is proposed:

1. Participants should refrain from opioid use for approximately 12 hours prior to induction.
2. Pre-dose baseline score on COWS should be greater than 8 (no signs of intoxication).
3. An initial 4 mg sublingual dose should be given and the participant observed for 1 hour. If symptoms improve (COWS score reduced by at least 2 points), the participant can be sent home with two 4 mg doses and instructed to take the additional doses if needed. If symptoms do not improve or worsen, an additional 4 mg is given and the participant observed for another hour and sent home with the remaining 4 mg dose.
4. The study medical clinician or a designated staff member should contact the participant by phone later the first day.

This induction scheme is relatively conservative and limits the first day dose to 12 mg. Alternative induction schedules, in which participants receive up to 16 mg in the first day, can be used if the study medical clinician believes it is necessary. These alternative induction schedules are described in the Operations Manual.

Including induction, all participants will receive BUP/NX for four weeks. At each visit during this phase, the study medical clinician may adjust the BUP dose in increments of up to 8mg. The maximum allowable dose is 32mg per day. Dose changes are to be determined after the study staff obtains vital signs, evaluation of illicit drug use (urine and self-report), craving, signs and symptoms of opiate withdrawal or over-medication, adverse events and current BUP/NX and other medication taken since the last visit. During Weeks 3 and 4 participants will taper off BUP/NX to zero dosage. Taper will begin around Study Day 15 and must end by Study Day 28.

All participants will also receive SMM, which consists of one 1-hour initial visit and one 15-20 minute follow-up visit during Week 1, with one individual session (15-20 minutes) per week during Weeks 2-4 and one 15-20 minute post-taper booster visit at Weeks 6 and 8.

Participants randomized to EMM will receive, in addition to SMM, two individual drug counseling sessions per week (approximately 45 minutes each) during the first four weeks of Phase 1, and one post-taper booster session in Week 6 and Week 8.

There will be *no* treatment visits during Weeks 9-12 of Phase 1.

Both SMM and EMM are manualized and will be administered as described in the following table.

Table 1.1 Phase 1 Weekly Treatment Visits

Period		Group 1 (SMM)	Group 2 (EMM)
Month 1	Week 1	Induction: 1 hour SMM Follow-up: 15-20 minute SMM	Induction: 1 hour SMM 45 minute (approx.) EMM Follow-up: 15-20 minute SMM 45 minute (approx.) EMM
	Week 2	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
	Week 3	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
	Week 4	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
Month 2	Week 5		
	Week 6	15-20 minute SMM	15-20 minute SMM One 45 minute (approx.) EMM
	Week 7		
	Week 8	15-20 minute SMM	15-20 minute SMM One 45 minute (approx.) EMM
Month 3	Week 9		
	Week 10	(follow-up visit only – no treatment)	(follow-up visit only – no treatment)
	Week 11		
	Week 12	(follow-up visit only – no treatment)	(follow-up visit only – no treatment)

1.2.2 PHASE 2

1.2.2.1 Research Questions - Phase 2

The **primary research question** for Phase 2 is whether **EMM** is superior to **SMM** in the context of a 12-week stabilization treatment with **BUP/NX** in the population of subjects that do not respond successfully to a four-week treatment with taper.

The **secondary research questions** for Phase 2 are:

1. What is the overall percentage of subjects that have failed a 4-week treatment with taper who experience substantial improvement with a 12-week BUP/NX stabilization treatment?
2. Does the probability of having positive urine screens for opioids decrease faster over the 12 weeks of Phase 2 stabilization treatment in the EMM group than in the SMM group? (Hypothesis: yes).
3. Will EMM subjects be more likely than SMM participants to have substantial improvement (defined below) at the end of 24 weeks of Phase 2, following the taper of BUP/NX during Weeks 13-16 and follow-up from Week 17 to Week 24? (Hypothesis: yes).

1.2.2.2 Hypothesis - Phase 2

Phase 2 Main Hypothesis: Among initial taper failures treated with 12 weeks of BUP/NX stabilization, regardless of their randomization assignment in Phase 1, the proportion of substantially improved subjects (defined below) will be higher in the group that receives EMM than in the group that receives SMM.

1.2.2.3 Primary Outcome Measure - Phase 2

The **primary outcome measure** for Phase 2 is “substantial improvement,” defined as abstaining from opioids during the last week AND for at least 2 of the previous 3 weeks of the third month of BUP/NX treatment. Abstinence is determined by self-reports of opioid abstinence (missing urines will be considered positive for opioids).

1.2.2.4 Phase 2 Study Design

All participants identified as treatment failures in Phase 1 will be offered the opportunity to be randomized to receive 12 weeks of BUP/NX stabilization treatment plus SMM or 12 weeks of BUP/NX stabilization treatment plus EMM (SMM + individual drug counseling). After the 12-week period, participants in Phase 2 will taper off of their BUP/NX dose during weeks 13-16. Taper will begin around Study Day 85 and must end by Study Day 112. During the taper period only SMM will be provided. Participants will be followed for an additional 8 weeks after the taper.

The randomization to SMM vs. EMM will be within site and will be stratified by whether participants received SMM or EMM in Phase 1.

Participants entering Phase 2 will not require induction if the time period between the end of Phase 1 and last BUP/NX dose is three days. If the period of time is four days, induction will be required prior

to entering Phase 2. This 1-day induction dose is limited to 16 mg. Follow-up for all participants will occur during Weeks 18, 20, 22 and 24 of Phase 2. As in Phase 1, the study medical clinician may adjust the BUP dose in Phase 2 at each visit in increments of up to 8mg. The maximum allowable dose is 32mg per day. Dose changes are to be determined after the study staff obtains vital signs, evaluation of illicit drug use (urine and self-report), craving, signs and symptoms of opiate withdrawal or overmedication, adverse events and current BUP/NX and other medication taken since the last visit.

Participants whose clinical status worsens during Phase 2 (e.g., increased opioid use, needle use, more dangerous behaviors such as overdoses) will be referred to other treatment options, e.g., participants will be told about methadone maintenance as well as more intensive psychosocial treatment; participants who relapse to regular opioid use in the context of severe and/or worsening pain may be referred to a pain clinic if clinically appropriate. All such participants will remain part of the study and will continue to be followed for research and safety monitoring. For coding purposes these participants will be considered treatment failures.

SMM in Phase 2 will consist of one 30-60 minute initial visit, then one individual session (15-20 minutes) per week during Weeks 1-16. EMM will consist of the same SMM schedule plus two individual sessions with a counselor per week (approximately 45 minutes) during Weeks 1 through 6, then one individual session with a counselor per week (approximately 45 minutes) during Weeks 7-12. During Weeks 13-16 both groups will receive SMM once a week, and during the follow-up period (Weeks 17-24) both groups will receive follow-up visits only.

Table 1.2 Phase 2 Treatment Visits

Period		SMM	EMM
Month 1	Week 1	Induction: 30-60 minute SMM Follow-up: 15-20 minute SMM	Induction: 30-60 minute SMM and 45-minute EMM Follow-up: 15-20 minute SMM and 45-minute (approx.) EMM
	Week 2	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
	Week 3	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
	Week 4	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
Month 2	Week 5	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
	Week 6	15-20 minute SMM	15-20 minute SMM Two 45 minute (approx.) EMM
	Week 7	15-20 minute SMM	15-20minute SMM One 45-minute (approx.) EMM
	Week 8	15-20 minute SMM	15-20minute SMM One 45-minute (approx.) EMM
Month 3	Week 9	15-20 minute SMM	15-20minute SMM One 45-minute (approx.) EMM
	Week 10	15-20 minute SMM	15-20minute SMM One 45-minute (approx.) EMM
	Week 11	15-20 minute SMM	15-20minute SMM One 45-minute (approx.) EMM
	Week 12	15-20 minute SMM	15-20minute SMM One 45-minute (approx.) EMM
Month 4	Week 13	15-20 minute SMM	15-20 minute SMM
	Week 14	15-20 minute SMM	15-20 minute SMM
	Week 15	15-20 minute SMM	15-20 minute SMM
	Week 16	15-20 minute SMM	15-20 minute SMM
Month 5	Week 17		
	Week 18	(follow-up visit only – no treatment)	(follow-up visit only – no treatment)
	Week 19		
	Week 20	(follow-up visit only – no treatment)	(follow-up visit only – no treatment)
Month 6	Week 21		
	Week 22	(follow-up visit only –no treatment)	(follow-up visit only – no treatment)
	Week 23		
	Week 24	(follow-up visit only – no treatment)	(follow-up visit only – no treatment)

Data will be collected weekly during Weeks 1-4 of Phase 1 and Weeks 1-16 of Phase 2. Data will be collected every other week during Weeks 5-12 of Phase 1 and Weeks 17-24 of Phase 2. Participants will provide urine samples at each of these assessments for opiates and other drugs of abuse. Severity of withdrawal symptoms, as assessed by Clinical Opiate Withdrawal Scale (COWS), visual analog scale craving scores, concomitant medications, pain assessments, and adverse event data will also be collected.

1.3 Study Population

Adult males and females seeking treatment for prescription opioid dependence, in the absence of chronic pain severe enough to require ongoing opioid therapy.

1.3.1 Eligibility Criteria

Males and females 18 years of age or older, seeking detoxification from prescription opioid dependence in the absence of chronic pain severe enough to require ongoing opioid therapy or an acute pain event within the past six months, will be entered into this trial. For participants who are receiving opioids for pain, the study medical clinician will consult with the participant's prescribing physician to ensure that the participant is medically stable enough to enter the trial (e.g., the participant does not have a malignant tumor causing the pain). Participants who use prescription opioids by injection may be included as long as they have never injected heroin.

All participants must meet the following inclusion criteria:

1. Participants must have the ability to read, understand (including passing a comprehension quiz), and provide written informed consent.
2. Participants must be 18 years of age or older.
3. Females of childbearing capacity must agree to use an acceptable method of birth control throughout the study. One of the following methods of birth control is acceptable for females:
 - a. hormonal contraceptives, including:
 - i. oral contraceptives
 - ii. intrauterine progesterone contraceptive system (IUD)
 - iii. levonorgestrel implant
 - iv. medroxyprogesterone acetate contraceptive injection
 - v. other hormonal method(s) approved by the study investigator
 - b. barrier (diaphragm or cervical cap) with spermicide or condom
 - c. complete abstinence from sexual intercourse
 - d. male partner sterilization

4. Participants who are receiving opioids for pain must have clearance from their prescribing physician to enter the trial.
5. Participants must have the ability to meet study requirements.
6. Participants must meet DSM-IV criteria for current opioid dependence.
7. Participants must be currently physically dependent on opioids (using prescription opioids at least 20 days/month) and in need of medical assistance for opioid withdrawal.
8. Participants must be in good general health (in the opinion of the study investigator after review of medical records and baseline evaluations) or, for participants requiring ongoing medical/psychiatric treatment (whether currently in such treatment or not), under the care of a physician willing to continue participants' medical management and to cooperate with study site investigators.
9. Participants must be non-psychotic and psychiatrically stable in the opinion of the study investigator.
10. Participants will be asked to provide locator information including their residential street address and a working telephone number; or, if they are homeless, they must provide the address and telephone number of a non-drug abusing relative or friend who can reach the participant in emergencies.
11. Prior to induction:
 - Participant should be in opioid withdrawal (COWS scale >8)
 - Participant's dose of methadone (if receiving it for pain; those receiving methadone treatment for opioid dependence are excluded, see below) should be less than or equal to 40 mg

Participants will be excluded if they:

1. Have a medical condition that would make participation medically hazardous, in the opinion of the study investigator, after consultation with the study physician (if not the same), based on a review of medical records and baseline evaluations.
2. Have known allergy or sensitivity to buprenorphine or naloxone.
3. Are psychotic or have any other acute severe psychiatric condition.
4. Are a suicide risk within the past 30 days.
5. Are dependent on alcohol, sedative-hypnotics or stimulants, and requiring immediate medical attention.
6. Have used heroin more than four days in the past 30 days.
7. Have participated in another investigational drug study within the last 30 days.

8. Have participated in methadone or buprenorphine maintenance treatment for opioid dependence within 30 days of study enrollment.
9. Have a current or pending legal status that would make them unlikely to remain in the local area for the duration of the study.
10. Lifetime opioid dependence that would be accounted for by heroin use alone.
11. Have ever used heroin by injection.
12. Have experienced a traumatic or major pain event within the past six months.
13. Are pregnant or lactating or a female unwilling to follow study required measures for pregnancy prevention.
14. Are unable to remain in the local area for the duration of Phases 1 and 2 of the study.
15. Have presence of pain of sufficient severity as to require ongoing pain management with opioids.
16. Have LFTs >5x upper limit of normal range.
17. Have surgery scheduled within the next six months that would preclude participation during the active treatment phase of the study.
18. Are currently receiving formal substance abuse treatment.

1.4 Study Intervention

1.4.1 *Induction and Post-Induction Treatment Schedules*

1.4.1.1 Induction Schedule - Day 1 of Treatment

Day One: All participants should refrain from opioid use for approximately 12 hours prior to induction. Pre-dose baseline scores on COWS should be greater than eight (8) (no signs of intoxication).

An initial four (4) mg dose of BUP/NX (two sublingual tablets with 2mg BUP/0.5mg NX) will be administered, and the participant observed for 1 hour. If symptoms improve (improvement of two points on COWS), the participant can be sent home with two 4mg doses and instructed to take the additional doses if needed.

If symptoms do not improve, or worsen, an additional 4mg is administered and the participant observed for another hour and sent home with the remaining 4mg dose.

Study investigators will contact the participant by phone later during the first day.

This one-day induction limits the first day's dose to 12 mg. Alternative induction schedules allowing a first-day dose of 16mg will be described in the Operations Manual.

1.4.1.2 Post-Induction

In addition to BUP/NX treatment, participants will receive SMM or EMM; i.e., SMM plus twice weekly drug counseling.

Including induction, all participants will receive BUP/NX for 4 weeks. The maximum BUP daily dose during Phase 1 is 32 mg. Dosage of BUP is flexible, and the study site investigators may adjust the dose according to the participant's well being. However, the daily BUP dose may not exceed 32 mg. Participants will taper off BUP/NX to zero (see below) during weeks 3-4. Taper will begin around Study Day 15 and must end by Study Day 28.

Participants who successfully complete this 4-week treatment and do not relapse to opioids (defined below) will go into an eight-week follow-up phase. EMM and SMM booster sessions are offered in Weeks 6 and 8 of the follow-up phase. Participants who relapse to opioids during either this 4-week treatment or during the eight weeks of follow-up will be invited to enter Phase 2 as soon as they meet failure criteria; in Phase 2, they will receive 12 weeks of BUP/NX treatment plus SMM or 12 weeks of BUP/NX treatment with EMM (SMM plus twice weekly counseling) for six weeks, then once weekly for six weeks).

1.4.2 Duration of Study

The total duration of study participation will be 12 weeks for Phase 1 and 24 weeks for Phase 2. For participants participating in both Phase 1 and Phase 2, the total duration of study participation may be up to 37 weeks. Duration of study time consists of: screening and baseline measurements, BUP/NX induction, stabilization, taper, and follow-up evaluations.

1.4.3 Safety Assessments

BUP/NX (Suboxone®) is an approved medication for the treatment of opioid dependence. Both BUP and NX have demonstrated a favorable safety profile among adults in treatment for opioid dependence. BUP/NX have been administered to thousands of heroin addicts with no known serious side effects attributed directly to the medication when taken as prescribed.

Participants will be provided with information about the study and their rights as study participants. They will be required to provide signed informed consent prior to initiating any study procedures for Phase 1 and re-consented prior to initiating Phase 2. All participants considered for study enrollment will have a physical examination (including vital signs, weight, medical history and history of prior medication use assessment), psychiatric evaluation, HIV risk assessment, clinical laboratory studies (blood chemistry, hematology, and urinalysis) and pain assessment performed during screening/baseline. Females of childbearing potential will be given a pregnancy test at baseline and monthly thereafter during treatment. Assessment of adverse events (AEs) and concomitant medication use will be performed at every visit during all periods of both Phase 1 and 2. Serious AEs (SAEs) will be reported to the appropriate authorities during the treatment, taper and follow-up phases of the study within 24 hours of discovery.

Signs and symptoms of withdrawal, abstinence from other drugs of abuse, concomitant medications, and adverse events will be recorded and reviewed for each participant.

Previously reported side effects of BUP/NX include sedation, physical dependence, precipitation of withdrawal, overdose (if taken with high doses of benzodiazepines or other sedatives), abuse (if multiple doses are taken simultaneously or if BUP/NX is diverted), and an opioid withdrawal syndrome (if injected by a person physically dependent on opioids). Potential side effects will be explained in the consent form and reviewed verbally, as well as in writing, with the participant.

1.4.4 Outcome Assessments

The **primary outcome measure** for **Phase 1** will be binary; i.e., “success” or “failure.”

Operationally, a participant is a “success” if all of the following criteria are satisfied during the 4-week treatment with taper and 8 weeks of follow-up:

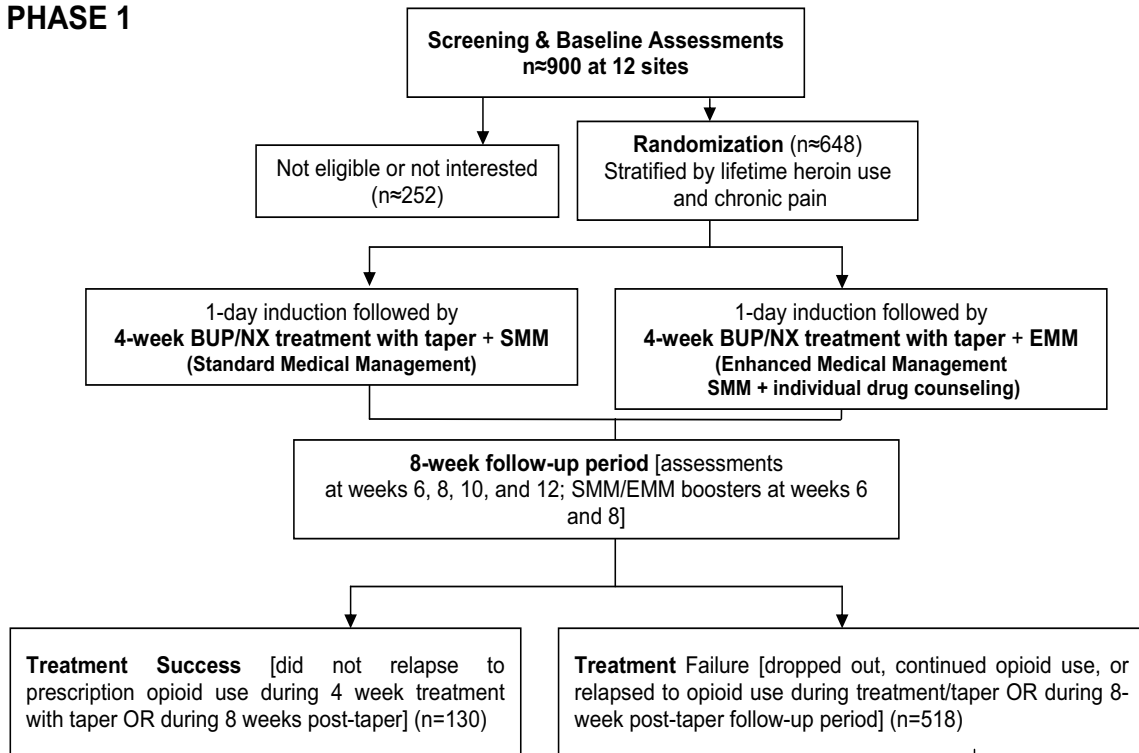
1. Use of opioids on four or fewer days per month (beginning after the end of Week 2) as evidenced by self-report.
2. Urine screen for opioids are never positive on two consecutive weeks (beginning after the end of Week 2).
3. Completion of the four-week medication regimen and eight-week follow-up period (including Week 6 and Week 8 SMM or EMM booster visits) without participating in other formal substance abuse treatment (e.g., methadone maintenance, drug counseling, etc.). Self-help groups such as Narcotics Anonymous and treatment for other issues such as medical or psychiatric problems do not count here.
4. Absence of needle use.
5. Absence of no more than one urine sample (beginning after the end of Week 2).

For Phase 1, the primary outcome will be measured by the comparison of the proportion of participants in SMM versus EMM who are treatment successes.

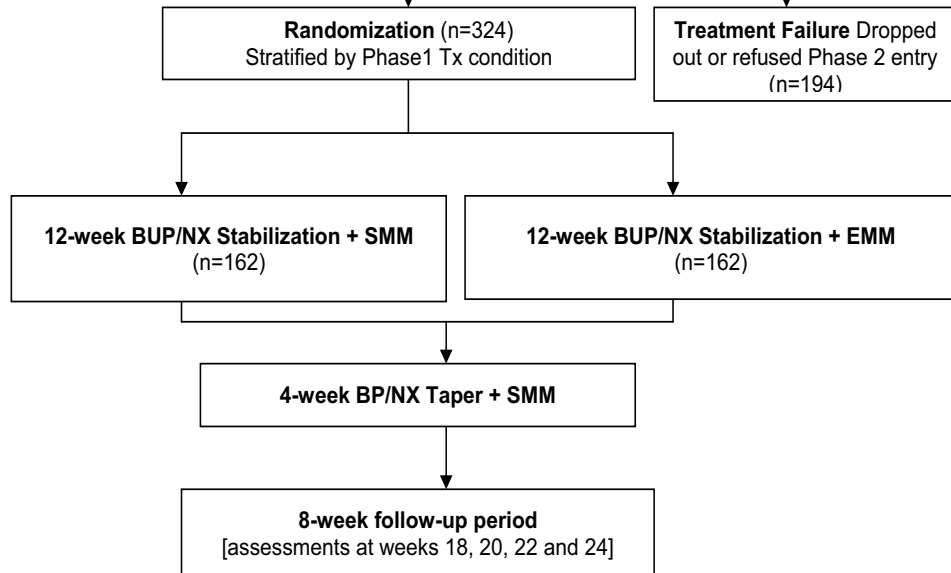
The **primary outcome measure** for Phase 2 is “substantial improvement,” defined as abstaining from opioids during the last week AND for at least 2 of the previous 3 weeks of the third month of BUP/NX treatment. Abstinence is determined by self-reports of opioid abstinence (missing urines will be considered positive for opioids). For Phase 2, the primary outcome will be measured by the comparison of the proportion of participants in EMM versus SMM who have shown substantial improvement.

Figure 1.1 Generalized Study Schema

PHASE 1



PHASE 2



1.5 Study Timetable

Table 1.3 Study Timetable
(Weekly Details Found in Visit Schedules - Tables 4.1 & 4.2)

Activity	Duration (Avg. min.)	Screening/ Baseline		Phase 1 SMM	Phase 1 EMM		Phase 2 SMM	Phase 2 EMM
Screening Assessments*	Where Applicable							
Informed Consent	25	X						
Inclusion/Exclusion		X						
Randomization				X	X		X	X
Demographics	5	X						
CIDI/Substance Use Diagnosis	40	X						
Safety Assessments								
Concomitant Treatment (including medications & psychosocial)	8	X		X	X		X	X
Medical & Psychiatric Evaluation	45	X						
Vital Signs	5	X		X	X		X	X
Lab Tests (Chemistry, Hematology, Urinalysis, LFTs)	10	X		X	X		X	X
Pregnancy Test	See Labs	X		X	X		X	X
Adverse Events	5			X	X		X	X
Serious Adverse Event				As needed	As needed		As needed	As needed
COWS	5	X		X	X		X	X
Efficacy Assessments								
Substance Use Report – Baseline	15	X						
Substance Use Report – Follow-up	5			X	X		X	X
VAS-Craving	1	X		X	X		X	X
Urine Drug Screen	See Labs	X		X	X		X	X
Pain Assessments								
Brief Pain Inventory	5	X		X	X		X	X
Beck Depression Inventory II	10	X		X	X		X	X
Pain & Opioid Analgesic Use History	10	X						
SF-36	10	X		X	X		X	X
Other Assessments								
CIDI/Depression-PTSD Diagnosis	30	X					X	X
Fagerstrom Test	2	X		X	X		X	X
ASI Lite	35	X						
ASI Lite Follow-up	15			X	X		X	X
Locator Form	5	X		X	X		X	X
Risk Behavior Survey	5	X					X	X
Treatment								
BUP/NX Induction Visit	60			X	X		X	X
SMM session (including BUP/NX dosing)	15-20			X	X		X	X
EMM Counseling session	45				X			X

2.0 Introduction

Page	Section
2-1	<i>Background</i>
2-2	<i>Clinical Profile</i>
2-3	<i>Study Rationale</i>

2.1 Background

While opioids have been used for decades to treat chronic pain, serious concerns about prescription opioid abuse have increased in recent years. The media's focus on addiction and deaths due to OxyContin® (controlled-release oxycodone) has directed attention to opioids, the most commonly abused prescription drugs. The Drug Abuse Warning Network's (DAWN) January 2003 report cited that the incidence of abuse of prescription opioid pain medications, such as hydrocodone, meperidine, oxycodone, and propoxyphene, has increased markedly. In 2001, there were an estimated 90,232 emergency department visits related to opioid analgesic abuse, a 117% increase since 1994. While prescription opiate abuse is increasing, there is an unmet need to provide adequate treatment to patients addicted to prescription opioids.

Patients with prescription opioid dependence may differ in some important ways from heroin addicts. For example, Brands et al. (2004) compared prescription opioid addicts with those dependent on heroin and those with mixed addictions, and found that exclusively prescription users were less likely to have injected drugs, and were less likely to have other co-occurring substance use disorders. Both of these would be good prognostic characteristics, although the greater frequency of ongoing psychiatric treatment and of pain problems in the prescription users could counterbalance this. With these differences between prescription users and heroin users, one cannot assume that the same treatment algorithm that would be recommended for heroin addicts would be recommended for those dependent upon prescription opioids. Developing a set of treatment guidelines and understanding the response to treatment among patients with prescription opioid dependence is thus a priority.

Buprenorphine (BUP) is a high affinity, partial mu-opioid agonist, approved as a pharmacotherapy for opioid dependence. Its tight binding and slow dissociation from opioid receptors produce a long duration of action, and explain the relatively mild withdrawal syndrome observed with BUP discontinuation (Lewis, 1978; Jasinski et al., 1978), making it useful for opioid maintenance and detoxification. Investigators showed that BUP could substitute for morphine, suppress withdrawal and decrease heroin self-administration (Jasinski, 1978; Mello and Mendelson, 1980; Mello et al., 1982). Both safety and efficacy were demonstrated in large-scale controlled clinical trials (Johnson et al., 1992; Johnson et al., 1995; Schottenfeld et al., 1994; Strain et al., 1996; Ling et al., 1998; Johnson et al., 2000).

While most of the controlled BUP studies administered the liquid preparation, a sublingual buprenorphine/naloxone (BUP/NX) tablet in a 4:1 combination of BUP:NX was approved by the FDA, and marketed in late 2002. Studies with this sublingual tablet preparation demonstrated a bioavailability of nearly 70% or more, compared to the liquid formulation. Most importantly, the

incorporation of naloxone deters intravenous (IV) administration so that the BUP/NX combination can be safely dispensed to adults (Mendelson et al., 1996; Fudala et al., 1998).

2.2 Clinical Profile

2.2.1 Clinical Efficacy

Buprenorphine (BUP) is a high affinity, partial mu-opioid agonist, approved for pharmacotherapy for opioid dependence, and for treatment of moderate to severe pain (PDR, 2004). Two sublingual tablet formulations of BUP available for the treatment of opioid addiction are: Subutex[®], which contains buprenorphine alone, and Suboxone[®], which contains buprenorphine plus naloxone in a 4:1 ratio. Under the provisions of the Drug Addiction Treatment Act (DATA) of 2000, qualifying physicians in the medical office and other appropriate setting outside the Opioid Treatment Programs (OTP) may prescribe and/or dispense Schedule III, IV and V opioid medications for the treatment of opioid addiction if such medications have been specifically approved by the FDA for that indication.

Buprenex[®], an injectable formulation of BUP, has previously been approved by the FDA for use as a parenteral analgesic.

2.2.1.1 Pharmacokinetics (Drug Studies)

2.2.1.1.1 Parameters Related to Product Characteristics

Absorption of BUP from sublingual tablets was linear over the dose range studied (4-16 mg). Both C_{max} and AUC of BUP increased linearly with increased dose (range of 4-16 mg), but the increase was not directly dose-proportional. Mean peak levels of BUP ranged from 1.84 to 5.47 ng/ml in the dose range of 4-16 mg BUP. Mean plasma half-life of BUP was 37.3 hours (range: 16 to 160 hours). BUP is approximately 96% protein bound. BUP is metabolized via N-dealkylation to norbuprenorphine and via glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme.

NX did not affect the pharmacokinetics of BUP. NX was absorbed from BUP/NX but plasma levels were low, or were below the limits of quantification. Mean peak NX levels ranged from 0.11 to 0.28 ng/ml in the dose range of 1-4 mg NX. Mean plasma half-life of NX was 1.06 hour (range: 0.39 to 2.45 hours). NX undergoes direct glucuronidation to naloxone 3-glucuronide, and N-dealkylation and reduction of the 6-oxo group.

2.2.1.1.2 Parameters Related to Subject Characteristics

In opioid dependent patients, the pharmacokinetics of BUP was described by either a 1- or 2-compartment model with first order absorption and an absorption lag time. Age and AST or ALT were covariates that predicted at least a 20% decrease in clearance (1-compartment model) from the population standard value. In the 2-compartment model, clearance of BUP decreased with increased bilirubin, increased ALT, and female gender.

There were no differences in C_{max} and AUC by age, ethnicity or gender.

2.2.1.1.3 Information Related to the Behavioral Therapies

CTN protocols are designed to reflect “real-life” clinic settings. Psychosocial treatment procedures similar to those in existence at CTPs will be followed throughout the study. All CTPs will be provided with self-help buprenorphine treatment booklets for distribution to study participants (*Opiate Dependence: Handbook for Recovery Using Buprenorphine* by Walter Ling, M.D.). This provision will assure that a basic platform of education is provided to all study participants. Treatment manuals will be provided to study medical clinicians and counselors providing SMM and EMM respectively. These manuals are based on the *Manual for Enhanced Medical Management of Opioid Dependence with Buprenorphine*, which is the individual counseling manual by Pantalon, Fiellin, Schottenfeld, Gordon, and O’Connor and the *Manual for Standard Medical Management of Opioid Dependence with Buprenorphine* by Fiellin, Pantalon, Schottenfeld, Gordon and O’Connor which will be used by study medical personnel. In consultation with the authors, the manuals have been revised to fit the study design for this trial and to address specific needs of this treatment population including individuals with chronic pain. The manuals are described below in *Rationale for the Choice of the Specific Enhanced Treatment in Phase 1 and 2* on page 2-5, and are included in Appendix C ~ Therapy Manuals.

2.2.2 Clinical Safety

Buprenorphine/naloxone has been established as a safe and effective alternative to methadone (Johnson et al., 1992; Ling et al., 1996, 1998; Amass et al., 2000). It has a greater margin of safety than full mu agonists such as methadone. Buprenorphine’s ceiling on agonist activity decreases the danger of overdose, and may limit its abuse liability (Walsh et al., 1994, 1995).

More than 50,000 patients have been treated with BUP in France. While there were reports of abuse, overdose deaths occurred at lower rates than with methadone, and the few BUP-related deaths appeared to be associated with abuse of other drugs (sedatives), high dose and/or IV BUP use, or benzodiazepines (Auriacombe, 2001).

The known risks for BUP/NX are small when compared to the risks of untreated or inadequately treated opioid dependence (criminal activity, HIV, hepatitis B & C, social/academic disruption, and death due to overdose).

2.3 Study Rationale

Patients with prescription opioid dependence may be able to benefit from pharmacological treatments shown to be effective in heroin addicts. Clinical research over the last ten years has established BUP as a safe and effective alternative to methadone. Sublingual buprenorphine tablets have been approved for pharmacotherapy for opioid dependence. Under the provisions of the Drug Addiction Treatment Act (DATA) of 2000, qualifying physicians may prescribe and/or dispense BUP and NX for the treatment of opioid addiction in an office-based setting. However, little is known about the use of buprenorphine in patients with prescription opioid dependence. For example, there are no data on the optimal length of BUP/NX treatment for this specific population, and the context in which this treatment should occur (i.e., a medical office setting versus a drug abuse treatment program setting).

The study will be conducted in two phases: 1) an initial four-week buprenorphine/naloxone treatment with taper with an 8-week follow-up and, for those who “fail” in Phase 1 (defined below), 2) a 12-

week buprenorphine/naloxone stabilization treatment, followed by a 4-week taper and an 8-week follow-up.

In each Phase, participants will be randomized to either SMM or EMM. EMM includes SMM plus individual drug counseling.

- Counseling in Phase 1 will occur twice a week for four weeks, with two follow-up sessions in Week 2 and Week 4 of Month 2.
- Counseling in Phase 2 will occur twice a week for six weeks, then once a week for six weeks.

The efficacy of detoxification in this population was chosen for examination for several reasons. First, detoxification is the prevailing practice among physicians using buprenorphine, according to a survey of 10% of all physicians who have been trained to use buprenorphine (CR Schuster, personal communication). There is great variability, however, in the use of ancillary drug counseling in conjunction with pharmacotherapy, with many physicians treating patients strictly in office practice, and others referring such patients to drug abuse treatment programs. No data indicating the superiority, or lack thereof, of either approach is currently known.

Studying patients participating in short-term buprenorphine/naloxone treatment (either with SMM or EMM) can also yield some important data regarding the overall likelihood of successful outcome with this particular population. Because many of the participants entering this study will be receiving opioids by prescription from a physician, a key question for physicians treating these individuals is whether their substance dependence can be managed within the medical setting or whether they should be referred to a specialty drug abuse treatment setting. Although SMM and EMM will, in this study, occur in the same setting, the contrast between these two models of care should help to answer the question of the optimal treatment setting for this population. Moreover, since many such patients may resist referral to a drug abuse treatment program, studying the efficacy of SMM could help determine whether treatment in the primary care setting without specialized counseling is a reasonable approach for this population. There is some evidence that a substantial minority of opioid-dependent patients who undergo even a brief detoxification from buprenorphine show substantial improvement. For example, Gandhi et al. (2003) examined 123 heroin-dependent men and women aged 18-25 years, who entered an outpatient buprenorphine 3-day detoxification program. Termination of buprenorphine was associated with dropout from treatment of all patients by day 10. However, at one-month follow-up, 75 of 119 participants located reported either no use of heroin (n=44, 46%) or reduced use of heroin (n=31, 33%). This trend toward reduced opioid use was maintained at 3- and 6-month follow-ups, despite lack of participation in any formal treatment for substance abuse. These are significantly better outcomes when compared with outcomes from two other studies of brief buprenorphine detoxification in older heroin-dependent individuals (mean age = 35). Katz et al. (2004) showed an 88% relapse rate by one week following detoxification, and Kakko et al. (2003) found that all 20 participants in their trial who received a one-week buprenorphine detoxification with a psychosocial adjunct had relapsed and dropped out of treatment before 3 months. These studies suggest that a relatively brief buprenorphine detoxification can be associated with better outcomes in younger individuals. Because Moore et al. (2004) found that participants in their study who were dependent on prescription opioids were significantly younger and had significantly fewer years of opiate use than heroin-dependent individuals, one might expect better outcomes following detoxification in this population than in traditional heroin-dependent populations. Moreover, Moore et al. (2004) also found substantially better outcomes for those dependent on prescription opioids than for participants dependent on heroin (63% vs. 31% of participants achieving 6 consecutive weeks of opiate-negative urines in a 24-week

BUP/NX trial); this trend is an additional reason to posit that individuals dependent on prescription opioids would fare better with detoxification than more traditional heroin-dependent populations.

A 4-week detoxification schedule was selected after speaking with a number of physicians and CTP directors experienced with buprenorphine use in opioid detoxification. While some practitioners use a more rapid taper schedule (as little as several days), a four-week taper is frequently utilized.

When considering what options to study in participants who have relapsed to opioids either during or following a 4-week BUP/NX treatment with taper, a longer period (12 weeks) of BUP/NX stabilization has been chosen to compare two different models of treatment: a medical model, such as BUP/NX plus SMM, as contrasted with a more standard drug abuse treatment model, such as BUP/NX plus EMM (SMM plus individual drug counseling).

What about the argument that 12 weeks of BUP/NX might be too short, that these participants should be recommended for maintenance? Since there is some evidence that prescription drug abusers may have a better prognosis than those with heroin dependence (Moore et. al., 2004; Brands et. al., 2004), it is important to see if shorter lengths of treatment could be beneficial to this population. However, if the treatment is insufficient for the participant in Phase 2, then the participant may require longer treatment with BUP/NX, or require some other type of treatment.

2.3.1 Rationale for the Choice of the Specific Enhanced Treatment in Phase 1 and 2

In choosing a psychosocial treatment to accompany the use of buprenorphine/naloxone, one would seek a treatment with the following properties:

- It is manualized.
- It has previously been used in a similar trial.
- It could be used in either a primary care or a specialized drug abuse treatment setting.
- It is easily delivered, with relatively little specialized training.
- Adherence to the manual is likely to be good.
- If successful, the treatment would be easily disseminated to either primary care or drug abuse treatment settings.

The *Manual for EMM of Opioid Dependence* by Pantalon, Fiellin, Schottenfeld, Gordon, and O'Connor, was chosen because it meets all of the criteria listed above. This manual was used in a similarly designed study (Fiellin et al., 2002), in which opioid dependent participants were randomly assigned to either SMM or EMM, both delivered in a primary care setting. The EMM was delivered by primary care nurses who did not have drug-counseling experience. Thus, the manual is somewhat simpler than what might be delivered in a drug abuse treatment program. While such simplification is not ideal, the alternative, a standard drug counseling manual such as that by Mercer and Woody (1992), would present the opposite problem; it would be too complicated for delivery in a primary care setting. Therefore, the Pantalon et al. manual was chosen because of the greater likelihood of widespread adoption of this treatment if it is found to be successful in this trial.

In the study referenced above, the investigators found lower medication adherence and lower treatment retention with the standard (as opposed to enhanced) medical management treatment, but little difference in the amount of reduction of illicit opioid use between the EMM and the SMM conditions (Fiellin et al., 2002). However, the difference in the amount of treatment received by the two groups in this study was rather small: 15 minutes a week for the SMM group and 45 minutes a week for the EMM group (David Fiellin, personal communication). A greater contrast was chosen for our proposed study.

- For SMM Phase 1:
 - One-hour initial visit and 15-20 minute follow-up visit in Week 1.
 - Weekly 15-20 minute visit for Weeks 2-4.
 - One 15-20 minute visit in each of Weeks 6 and 8 of follow-up period.
- For SMM Phase 2:
 - One 30-60 minute initial visit and 15-20 follow-up visit in Week 1.
 - Weekly 15-20-minute visits in Weeks 2-16.

The *enhancement* will consist of individual drug counseling visits lasting approximately 45 minutes each, as follows:

- For EMM Phase 1:
 - Twice weekly individual drug counseling for Weeks 1-4.
 - One weekly individual drug counseling session in each of Weeks 6 and 8 of follow-up period.
- For EMM Phase 2:
 - Twice-weekly individual drug counseling for Weeks 1-6.
 - Once-weekly individual drug counseling in Weeks 7-12.

The enhancement in our study is additive (i.e., *in addition to SMM*) rather than comparative.

The frequency of counseling visits during active treatment in Phase 2 (twice a week for the first half and weekly in the second half of the Phase) parallels the visit schedule for individual drug counseling in the NIDA Collaborative Cocaine Treatment Study (Crits-Christoph et al., 1999), in which individual drug counseling had the best results of the individual treatments tested. The decreasing frequency also more closely resembles usual treatment practices in CTPs and will likely lead to greater treatment adherence.

A combination of weekly individual drug counseling and group drug counseling, which was the most successful treatment combination in the NIDA Collaborative Cocaine Treatment Study (Crits-Christoph et al., 1999) and resembles the type of treatment delivered in some CTPs, was considered for this study. However, the logistics of implementing a group in this setting can be quite daunting (the

requirement to recruit enough participants at once to form a meaningful group, the distaste that some participants have for groups, and the common scenario that even some people who are willing to attend a group cannot come on the scheduled group night). Moreover, primary care settings that might be able to modify their practice methods to deliver individual counseling might be unable to deliver a group intervention.

The EMM treatment, according to the Pantalon et al. (1999) manual, was delivered with adequate levels of adherence (Michael Pantalon, personal communication), and the types of interventions that are included in the manual (12-step-oriented interventions and relapse prevention) are commonly delivered in community drug abuse treatment programs. An alternative model that was considered, cognitive-behavioral therapy, is delivered in some CTPs; however, a survey of CTPs in the Northern New England node showed that nearly all of the staff delivering treatment are counselors, and very few counselors have had any cognitive-behavioral training. Since an important goal of this study is to develop a treatment that can be disseminated to and delivered in a wide variety of treatment settings following completion of the study, the model of treatment in the Pantalon et al. manual was chosen.

2.3.2 Rationale for Pain Assessment and Intervention

The purposes of the pain assessments are:

- To determine the prevalence and characteristics of chronic pain among individuals presenting for treatment of prescription opioid dependence.
- To determine the impact of chronic pain on the outcome of prescription opioid dependence treatment.
- To assess an interaction between chronic pain and treatment in the randomized phase of this study.

Because some participants entering the protocol will have received opioids for pain (perhaps currently), it was desired that pain be addressed in the protocol. However, this is not a pain treatment protocol; it is a treatment for opioid dependence. Treatment of pain per se is beyond the scope of this project. Thus, participants with pain will be asked in each medical management visit about their pain. For pain intervention, participants in both SMM and EMM will receive a self-guided pain management manual (Robert Jamison's patient self-help book; see Appendix F), in both phases. For the EMM group, components will be added to the Pantalon et al., EMM manual that address pain as it impacts recovery from substance dependence (e.g., as a potential trigger for substance abuse relapse); pain will be addressed by the counselors as clinically appropriate (see Appendix F), and will focus on the relationship between pain and substance abuse, which will distinguish it from the SMM treatment. In addition, medical clinicians and counselors will be trained in pain issues. Counselors will be trained in particular about ways in which pain may influence recovery from substance dependence. Study medical clinicians may refer participants with pain to their own physician or to a pain program, but will not be treating the participant for pain (other than briefly for withdrawal discomfort) within the context of the study; e.g., with NSAIDS, etc.

3.0 Study Objectives

Page	Section
3-1	<i>Primary Objective</i>
3-1	<i>Secondary Objectives</i>

3.1 Primary Objective

The **primary objective** of this study is to determine whether the addition of individual drug counseling to the prescription of buprenorphine/naloxone (BUP/NX) along with SMM for subjects dependent on prescription opioid analgesics improves outcome both during a) an initial four-week outpatient treatment with taper and b) a 12-week stabilization outpatient treatment for those who do not respond successfully to the initial taper.

This two-phase **outpatient** study (see study schema below) will include participants meeting DSM-IV criteria for opioid analgesic dependence (i.e., physical dependence is not sufficient for study participation) who do not require ongoing opioid therapy for pain. Participants will undergo an initial four-week BUP/NX outpatient treatment with taper, and will be randomized to SMM or Enhanced Medical Management (EMM), which consists of SMM plus twice weekly individual outpatient drug counseling. After the initial treatment with taper, participants who thus far respond successfully will be followed for eight weeks to assess success or failure (see definitions below). Initial treatment failures will be eligible for treatment in Phase 2. Phase 2 consists of a 12-week outpatient stabilization treatment with BUP/NX, plus random assignment to SMM or EMM, followed by a four-week taper and eight weeks of follow-up. Failures can also elect to remain in Phase 1 through Week 12 follow-up and can make the transition to Phase 2 at any time up until the conclusion of Phase 1.

The **overall research question** for the study is: What benefit does EMM offer over SMM a) in a short-term treatment paradigm (a four-week BUP/NX treatment with taper) and b) in a longer-term treatment paradigm (12 weeks of a stabilization dose of BUP/NX) for subjects who have not responded successfully to the initial short-term BUP/NX treatment with taper?

For **Phase 1**, it is hypothesized that there will be a higher rate of success (defined below) to an initial BUP/NX treatment with taper among subjects receiving EMM (i.e., SMM plus individual drug counseling) than among subjects receiving BUP/NX and SMM alone.

For **Phase 2**, it is hypothesized that among subjects who have been unsuccessful in a four-week BUP/NX treatment with taper, regardless of their randomization assignment in Phase 1, the proportion of substantially improved subjects (defined below) after 12 weeks of BUP/NX stabilization treatment will be higher in the group that receives EMM than in the group that receives SMM alone.

3.2 Secondary Objectives

Secondary objectives will determine:

- Subject characteristics that predict likelihood of successful outcomes. Measures included in these analyses will include a) pain status; b) reason for initial use of opioids; c) sociodemographic characteristics (sex, race, age); d) severity of withdrawal symptoms; e) severity of craving; f) presence of current or past heroin use; g) presence of other substance use disorders; h) presence of other psychiatric disorders; i) level of depression; and j) number of previous treatment experiences.
- The percentage of this subject population that responds successfully (as defined below) to a 4-week initial treatment with BUP/NX, either with or without concomitant drug counseling.
- Among subjects who have been unsuccessful in a four-week BUP/NX treatment with taper, the overall percentage of subjects who experience substantial improvement with a 12-week BUP/NX stabilization treatment.
- Whether the probability of having positive urine screens for opioids decreases faster over the 12 weeks of Phase 2 stabilization treatment in the EMM group than in the SMM group (Hypothesis: yes).
- Whether EMM subjects will be more likely than SMM subjects to have substantial improvement at the end of 24 weeks of Phase 2, following the taper of BUP/NX during weeks 13-16 and eight weeks of follow-up (Hypothesis: yes).
- The role of pain in determining or moderating the response to EMM.
- The prevalence and nature of adverse events and serious adverse events in this population with this treatment regimen.

4.0 Study Design

Page	Section
4-1	<i>Overview of Study Design</i>
4-3	<i>Data Collection Phase 1 and Phase 2</i>
4-3	<i>Duration of Study and Visit Schedule</i>
4-3	<i>Feasibility Review</i>

4.1 Overview of Study Design

In this two phase **outpatient** study, participants seeking treatment for prescription opioid dependence will be enrolled in an open-label, multi-center study after screening and baseline assessments. All participants will receive a 1-day BUP/NX induction regimen, which begins the 4-week BUP/NX outpatient treatment with taper.

4.1.1 Phase 1 Induction and Treatment

4.1.1.1 Induction

For the 1-day induction phase:

- All participants should refrain from opioid use for approximately 12 hours.
- Pre-dose baseline scores on COWS should be greater than eight (8) (no signs of intoxication but not in serious withdrawal).
- An initial 4 mg dose of BUP/NX (two sublingual tablets with 2 mg BUP/0.5 mg NX) will be administered, and the participant observed for 1 hour.
 - If symptoms improve (at least a 2-point reduction in COWS score), the participant can be sent home with two 4 mg doses and instructed to take the additional doses if needed.
 - If symptoms do not improve, or worsen, an additional 4 mg is administered; the participant is observed for another hour, and sent home with the remaining 4 mg dose.
- All participants will be sent home with additional doses of BUP/NX to last until the next study visit, which will also be scheduled during the first week of treatment.
- Study staff will contact the participant by phone later during the first day.
- This 1-day induction limits the first day dose to 12 mg. Alternative induction schedules allowing a first-day dose of 16mg will be described in the Operations Manual.

4.1.1.2 Phase 1 Treatment

Including induction, all participants will receive BUP/NX for 4 weeks. The maximum BUP daily dose is 32 mg. Dosage of BUP is flexible, and the study site investigators may adjust the dose according to the participant's wellbeing. Extra visits may be utilized to reach appropriate dosing. However, the daily BUP dose may not exceed 32 mg. All participants will taper off BUP/NX during weeks 3 and 4. Taper will begin around Study Day 15 and must end by Study Day 28.

Participants will be randomized in Phase 1 to receive either SMM or EMM (SMM plus twice weekly individual drug counseling) in addition to BUP/NX. SMM, which is described below, consists of an initial hour-long visit, a 15-20 minute follow-up visit in Week 1, then weekly 15-20 minute visits during weeks 2-4 (the BUP/NX phase). Follow-up visits will be held at Weeks 6 and 8. Drug counseling visits for EMM participants are 45 minutes long and held twice a week for 4 weeks, then once at Weeks 6 and 8.

At the end of the 4-week treatment and taper (Phase 1), participants will be defined as treatment successes or treatment failures. A participant is a "success" if all of the following criteria are satisfied during the 4-week treatment with taper and eight weeks of follow-up:

1. Use of opioids on four or fewer days per month (beginning after the end of Week 2) as evidenced by self-report.
2. Urine screen for opioids are never positive on two consecutive weeks (beginning after the end of Week 2).
3. Completion of the 4-week medication regimen and 8-week follow-up period (including Week 6 and Week 8 SMM or EMM booster visits) without participating in other formal substance abuse treatment (e.g., methadone maintenance, drug counseling, etc.). Self-help groups such as Narcotics Anonymous and treatment for other issues such as medical or psychiatric problems do not count here.
4. Absence of needle use.
5. Absence of no more than one urine sample (beginning after the end of Week 2).

Participants meet "failure" criteria if they fail one or more of the criteria for "success." Participants who meet failure criteria *at any time* during the Phase 1 four-week treatment with taper or during the eight-week follow-up will be invited to enter Phase 2. Participants who meet failure criteria do not necessarily complete all 12 weeks of Phase 1 prior to entering Phase 2. Failures can elect to remain in Phase 1 through Week 12 follow-up and can make the transition to Phase 2 at any time up until the conclusion of Phase 1.

All treatment success participants will continue to have visits every other week for eight weeks following the end of the taper. If they continue to be successful throughout the four-week BUP/NX treatment period and the eight weeks of follow-up, these participants will have completed the study.

4.1.2 Phase 2 Induction and Treatment

Participants who meet failure criteria at any time during the four-week treatment with taper or during the eight-week follow-up of Phase 1 will be invited to enter Phase 2. Participants who miss three or

more days of BUP/NX and are continuing in Phase 2 the study will need to be re-induced with BUP/NX. This 1-day induction dose is limited to 16 mg.

Participants who meet failure criteria in Phase 1 who choose to continue to Phase 2 will be re-consented and randomized in Phase 2 to receive 12 weeks of BUP/NX with SMM or 12 weeks of BUP/NX with EMM that also provides individual drug counseling (see Figure 1.1 on page 1-14, *Generalized Study Schema*). After the 12-week BUP/NX stabilization treatment, participants in both groups will be tapered off BUP/NX over four weeks (Weeks 13-16) while receiving SMM only. Taper will begin around Study Day 85 and must end by Study Day 112.

The **primary outcome measure** for Phase 2 is “substantial improvement,” defined as abstaining from opioids during the last week AND for at least two of the previous three weeks of the third month of BUP/NX treatment. Abstinence is determined by self-reports of opioid abstinence (missing urines will be considered positive for opioids).

SMM in Phase 2 will consist of one 30-60 minute initial visit and one 15-20 minute follow-up visit in Week 1, then one individual session (15-20 minutes) per week during Weeks 2-16.

EMM will consist of the same SMM schedule plus two individual sessions with a counselor per week (45 minutes) during Weeks 1 through 6, then one individual session with a counselor per week (45 minutes) during Weeks 7-12.

During Weeks 13-16 both groups will receive SMM once a week, and during the follow-up period (Weeks 17-24) both groups will attend follow-up visits only.

4.2 Data Collection Phase 1 and Phase 2

Data will be collected weekly until the end of the taper phase in Phase 1 and 2, then follow-up data collected every two weeks for eight weeks post-taper. Participants will provide urine samples at each research visit for opiates and other drugs of abuse. Severity of withdrawal symptoms (as assessed by the COWS), craving scores, concomitant medications, pain assessments, BDI, and adverse event data will also be collected according to the schedules in Table 4.1 and Table 4.2.

4.3 Duration of Study and Visit Schedule

The total duration of study participation will be up to 12 weeks for Phase 1 and a total of 24 weeks for Phase 2.

4.4 Feasibility Review

The study will be first initiated at three of the 12 sites to assess logistical parameters of the study. After the first 30 subjects have been randomized, the protocol team will review the following:

- Accrual rates
- Screening rates
- Reasons for screen failures/refusal

- Intervention/instrument use
- Staff training adequacy
- Failure rate for Phase 1
- Likelihood of uptake from Phase 1 to Phase 2
- Study design parameters
- Scope of subject population

If changes to the protocol that have an impact on participant safety or data integrity are required, the Lead Investigators will request review by the DSMB prior to the implementation of any changes.

Table 4.1 Visit Schedule Phase 1 for EMM and SMM: 12-week Study Period

Assessments	Screening/ Baseline Measures	PHASE I – 12 WEEK STUDY PERIOD												
		BUP/NX Treatment w/Taper					Follow-Up						FINAL VISIT	
		1a	1b	2	3	4	5	6	7	8	9	10	11	Tx success (Wk 12) OR Tx failure (if transitioning to Phase 2)*
WEEK NUMBER >>			+/- 4 days	+/- 3 days of target date			**		**		**		**	
PERMITTED WINDOW >>														**
SCREENING ASSESSMENTS														
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Demographics	X													
Randomization		X												
CIDI/Substance Use Diagnosis	X													
SAFETY ASSESSMENTS														
Clinical Opiate Withdrawal Scale (COWS)		X	X	X	X	X		X		X				X
Medical/Psychiatric Evaluation (including physical exam)	X													**** Physical Exam Only
Vital Signs	X	X	X	X	X	X		X		X		X		X
Lab Tests (LFTs, Chemistry, Hematology, Urinalysis)	X													X
Pregnancy Test	X					X								X
Adverse Event (AE) Evaluation		X	X	X	X	X		X		X		X		X
Serious Adverse Event (SAE) Evaluation		<< Completed when necessary >>												
Concomitant Treatments (including medications & psychosocial)	X	X	X	X	X	X		X		X		X		X
EFFICACY ASSESSMENTS														
Craving Visual Analog Scale (VAS)	X	X	X	X	X	X		X		X		X		X
Substance Use Report-Baseline	X													
Substance Use Report-Follow-up		X	X	X	X	X		X		X		X		X
Urine Drug Screen*****	X	X	X	X	X	X		X		X		X		X
PAIN ASSESSMENTS														
Pain & Opioid Analgesic Use History	X													
Brief Pain Inventory	X					X				X				X
Brief Pain Inventory abbrev (if pain stratification)		X	X	X	X									
Beck Depression Inventory II	X					X				X				X
SF-36	X													X
OTHER ASSESSMENTS														
Addiction Severity Index (ASI Lite)	X													
Addiction Severity Index (ASI Lite) Follow-Up														X
RBS (Risk Behavior Survey)	X													
CIDI/Depression & PTSD Diagnosis	X													
Fagerstrom Test for Nicotine Dependence	X													X
TREATMENT PLAN														
BUP/NX Induction		X												
BUP/NX Dosing or Taper ***		X	X	X	X	X								X (if applicable)
Medication Accountability		X	X	X	X	X								X (if applicable)
Standard Medical Management		X	X	X	X	X		X		X				X (if applicable)
Enhanced Medical Management		X	X	2X	2X	2X		X		X				X (if applicable)
VISIT DURATION (minutes)	240	60-90					60-90					30	120	

* If participant is a Phase 1 treatment failure AND eligible for Phase 2 AND elects to participate in Phase 2, the final visit CRFs for Phase 1 (Final Visit column) should be completed and then continue to Table 4.2. If the participant does not elect to transition to Phase 2, the regular visit CRFs should be completed according to visit schedule.

** Permitted window of completion is +/- 7 days of scheduled visit during Weeks 6, 8, 10, and 12.

*** May require additional visits for dose adjustment.

**** Physical exam is omitted if participant is transitioning to Phase 2.

***** Urine drug screen for BUP administered in Weeks 10 and 12.

Table 4.2 Visit Schedule Phase 2 for EMM and SMM: 24 Week Study Period

Assessments	*Final Visit Phase 1 (duplicates last column Table 4.1)	PHASE 2 – 24 Week Study Period																								
		BUP/NX Stabilization												BUP/NX Taper				Follow-Up								
		1a	1b	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
WEEK NUMBER >>																										
PERMITTED WINDOW >>		+/- 4 days	+/- 3 days of scheduled visit																	**		**		**		**
SCREENING ASSESSMENTS																										
Consent Review		X																								
Eligibility Review		X																								
Randomization		X																								
SAFETY ASSESSMENTS																										
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lab Tests (LFTs, Chemistry, Hematology, Urinalysis)	X																X									
Pregnancy Test	X					X							X				X									
Adverse Event (AE) Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Event (SAE) Evaluation		<<Completed when necessary>>																								
Physical Exam	X																									
Clinical Opiate Withdrawal Scale (COWS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Treatments (including medications & psychosocial)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EFFICACY ASSESSMENTS																										
Craving Visual Analog Scale (VAS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Substance Use Report Follow-up	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Drug Screen****	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PAIN ASSESSMENTS																										
Brief Pain Inventory	X					X				X				X			X				X				X	
Brief Pain Inventory abbrev (if pain stratification)		X	X	X	X		X	X	X		X	X	X		X	X	X									
Beck Depression Inventory II	X					X							X				X				X				X	
SF-36	X												X												X	
OTHER ASSESSMENTS																										
Addiction Severity Index (ASI Lite) Follow-up	X																								X	
Fagerstrom Test for Nicotine Dependence	X																								X	
TREATMENT PLAN																										
BUP/NX Induction (if applicable)		X																								
BUP/NX Dosing or Taper ***	X (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication Accountability	X (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Standard Medical Management	X (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Enhanced Medical Management	X (if applicable)	X	X	2X	2X	2X	2X	2X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
VISIT DURATION (minutes)	120	60-90												60				30								60

* If participant is a failure in Phase 1 and chooses to transition to Phase 2, the final visit of Phase 1 is considered the *baseline visit* for Phase 2.
 ** Permitted window of completion is +/- 7 days of scheduled visit during Weeks 18, 20, 22, and 24.
 *** May require additional visits for dose adjustment.
 **** Urine drug screen for BUP administered in Weeks 22 and 24.

5.0 Study Population

Page	Section
5-1	<i>Subject Recruitment</i>
5-3	<i>Community Treatment Programs (CTPs)</i>

Study Population: Adult males and females seeking treatment for prescription opioid dependence, in the absence of pain that requires ongoing opioid therapy.

5.1 Subject Recruitment

5.1.1 Eligibility Criteria

Males and females 18 years of age or older, seeking detoxification from prescription opioid dependence in the absence of chronic pain severe enough to require ongoing opioid therapy or an acute pain event within the past six months will be entered into this trial. For participants who are receiving opioids for pain, the study physician will consult with the participant’s prescribing physician to ensure that the participant is medically stable enough to enter the trial (e.g., the participant does not have a malignant tumor causing the pain). Participants who use prescription opioids by injection may be included as long as they have never injected heroin.

All participants must meet the criteria outlined in the following section, *Inclusion Criteria*.

5.1.1.1 Inclusion Criteria

1. Participants must have the ability to read, understand (including passing a comprehension quiz), and provide written informed consent.
2. Participants must be 18 years of age or older
3. Females of childbearing capacity must agree to use an acceptable method of birth control throughout the study. One of the following methods of birth control is acceptable for females:
 - a. hormonal contraceptives, including:
 - i. oral contraceptives
 - ii. intrauterine progesterone contraceptive system (IUD)
 - iii. levonorgestrel implant
 - iv. medroxyprogesterone acetate contraceptive injection
 - v. other hormonal method(s) approved by the study investigator

- b. barrier (diaphragm or cervical cap) with spermicide or condom
 - c. complete abstinence from sexual intercourse
 - d. male partner sterilization
4. Participants who are receiving opioids for pain must have clearance from their prescribing physician to enter the trial.
 5. Participants must have the ability to meet study requirements.
 6. Participants must meet DSM-IV criteria for current opioid dependence.
 7. Participants must be currently physically dependent on opioids (using prescription opioids at least 20 days/month) and in need of medical assistance for opioid withdrawal.
 8. Participants must be in good general health (in the opinion of the study investigator after review of medical records and baseline evaluations) or, for participants requiring ongoing medical/psychiatric treatment (whether currently in such treatment or not), under the care of a physician willing to continue participants' medical management and to cooperate with study site investigators.
 9. Participants must be non-psychotic and psychiatrically stable in the opinion of the study investigator.
 10. Participants will be asked to provide locator information including their residential street address and a working telephone number; or, if they are homeless, they must provide the address and telephone number of a non-drug abusing relative or friend who can reach the participant in emergencies.
 11. Prior to induction:
 - Participant should be in opioid withdrawal (COWS scale >8)
 - Participant's dose of methadone (if receiving it for pain; those receiving methadone treatment for opioid dependence are excluded, see below) should be less than or equal to 40 mg

5.1.1.2 Exclusion Criteria

Participants will be excluded if they:

1. Have a medical condition that would make participation medically hazardous, in the opinion of the study investigator, after consultation with the study physician (if not the same), based on a review of medical records and baseline evaluations.
2. Have known allergy or sensitivity to buprenorphine or naloxone.
3. Are psychotic or have any other acute severe psychiatric condition.
4. Are a suicide risk within the past 30 days.

5. Are dependent on alcohol, sedative-hypnotics or stimulants, and requiring immediate medical attention.
6. Have used heroin more than four days in the past 30 days.
7. Have participated in another investigational drug study within the last 30 days.
8. Have participated in methadone or buprenorphine maintenance treatment for opioid dependence within 30 days of study enrollment.
9. Have a current or pending legal status that would make them unlikely to remain in the local area for the duration of the study.
10. Lifetime opioid dependence that would be accounted for by heroin use alone.
11. Have ever used heroin by injection.
12. Have experienced a traumatic or major pain event within the past six months.
13. Are pregnant or lactating or a female unwilling to follow study required measures for pregnancy prevention.
14. Are unable to remain in the local area for the duration of Phases 1 and 2 of the study.
15. Have presence of pain of sufficient severity as to require ongoing pain management with opioids.
16. Have LFTs >5x upper limit of normal range.
17. Have surgery scheduled within the next six months that would preclude participation during the active treatment phase of the study.
18. Are currently receiving formal substance abuse treatment.

5.2 Community Treatment Programs (CTPs)

5.2.1 Number of CTP Sites

It is estimated that 12 CTP sites will participate in this study.

5.2.2 CTP Characteristics

CTPs participating in the study must demonstrate capacity to:

1. Provide outpatient BUP services.
2. Provide outpatient individual counseling services.
3. Recruit 54 study-eligible opioid analgesic dependent participants over 18 months (approximately three per month).

4. Have at least two counselors willing to participate in the protocol and provide twice-weekly individual manualized counseling.
5. Be willing to implement the Standard Medical Management (SMM) and Enhanced Medical Management (EMM) interventions for prescription opioid dependence in lieu of TAU for participants in the trial.
6. Establish and maintain a relationship with local primary care clinics and/or pain management centers (if available in the community) for the purposes of recruitment and referral of participants with pain.
7. Provide drug storage facilities in compliance with all federal (DEA and FDA) and local regulations and laws for a Schedule 3 drug.

6.0 Outcome Measures

Page	Section
6-1	<i>Primary Outcome Measures</i>
6-2	<i>Secondary Outcome Measures</i>

6.1 Primary Outcome Measures

The **primary outcome measure** for **Phase 1** will be binary; i.e., “success” or “failure.”

6.1.1 “Success” in Phase 1

“Success” in Phase 1 will be defined as follows: a participant is a “success” if all of the following criteria are satisfied during the 4-week treatment with taper and eight weeks of follow-up:

1. Use of opioids on four or fewer days per month (beginning after the end of Week 2) as evidenced by self-report.
2. Urine screen for opioids are never positive on two consecutive weeks (beginning after the end of Week 2).
3. Completion of the 4-week medication regimen and 8-week follow-up period (including Week 6 and Week 8 SMM or EMM booster visits) without participating in other formal substance abuse treatment (e.g., methadone maintenance, drug counseling, etc.). Self-help groups such as Narcotics Anonymous and treatment for other issues such as medical or psychiatric problems do not count here.
4. Absence of needle use.
5. Absence of no more than one urine sample (beginning after the end of Week 2).

6.1.2 “Failure” in Phase 1

Participants who fail one or more of the criteria for “success” will be considered Phase 1 “failures.”

6.1.3 “Substantial Improvement” in Phase 2

The primary outcome measure for **Phase 2** is “substantial improvement,” defined as abstaining from opioids during the last week AND for at least two of the previous three weeks of the third month of BUP/NX treatment. Abstinence is determined by self-reports of opioid abstinence (missing urines will be considered positive for opioids).

6.2 Secondary Outcome Measures

Secondary measures include:

- Withdrawal symptoms, assessed with the COWS.
- Craving, assessed with a visual analog scale (VAS).
- Characteristics of participants who respond to the different treatment regimens, including the presence or absence of significant pain, any heroin use, and presence of co-occurring substance use disorders.
- Effect of EMM to reduce drug use, as determined by the proportion of negative urine screens over time in Phase 2.
- Effect of pain in determining or mediating the response to EMM.
- Concomitant medications at the end of taper period and at 1- and 2-month post treatment with taper follow-ups.
- The frequency and nature of adverse events and serious adverse events.

7.0 Study Procedures

Page	Section
7-1	<i>Recruitment and Enrollment</i>
7-2	<i>Baseline Assessment</i>
7-3	<i>Randomization</i>
7-4	<i>Treatment Discontinuation & Study Termination</i>
7-5	<i>Follow-Up</i>
7-6	<i>Binding</i>
7-7	<i>Prevention of Study Dropouts</i>

7.1 Recruitment and Enrollment

7.1.1 Recruitment Plan

Recruitment plans and strategies are located in Appendix E ~ Recruitment Plan and Strategy.

7.1.2 Projected Recruitment Rate

It is estimated that sites will recruit three participants per month.

7.1.3 Initial Subject Screening

Study site personnel will be thoroughly trained in the protocol in operation at their site, and specifically with regard to inclusion and exclusion criteria detailed in *Inclusion Criteria* on page 5-1 and *Exclusion Criteria* on page 5-2.

Potential participants who are identified as meeting the inclusion criteria will be provided basic information about the protocol, and if interested, provided with an appointment for the purposes of obtaining informed consent and baseline assessments. Participants who do not meet inclusion criteria will be referred to standard treatment services within the CTP or at another local treatment facility. Participants will not be inducted onto study drug until the results of all baseline assessments and blood chemistries are obtained, and eligibility is determined.

7.1.3.1 Testing Completed

Once signed informed consent is obtained, participants will complete:

- Demographic questionnaire

- Visual Analog Scale (VAS) for craving
- Addiction Severity Index (ASI Lite)
- Clinical Withdrawal Scale (COWS)
- Fagerstrom Test for Nicotine Dependence
- Pain and Opioid Analgesic Use History
- Concomitant Treatment Assessment
- Substance Use Report
- Risk Behavior Survey
- CIDI assessment for substance use disorders, depressive disorders, and PTSD
- Complete medical and psychiatric history, vital signs and physical exam
- Brief Pain Inventory
- Beck Depression Inventory II
- SF-36

Blood samples will be obtained for:

- Blood chemistry
- Liver function tests (LFTs)
- Complete blood count (CBC)

Urine samples will be obtained for:

- Standard urinalysis
- Drugs of abuse screen
- Pregnancy test for females of child-bearing potential

7.1.4 Informed Consent Procedures

Prior to the initiation of any clinical research procedures, the Study Coordinator (or person assuming this role) at each CTP will review study procedures and the informed consent document and obtain signed, informed consent for study participation (See Appendix A ~ Sample Informed Consent). Potential participants will be provided with a consent form describing the study's purpose, general procedures, risks and benefits as well as the participant's role in the study.

Because participants will self-administer BUP/NX, they will also be asked to sign an IRB-approved Treatment Agreement detailing agreements between the participant and the provider regarding acceptable behavior and responsible use of medication.

Participants who were defined as treatment failures during Phase 1 of the study (see criteria in “*Failure*” in Phase 1 on page 6-1) will be re-consented in Phase 2.

7.1.4.1 Comprehension Assessment

The participant’s understanding of the study protocol and informed consent will be assessed using the Informed Consent Evaluation form (See Appendix B ~ Sample Comprehension Tool) and study staff judgment. Only those participants who successfully complete the assessment (as evidenced by correctly answering 100% of the items) will be enrolled into the study.

7.1.4.2 Other Procedures for Vulnerable Populations

For pain assessment, participants will complete BPI, BDI, and a Pain and Opiate Analgesic Use History assessment. For participants who are receiving opioids for chronic pain, the study medical clinician will consult with the participant’s prescribing physician to ensure that the individual is appropriate for the protocol, e.g., that the participant’s pain is not due to an underlying malignancy, trauma within the past six months, or that further diagnostic testing is needed to determine the source of the pain. Subjective report of pain and the BPI abbreviated will be collected weekly during study treatment to monitor pain status in patients with chronic pain.

7.2 Baseline Assessment

Baseline assessments will include a comprehensive evaluation of demographics, drug history and lifetime diagnoses, addiction severity, concomitant medications (over the counter or by prescription), withdrawal status, medical and psychiatric status, assessment of HIV risk, and pain. Medical status will be determined by medical history, physical examination, and clinical laboratory evaluations (including complete blood count, chemistry profile, liver function profile, urinalysis, and urine screen for drugs of abuse). Vital signs will also be obtained.

All females of child-bearing potential will be required to have a pregnancy test prior to receiving their first dose of investigational agents. All female participants of childbearing potential will be required to practice acceptable birth control (e.g., oral or depot contraceptives, foam, sponges, and/or condoms). Birth control methods will be documented on the CRF. Female participants who become pregnant will be withdrawn from the study and provided immediate access to methadone maintenance services at the CTP or another local treatment provider. Women refusing methadone maintenance will be referred to another local provider.

7.3 Randomization

7.3.1 Method

Participants who fulfill eligibility criteria, provide informed consent, and wish to participate in the study will be randomized to either the EMM arm or the SMM arm. After the site personnel have

completed the screening process, they will call a 24-hour toll free number for randomization. Treatment will be assigned through an IVRS (interactive voice response system) or randomization personnel.

A permuted block randomization scheme will be employed for both phases. For phase I, the randomization will be stratified by whether or not the participant has ever used heroin, and whether or not the participant currently has chronic pain. Whereas for phase II, it will be stratified by the treatment received in phase I (EMM or SMM). To keep the sequencing of treatment assignment confidential, block size will not be revealed to the investigators.

7.4 Treatment Discontinuation & Study Termination

7.4.1 Participant-Initiated Discontinuation

Participation in this study is voluntary. If the participant chooses not to receive study medication, SSM, and/or EMM (i.e. individual drug counseling), that will not affect his/her relationship with that particular study site, or his/her right to health care or other services. The participant is free to withdraw his/her consent and discontinue participation in study treatments and/or study research at any time without prejudice to his/her future health care.

Discontinuation from study treatment refers to the discontinuation of one or more of the following:

- BUP/NX
- SMM
- EMM

In most cases, even if treatment is discontinued, site staff will continue to follow participants for the purposes of collecting research and safety information. Discontinuation of study treatment (either participant initiated, investigator initiated, or mutually agreed) and discontinuing research visits should be viewed as separate events in most cases and negotiated as such with participants.

7.4.2 Investigator-Initiated Discontinuation

The investigator may discontinue study medication, EMM, and/or SMM treatment if circumstances arise, including but not limited to:

- Adverse reaction to study medication that require removal from the medication (e.g. allergic reaction)
- A change in medical status that makes it unsafe for a participant to continue participating
- A participant becomes ill during the study
- Serious behavioral problems or negative behaviors such as selling drugs at the study site

Participants discontinued from study treatment will be provided appropriate referrals to alternative treatments in the area by study personnel.

7.4.2.1 Treatment Discontinuation

Efforts will be made to assess participant status at all follow-up time points. When possible, the reason the participant discontinued from treatment will be noted on the appropriate treatment discontinuation CRF.

7.4.2.2 Procedures for Discontinuation

If EMM, SMM, or BUP/NX treatment is discontinued, either participant-initiated or investigator-initiated, the participant may continue to participate in the other study treatments; except if SMM is discontinued, he/she can not continue to receive BUP/NX. In most cases when all components of the participant's study treatment is discontinued, only study research visits will be expected from that point forward. Occasionally, a participant who has discontinued from study treatment may elect to return to one or more components of treatment. In this case, if the participant remains appropriate and within the treatment window based on the randomization date, the participant may be allowed to return to treatment. This may occur in Phase 1 or Phase 2 (up to the final day of the week 8 SMM visit window in Phase 2). As such, if a participant discontinues BUP/NX in Phase 2 and wishes to be restarted on BUP/NX, re-induction of BUP/NX can occur in Phase 2 until week 8 only.

Upon completion of the tapering phase, or in cases of early dropout, participants may continue in treatment at the CTP (if available), or may be referred to available local treatment resources. In the event that any participant desires additional pharmacological treatment for his/her opiate dependence, or if the study staff finds that additional treatment is clinically indicated, the site will refer the participant to a local provider of methadone or buprenorphine.

Participants whose clinical status worsens substantially during the study (e.g., increased opioids use, needle use, more dangerous behaviors such as overdose) may be referred to other treatment options; for instance, participants will be told about methadone maintenance as well as more intensive psychosocial treatment, or participants who relapse to regular opioids use in the context of severe and/or worsening pain may be referred to a pain clinic if clinically appropriate. All such participants will remain part of the study and will continue to be followed for research. A decision as to whether it is appropriate for such participants to continue with study treatment will be made by the local study medical clinician in consultation with the Lead Investigator (LI) or designee.

7.4.2.3 Replacement of Subjects

Participants will not be replaced.

7.4.2.4 Study Termination

Study termination refers to the end of all study treatment AND study research data collection (e.g. final visits in Phase 1 and Phase 2), and is treated separately from treatment discontinuation. Early study termination may take place if a participant withdraws his/her consent to participate. The reason for study termination will be noted on the appropriate study termination CRF.

7.5 Follow-Up

Follow-up is scheduled every other week for all participants for eight weeks following completion of the taper in Phases 1 and 2 (although a participant can end Phase 1 and enter Phase 2 before the eight weeks of Phase 1 follow-up have been completed, if the participant meets failure criteria). The standard procedure for follow-up visits is a face-to-face assessment completed at the study site. However, in limited circumstances as defined by the Operations Manual, sites can collect limited research and safety data by telephone, provided the participant has not withdrawn consent.

7.6 Binding

This is an open-label study.

7.7 Prevention of Study Dropouts

Outreach efforts will be ongoing so participants are not lost at key assessment points and remain engaged in the study. Study site staff will call participants and/or their contacts on a regular basis to keep participants engaged, and to track and document any changes in living situation or status that will facilitate follow-up. Participants may discontinue study participation at any time.

Participants will be compensated with cash or cash equivalent in retail vouchers or coupons upon completing the baseline interview procedures, weekly research visits during treatment, and for each follow up research assessment. For a more detailed discussion of our retention efforts, please refer to the Data Safety and Monitoring Plan.

8.0 Study Treatments

Page	Section
8-1	<i>Treatment by Phase</i>
8-3	<i>Behavioral Therapies</i>
8-5	<i>Study Intervention</i>
8-8	<i>Training Procedures</i>

8.1 Treatment by Phase

8.1.1 PHASE 1

8.1.1.1 Induction Schedule

Day 1: All participants will receive an initial 4 mg sublingual dose of BUP/NX (two tablets of 2 mg BUP/0.5 mg NX), and will be observed for one hour. If symptoms improve (COWS score reduction of at least two points), the participant can be sent home with two 4 mg doses and instructed to take the additional doses if needed. If symptoms do not improve or worsen, an additional 4 mg BUP is administered, and the participant is observed for another hour and sent home with the remaining 4 mg dose. This induction scheme is relatively conservative, and limits the first day dose to 12 mg. Alternative induction schedules, in which participants receive up to 16 mg in the first day, can be used if the study medical clinician believes it is necessary, and are described in the Operations Manual. All participants will be sent home with additional doses of BUP/NX to last until the next study medical visit, which will also be scheduled during the first week of treatment.

8.1.1.2 Post-Induction

Including induction, participants will receive BUP/NX for four weeks. At each visit during this phase, the study medical clinician may adjust the BUP dose in increments of up to 8 mg. The maximum allowable dose is 32 mg per day, and the minimum allowable dose is 8 mg per day. During weeks 3 and 4 participants will taper off BUP/NX to zero. Taper will begin around Study Day 15 and must end by Study Day 28. Taper Guidelines for BUP/NX during taper are found in *Dosing During Taper* on page 8-5.

Participants who are successes at the end of four weeks treatment with taper will be followed every other week for the next eight weeks. Participants who are successes for the complete 12 weeks of Phase 1 will have completed the study.

Participants who meet criteria for treatment success after the 1st month of Phase 1 but relapse to opioid use in the next two months are considered Phase 1 failures and are eligible to enroll in Phase 2. Thus, if a participant meets the criteria for treatment failure at any time during Phase 1, s/he may continue on to Phase 2. Participants entering Phase 2 will not require induction if the time period between the end

of Phase 1 and last BUP/NX dose is less than or equal to three days. If the period of time is four or more days, induction will be required prior to entering Phase 2. This 1-day induction dose is limited to 16 mg, in divided doses of 8 mg/8 mg or 8 mg/4 mg/4 mg.

In addition to the BUP/NX pharmacotherapy, participants will be randomly assigned to receive either SMM or EMM.

SMM in Phase 1 will consist of one hour-long initial visit, one individual 15-20 minute visit later in Week 1, and then one individual 15-20 minute visit per week through the end of Week 4 (the end of the BUP/NX treatment). Participants will have a 15-20 minute SMM visit at Week 6 and at Week 8, although they will not be receiving medication at that time. EMM in Phase 1 will consist of SMM plus two individual sessions with a counselor per week (45 minutes each) through Weeks 1-4, and one 45-minute counseling visit at Week 6 and at Week 8.

8.1.2 PHASE 2

All treatment failure participants from Phase 1 who enter Phase 2 will be randomized to receive a 12-week BUP/NX treatment plus SMM or a 12-week BUP/NX treatment plus EMM (SMM plus twice weekly individual drug counseling). After the 12-week period, participants in Phase 2 will taper off of their BUP/NX dose over four weeks (month 4 of Phase 2). Taper will begin around Study Day 85 and must end by Study Day 112. During the taper period, only SMM will be provided.

Phase 2 participants will not require induction if the time period between the end of Phase 1 and last BUP/NX dose is three days. If the period of time is four or more days, induction will be required prior to entering Phase 2. This 1-day induction dose is limited to 16 mg. As in Phase 1, the study medical clinician may adjust the BUP dose in Phase 2 at each visit in increments of up to 8 mg. The maximum allowable dose is 32 mg per day. Dose changes are to be determined after the study staff obtains vital signs, evaluation of illicit drug use (urine and self-report), craving, signs and symptoms of opiate withdrawal or over-medication, adverse events and current BUP/NX and other medication taken since the last visit.

For Phase 2, SMM will consist of one 30-60 minute initial visit and one 15-20 minute follow-up visit in Week 1, and then one individual session (15-20 minutes) per week through Week 12. EMM will consist of the same medical management schedule plus two individual sessions with a counselor per week (45 minutes each) during Weeks 1-6 and one individual session with a counselor per week (45 minutes each) during Weeks 7-12.

Participants whose clinical status worsens during Phase 2 (e.g., increased opioid use, needle use, more dangerous behavior such as overdoses) will be referred to other treatment options; for instance, participants will be told about methadone maintenance as well as more intensive psychosocial treatment, or participants who relapse to regular opioids use in the context of severe and/or worsening pain may be referred to a pain clinic if clinically appropriate. All such participants will remain part of the study and will continue to be followed, but for coding purposes will be considered treatment failures.

8.2 Behavioral Therapies

8.2.1 Standard Medical Management (SMM)

SMM will be delivered to all participants in Phase 1 and in Phase 2. SMM will be delivered according to the *Manual for SMM of Opioid Dependence with Buprenorphine* by Fiellin et al. (1999). SMM was originally designed for use by medical personnel in primary care settings, and consists of relatively brief (i.e., 15-20 minutes) medically focused visits that combine standard medication (i.e., buprenorphine) management along with brief counseling methods to help participants attain and maintain abstinence from illicit opioid use. Key elements of SMM include the following.

- Monitoring substance use
- Monitoring medication adherence
- Educating participants about opioid dependence and buprenorphine
- Encouragement to abstain from illicit opioids and other substances of abuse
- Encouragement to attend Alcoholics Anonymous, Narcotics Anonymous or other self-help groups
- Encouragement to make lifestyle changes that would help facilitate recovery
- Identification of other medical problems
- Referral to specialty services if needed
- Asking about pain (specifically for our protocol)

SMM is administered by a licensed medical clinician. The initial session in Phase 1 is approximately one hour long, during which the physician reviews the participant's medical, psychiatric, and substance use problems, reviews the diagnosis of opioid dependence, develops a treatment plan, advises the participant to abstain from all substances of abuse, refers the participant to Narcotics Anonymous or other self-help groups, reviews the overall treatment program, and answers questions. The initial session in Phase 2 is approximately 30-60 minutes depending on medical necessity. Subsequent visits last approximately 15-20 minutes each, and are held as part of post-induction follow-up in Week 1 of both phases, then weekly. At these visits, the medical clinician does the following.

- Reviews the participant's substance use since the previous visit (including urine toxicology results)
- Reviews the participant's adherence to medication since the previous visit
- Reviews the response to buprenorphine and any adverse events
- Advises abstinence
- Addresses non-adherence to treatment if indicated

- Asks about NA or other self-help group participation and lifestyle issues
- Asks about pain (specific to this protocol)
- Makes referrals and asks about previous referrals if indicated
- Dispenses buprenorphine

The two visits in Month 2 of Phase 1 consist of all of these elements except for those directly related to buprenorphine.

The SMM manual discusses difficulties that might arise in visits, including suicidal ideation, complaints regarding side effects, and arriving at a visit intoxicated. SMM was able to be delivered with adequate adherence and competence in a previous study by Fiellin et al. (2002) (Michael Pantalon, personal communication).

8.2.2 Enhanced Medical Management (EMM)

EMM is a counseling manual designed to provide an intensive counseling approach for participants with opioid dependence being treated with buprenorphine. In the study for which EMM was previously used (Fiellin et al. 2002), EMM was compared to SMM, rather than being administered in *addition* to SMM. Moreover, EMM in this previous study was administered typically by primary care nurses with little or no addiction background. Because EMM from that study contains some aspects of SMM, the EMM manual as currently constituted (Pantalon et al., 1999) was adapted for this study by removing the strictly medical aspects of the manual (e.g., identification and treatment of medical complications of opioid use). Rather, the EMM manual focuses primarily on drug abuse counseling *per se*. The EMM manual was revised to allow for use in Phase 1 and Phase 2. This included providing counselors with guidance regarding selection of modules, repeating modules, and how to manage patients in Phase 2 who have and have not received EMM previously in Phase 1. Finally, the manual was revised to address physical pain. A module specific to physical pain and its impact on achieving and maintaining abstinence was written to provide education about the potential significance of physical pain on drug abuse outcome to opioid dependent patients who have physical pain.

EMM is a manualized drug-counseling program designed to be administered to opioid-dependent participants receiving buprenorphine. The manual integrates addiction and recovery education with a discussion of medication (buprenorphine). Drug counseling visits can be conducted by drug counselors, psychologists, social workers, or nurses. In the original study in which EMM was delivered, nurses and physicians with little or no addiction treatment experience administered EMM with good adherence and competence. While substance abuse experience is not required to administer the counseling, for this study, all counselors will be experienced substance abuse counselors.

Drug counseling visits in EMM would include discussion of the following topics.

- Substance use since the prior visit, including a review of urine toxicology screens
- Medication adherence issues
- NA or other self-help group participation
- Lifestyle changes

- Advice to abstain

In addition, the drug counseling sessions each cover an educational topic, which are supplemented by handouts (see manual in Appendix C for examples). At each session, a topic is discussed. These topics, like the counseling manual, have been adapted from the *Group Drug Counseling* manual of Mercer et al. (1992) and the *12-step Facilitation Therapy Manual* by Nowinski et al. (1992).

Topics include:

- Understanding addiction
- The process of recovery
- The stages of recovery
- Self-help groups and support systems
- Managing feelings
- Coping with shame and guilt
- Coping with pain (specific to our protocol)

There are 13 modules (including the physical pain module described above), and modules can be discussed for two sessions. Because Phase 2 consists of 18 sessions, some modules will only be discussed once. There is some flexibility in the manual, so that some topics can be discussed more often and others less often. Because Phase 1 consists of only 10 sessions, not every topic in the manual will be covered. The counselor, in conjunction with the participant, will choose the topics most relevant for that particular session; this type of flexibility is consistent with clinical practice and was utilized successfully in administering the behavioral therapy intervention in the multi-site NIAAA COMBINE study (Combine Research Group, 2003). EMM was administered in the Fiellin et al. (2002) study with good adherence and competence (Michael Pantalon, personal communication).

8.3 Study Intervention

8.3.1 Dosing During Taper

Taper guidelines are provided in **Table 8.1** (Phase 1) and **Table 8.2** (Phase 2) for participants on stabilization doses of 8, 16, 24, and 32 mg BUP (with appropriate corresponding amounts of naloxone, i.e., 2 mg NX for each 8 mg BUP). The study medical clinician may deviate from the guidelines and individualize the taper to the extent indicated by clinical considerations (missed doses, emergent withdrawal signs, etc.) but the taper must be completed within the specified timeframe, and the dosing schedule recorded on the appropriate form.

Table 8.1 Phase 1 Dose Taper Schedule Using BUP/NX Tablets (Over 14 Days)

Taper Day	Stabilization Dose			
	32 mg	24 mg	16 mg	8 mg
1-2	32	24	16	8
3-4	24	16	12	6
5-6	16	12	10	6
7-8	12	10	8	6
9-10	8	8	8	4
11-12	6	6	6	4
13	4	4	4	2
14	2	2	2	2

Table 8.2 Phase 2 Dose Taper Schedule Using BUP/NX Tablets (Over 28 Days)

Taper Day	Stabilization Dose			
	32 mg	24 mg	16 mg	8 mg
1-3	32	24	16	8
4-6	24	16	12	6
7-9	16	12	10	6
10-12	12	10	8	6
13-15	10	8	8	4
16-18	8	6	6	4
19-21	6	4	4	4
22-24	4	4	4	2
25-27	2	2	2	2
28	2	2	2	2

8.3.2 Dispensing of Study Medication

BUP/NX will be dispensed for the first day of dosing by a medical clinician at each study site in accordance with state and federal regulations. Participants will be seen once again in Week 1 and then once weekly thereafter for dispensing of BUP/NX and clinical assessments. Take-home doses of BUP/NX will be provided to participants to self-administer at home on days between clinic visits. An additional visit may be occasionally required to adjust a participant's dose, or dispense additional medication to accommodate an increased dosage.

Participants receiving BUP/NX will be instructed to hold the tablet(s) under their tongue until the tablet(s) have completely dissolved. This may take several minutes. The tablet(s) should not be swallowed. A medical clinician will monitor dissolution of tablets at each study site. It is recommended that the participants be observed for at least 1 hour on the first day of treatment following the administration of BUP/NX.

8.3.3 Drug Packaging/Handling/Storage/Accountability

BUP/NX combination (Suboxone®) is available as a sublingual tablet in two doses: 2 mg BUP with 0.5 mg NX and 8 mg BUP with 2 mg NX. Study medication will be distributed to investigational sites in bottles of 30 sublingual tablets, and labeled with "For Experimental Use Only, Not to be Sold." The site investigator or pharmacist will be responsible for maintaining the study drug inventory and notifying NIDA (or designee) for replacement materials. Accurate recording of all BUP/NX received, dispensed, administered, returned, or destroyed will be made.

This is an open-label study. Each site will prepare individual prescriptions for each participant visit. These prescriptions will be provided in participant-numbered, child resistant packaging and clearly labeled with local regulatory requirements.

All study drug will be stored in the controlled access of the facility in compliance with local and federal regulations. Store at 25°C (77°F), with excursions permitted to 15-30°C. Unused drug supply will be returned to a NIDA-designated location at the completion of the study.

8.4 Training Procedures

Training procedures are described in the Operations Manual. EMM interventionists will be substance abuse or mental health professionals (e.g., counselors, social workers, psychologists, nurses) employed by the CTP. SMM interventionists will be licensed medical clinicians.

9.0 Concomitant Therapy

Page	Section
9-1	<i>General Considerations</i>
9-1	<i>Medications Allowed During the Trial</i>

9.1 General Considerations

A number of participants entering this trial will have pain, and many will be receiving other medications (e.g., non-steroidal anti-inflammatory drugs, gabapentin, antidepressants) and/or non-pharmacologic treatments (e.g., acupuncture, physical therapy, hypnosis) to assist them with their pain. Indeed, some participants, although medically stable, will be enrolled in pain management programs and will be referred to this study because their opioid use is out of control and the participant and his/her physician agree that discontinuing opioids would be advisable. This trial will not restrict the use of concomitant medications used by a participant's outside physician for pain management with the exception of opioids. Concomitant other treatments will be assessed at each scheduled visit and recorded.

9.2 Medications Allowed During the Trial

Prior to study initiation (induction) participants should not have taken or been administered any opioid medications or heroin for approximately 12 hours.

9.2.1 *Ancillary Detoxification Comfort Medications*

All participants will have the option to receive ancillary detoxification comfort medications during stabilization, during the taper, and beyond the taper. Study physicians should limit the duration of the prescription to the time in which a subject is enrolled in that phase of the study. Use of any medications will be recorded on a CRF. Prescribing of ancillary medications will be at the physician's discretion in accordance with clinical need to assist with the management of withdrawal symptoms but should be limited only to those medications listed below. Each participant will be instructed on the use of each medication prescribed and told they can self-administer the medication in accordance with the instructions. The use of ancillary medications will be closely monitored for the duration of the study. The following list provides the typical dose, schedule and indication for ancillary medication use:

- *For anxiety and restlessness:* hydroxyzine hydrochloride 50 mg, po q6 hrs prn; not to exceed 200 mg per 24 hrs
- *For bone pain and arthralgias:* non-steroidal anti-inflammatory agent (NSAID) such as ibuprofen (Advil, Motrin and others-use within current guidelines) 800 mg po q8 hrs with food, not to exceed 2400 mg per 24 hrs; if an NSAID is not appropriate, acetaminophen – not to exceed 3 gm/day

- *For abdominal cramps:* dicyclomine (Bentyl) 20 mg QID, increase up to 40 mg QID (usual daily maximum 160 mg)
- *For nausea:* trimethobenzamide (Tigan) 300 mg po q8 hrs prn, not to exceed 900 mg per 24 hrs. OR prochlorperazine (Compazine) 5 - 10 mg TID/QID (usually daily maximum 40 mg) OR promethazine (Phenergan) 12.5-25 mg Q4-6 hours as needed
- *For diarrhea:* loperamide (Immodium) 2 mg, 2 caps followed by 1 cap after each unformed stool; not to exceed 8 mg per 24 hrs OR Donnatal 1-2 tablets po q6-8 hrs prn; not to exceed 8 tablets/day
- *For insomnia:* trazodone hydrochloride 50 mg, 1-4 tabs, po qhs prn OR doxepin hydrochloride 50 mg, 1-3 tabs, po qhs prn OR diphenhydramine 25-50 mg, may repeat once up to 100mg, OR zolpidem tartrate (Ambien) 10 mg, 1-2 tabs, po qhs prn OR ramelteon (Rozerem) One 8 mg tablet 30 minutes prior to bedtime

10.0 Study Assessments

Page	Section
10-2	<i>Study Timetable</i>
10-3	<i>Protocol Specific Assessments</i>
10-7	<i>Common Assessment Battery (CAB)</i>

10.1 Study Timetable

Table 10.1 Study Timetable
(Weekly Details Found in Visit Schedules – Tables 4.1 & 4.2)

Activity	Duration (Avg. min.)	Screening/ Baseline		Phase 1 SMM	Phase 1 EMM		Phase 2 SMM	Phase 2 EMM		
Screening Assessments	Where Applicable		R A N D O M I Z A T I O N			R A N D O M I Z A T I O N				
Informed Consent	25	X								
Inclusion/Exclusion		X								
Randomization					X		X		X	X
Demographics	5	X								
CIDI/Substance Use Diagnosis	40	X								
Concomitant Treatment (including medications and psychosocial)	8	X			X		X		X	X
Safety Assessments										
Medical & Psychiatric Evaluation	45	X								
Vital Signs	5	X			X		X		X	X
Lab Tests (Chemistry, Hematology, Urinalysis, LFTs)	10	X			X		X		X	X
Pregnancy Test	See Labs	X			X		X		X	X
Adverse Events	5				X		X		X	X
Serious Adverse Event					As needed		As needed		As needed	As needed
COWS	5	X			X		X		X	X
Efficacy Assessments										
Substance Use Report – Baseline	15	X			X		X		X	X
Substance Use Report – Follow-up	5									
VAS-Craving	1	X			X		X		X	X
Urine Drug Screen	See Labs	X			X		X		X	X
Pain Assessments										
Brief Pain Inventory	5	X			X		X		X	X
Beck Depression Inventory II	10	X			X		X		X	X
Pain & Opioid Analgesic Use History	10	X		X	X		X	X		
SF-36	10	X		X	X		X	X		
Other Assessments										
CIDI/Depression-PTSD Diagnosis	30	X								
Fagerstrom Test	2	X		X	X		X	X		
Locator Form	5	X		X	X		X	X		
ASI Lite	35	X		X	X		X	X		
Risk Behavior Survey	5	X								
Treatment										
BUP/NX Induction Visit	60			X	X		X	X		
SMM session (including BUP/NX dosing)	15-20			X	X		X	X		
EMM session	45				X			X		

10.2 Protocol Specific Assessments

10.2.1 Laboratory Tests (e.g., Pregnancy Test, Liver Profile)

- *Pregnancy Testing:* Female participants of child-bearing potential will be required to have a negative pregnancy test (urine hCG,) prior to induction, and monthly thereafter while receiving BUP/NX. Buprenorphine is a Pregnancy Category C Drug. Female participants of childbearing potential will also be expected to practice acceptable birth control. Women who become pregnant will be withdrawn from the study, tapered off BUP/NX, and referred for opioid replacement therapy at the CTP or to another local treatment provider.
- *Blood Chemistries and Liver Function Tests:* Blood will be collected in appropriate vacutainer tubes, and handled according to standard procedures. Quantitative analysis will be performed for a standard chemistry and liver function profile. The following analytes will be recorded on the appropriate case report form: sodium, potassium, chloride, bicarbonate, glucose, creatinine, albumin, total protein, calcium, cholesterol, triglycerides, phosphorous, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, alkaline phosphatase (ALP), and blood urea nitrogen (BUN). Subjects with LFTs > 5X upper limit of normal range at screening will be ineligible for the study.
- *Hematology:* Blood will be collected in appropriate vacutainer tubes, and handled according to standard procedures. Quantitative analysis will be performed for a standard hematology profile. The following analytes will be recorded on the appropriate case report form: hemoglobin (Hgb), hematocrit (Hct), RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets.
- *Urinalysis:* Urine will be collected and analyzed for a standard urinalysis profile. The following results will be recorded on the appropriate case report form: specific gravity, pH, color, appearance, glucose, bilirubin, ketones, occult blood, protein, nitrite, leukocyte esterase.
- *Urine drug screen:* Urine will be collected, analyzed, and recorded on the appropriate CRF for the following analytes: oxycodone, benzodiazepines, THC, methadone, cocaine, amphetamine, methamphetamine, propoxyphene, and the Opiate 300 group analytes (morphine, heroin, and codeine).

10.2.2 Clinical Assessments (e.g. Medical History and Physical Exam)

The study medical clinician (or other qualified medical study staff) will complete a physical examination to help determine eligibility. The physical exam will also ensure that there are no medical concerns regarding participation and to gather baseline information about the participant's health. The physical examination will be repeated at the end of the study (last study visit). Pertinent laboratory tests (LFTs, CBC, chemistry) will be reviewed at the visits specified in Table 4.1 on page 4-5 and Table 4.2 on page 4-6. See the *Operations Manual* for guidance on laboratory value parameters. Participants with abnormal laboratory values will be notified and counseled to seek medical evaluation and care.

For participants receiving opioids for chronic pain, the study medical clinician will consult with the participant's prescribing physician to ensure that the participant is appropriate to participate in this protocol; e.g., that the participant's pain is not due to an underlying malignancy or that further diagnostic testing is not needed to determine the source of the pain.

10.2.3 Efficacy Assessments

10.2.3.1 Urine Drug Testing

Urine samples will be collected and analyzed for drugs of abuse prior to dispensing medication. All urine specimens will be analyzed by staff using drug test cups with temperature-controlled monitoring. These cups will be provided by a central supplier to all study sites. OxyImmunoassay and drug screen cards will be used to identify the following substances: oxycodone, benzodiazepines, THC, methadone, cocaine, amphetamine, methamphetamine, propoxyphene, and the Opiate 300 group analytes (morphine, heroin, and codeine). Other drugs may be detected by these analytes at high concentrations. For example, hydrocodone may be detected under the oxycodone test at high concentration levels. The cards will be provided to all study sites from a central supplier.

Urine will be collected at baseline just prior to BUP/NX induction, at each of the weekly visits thereafter, and at each follow-up visit. Urine screens for BUP will be available at Weeks 10 and 12 in Phase 1 and Weeks 22 and 24 in Phase 2. The urine screens for BUP will be used to monitor whether participants defined as "successes" at the end of Phase 1 and "substantially improved" at the end of Phase 2 (in both instances, when they are supposed to be off buprenorphine) are, in fact, taking buprenorphine that they have obtained outside the study.

The results will be recorded on the appropriate CRF.

10.2.3.2 Substance Use Report

Drug use data will be collected in conjunction with weekly medical management visits. A calendar technique similar to the Timeline Followback will be used to fill in each day since the last visit, which helps to fill in missing data in case of missed visits. Baseline data collection will review past 30 days of substance use. The use of opioids, other drugs of abuse, and alcohol will be recorded. A urine drug screen will be performed at each of these visits as well.

10.2.3.3 Clinical Opiate Withdrawal Scale (COWS)

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

10.2.3.4 Visual Analog Scales (VAS)

Five visual analog scales will be completed at each clinic visit during treatment to assess craving for opiates. The VAS will also be collected at all follow-up visits in Phase 1 and at the Week 20 and Week 24 follow-up visits in Phase 2.

10.2.4 Safety Assessments

Safety assessments will consist of physical examination, vital signs, laboratory tests, pregnancy tests, adverse event reporting, and concomitant medications use.

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

Serious adverse events (SAEs) are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs hospitalization, any congenital anomaly, or any event that required intervention to prevent one of the above outcomes. This category includes any event that a study investigator or the DSMB judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution. For the purposes of this study, admission to a hospital or free-standing residential facility for the treatment of drug dependence (e.g., detoxification or rehabilitation) is not defined as an SAE, but the event will be recorded on the concomitant treatment CRF.

An **unexpected event** is one that is not described with respect to nature, severity or frequency in the current Investigator Brochure, or is standard symptomatology for opioid withdrawal.

10.2.5 Pain and Other Assessments

10.2.5.1 Brief Pain Inventory

The Brief Pain Inventory-SF (BPI; Cleeland & Ryan, 1994) is a 9-item assessment of intensity of pain and interference of pain in life. Originally developed for cancer pain, it is widely used to assess nonmalignant acute and chronic pain (Tan, Jensen, Thornby & Shanti, 2004).

The complete BPI-SF will be collected at baseline and monthly during Phase 1 and Phase 2. For patients identified at baseline and stratified as chronic pain patients, four BPI-SF items will be asked weekly throughout treatment as part of their medical visit for the purpose of monitoring any potential changes in physical pain. In addition to verbal patient report of pain, these items will permit study clinicians to monitor for any clinical deterioration in pain status that may require follow-up and/or referral.

10.2.5.2 Beck Depression Inventory II

This 21-item scale (Beck et al., 1961) assesses common features of depression on a 4-point severity scale, with a focus on cognitions. It is widely used in both drug and psychosocial treatment studies of depression, and is commonly used in studies of pain (Dworkin et al., 2005). The BDI has also been

found in two studies (Rounsaville et al., 1979; Weiss et al., 1989) to be reliable in substance dependent patients. The BDI will be collected at baseline and monthly during Phase 1 and Phase 2.

10.2.5.3 Pain and Opioid Analgesics Use History

Information will be collected at the Phase 1 baseline visit to determine a variety of **pain-associated issues** (body region(s) affected by pain, participant description of pain diagnosis, duration of pain, number of days in past 30 days and past 6 months with pain, past history of pain if not currently experiencing pain; pain treatment history) and **opioid analgesics use issues** [initial reason for initiating opiate use (e.g. pain relief versus illicit use), current and past sources of opiate analgesics, current and past types of opioid analgesics].

10.2.5.4 CIDI Section E and Section K

Questions from Section E (Major Depressive Disorders) and Section K (PTSD) of the Composite International Diagnostic Interview (CIDI) (<http://www.crufad.unsw.edu.au/cidi/cidi.htm>; CIDI) will be administered during baseline by a trained and certified study staff member.

The results will be used to characterize the prescription opioid dependent population consistent with the exploratory research question of whether these disorders moderate the effect of treatment on outcome.

10.2.5.5 SF-36

The SF-36 version 2 is a 36-item, participant administered instrument examining health-related quality of life changes as a function of treatment (Ware and Sherbourne, 1992). Most items are rated on a 5-point scale. The SF-36 v. 2 will be completed at Phase 1 and Phase 2 baseline, and at the end of Phase 1 and Phase 2.

10.2.5.6 Fagerstrom Test for Nicotine Dependence

The Fagerstrom Test for Nicotine Dependence is a widely used assessment procedure for determining the level of nicotine dependence. The Fagerstrom will be completed at baseline and final follow-up visit.

10.2.5.7 Locator Information

Basic locator data will be collected and kept confidential in the participant's record. Locator information typically includes contact information such as residential street address, or an address of someone who knows where to contact the participant if they are homeless, and a phone number where they can be reached. Additional information includes the names and addresses of two or three individuals who would likely know their whereabouts, particularly relatives or close friends. This information will be obtained at baseline and will be updated as necessary. This information will be used to facilitate contact with the participant during the study and at follow-up.

10.2.6 Treatment Compliance

Medication compliance will be measured using pill counts done at the weekly SMM visits. Treatment participation will be measured using an SMM and EMM session CRF.

Participation in medical and psychosocial treatment and self-help outside of the study will be captured on a concomitant treatment CRF.

10.2.7 Process Measures

The DSMB Plan and protocol will not define a minimally effective dose for psychosocial treatments, as this amount is not known. However, the study executive group will monitor session attendance to identify study sites and clinicians with particularly low attendance rates, and implement a corrective action plan, as discussed in the Data and Safety Monitoring Plan.

10.2.7.1 Projected Timetable for Assessments

Please refer to Table 4.1 on page 4-5 and Table 4.2 on page 4-6 for Phase 1 and Phase 2 visit schedules.

10.3 Common Assessment Battery (CAB)

10.3.1 Brief Demographics Form

Basic demographic information assessing for age, ethnicity/race, and gender will be collected at baseline.

10.3.2 Addiction Severity Index (ASI) - Lite

The ASI Lite is a standardized, multidimensional, semi-structured, comprehensive clinical interview that provides clinical information necessary to formulate treatment plans as well as problem severity profiles in 6 domains commonly affected in substance abusers (McLellan et al., 1985). The domains include chemical abuse (alcohol and drug), medical, psychiatric, legal, family/social and employment/support. Composite Scores for each problem domain are derived mathematically and used as change measures or outcome indicators as a function of treatment intervention. The ASI Lite also provides clinically useful information on whether the participant is at imminent risk for suicidality, thus permitting evaluators to implement any needed immediate and/or early intervention strategies. A revised version of the ASI 5th Edition, 1997 version (ASI Lite) that includes only those questions used to derive the composite scores along with some demographic information will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. Composite scores will be calculated according to the methods described by McGahan et al., (1982), and Carroll et al., (1994). The ASI Lite will be administered at Phase 1 baseline. The ASI Lite Follow-up Assessment will be administered in Phase 1 at Week 12, and in Phase 2 at baseline as well as Week 24.

10.3.3 Risk Behavior Survey

This is a brief, 12-item (with multiple sub-items) interviewer-administered assessment of HIV risk behaviors including intravenous drug use and sexual risks. This survey will be utilized to assess degree of HIV-infection risk by looking at risk behavior. Measures will include extent and methods of past drug use, sexual preference, sexual history, and extent of unprotected sex; and assessment of travel to international locations of increased-HIV infection rates. This measure takes approximately 15 minutes to administer and will be collected at baseline.

10.3.4 Composite International Diagnostic Interview (CIDI)

The CIDI is a comprehensive, standardized instrument for assessment of mental disorders according to the definitions and criteria of ICD-10 and DSM-IV. It has been developed by the World Health Organization in consultation with numerous experts, and tested in many countries. As part of the CAB assessments, CIDI Section J (Alcohol Use Disorders) and Section L (Substance-related Disorders) will be used to assess addiction for baseline characterization and exclusion criteria purposes. Training on the proper use of the CIDI and its material will be provided to the CTP interviewer staff.

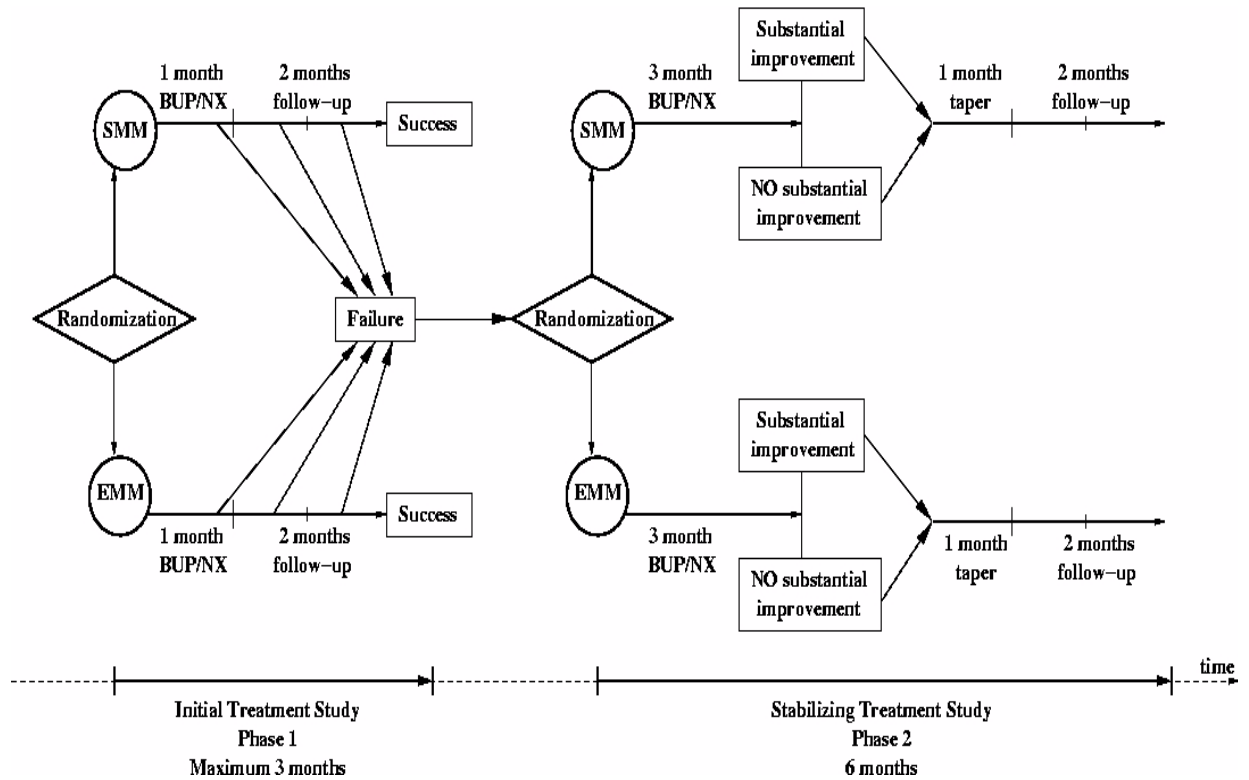
11.0 Statistical Analysis

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11-5	<i>Phase 1: Initial Treatment Study</i>
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11-14	<i>Rationale for Sample Size and Statistical Power</i>

11.1 Overview of Study Design

The study will have two phases (see Figure 11.1 below). **Phase 1** is an initial treatment study for subjects meeting DSM-IV criteria for opioid analgesic dependence who do not require ongoing opioid treatment for pain. Initial treatment consists of BUP/NX for one month plus a random assignment to SMM or EMM. Participants are followed for two more months and treatment failure is assessed continuously. Phase 1 treatment failures are eligible for treatment in Phase 2. **Phase 2** is a stabilization treatment study for failures to initial treatment. Stabilization treatment consists of BUP/NX for three months plus a random assignment to SMM or EMM. The three months of treatment are followed by one month of taper and two months of follow up.

Figure 11.1 CTN-0030 Detailed Study Schema



11.2 General Analytic Strategy

11.2.1 Significance Testing

All hypotheses will be tested by two-sided tests with level of significance $\alpha=0.05$. All exploratory analyses will be reported as such and will be thoroughly described in any publication. In particular, the modeling strategy for identification of predictors of outcome (such as inclusion of multiple covariates and interactions) will be explained in detail to allow adequate assessment of the strength of inferences based on data-driven statistical models.

11.2.2 Preliminary Analysis

Prior to the analysis of the primary hypothesis, the distributions of the outcome measures will be examined and possible outliers identified. Outliers will be thoroughly checked for collection or entry errors and will not be used in the analysis unless confirmed as correct and valid data. The final decision to include in the analysis outliers remaining (after data cleaning) will be based on discussion with the Lead Investigator (who will be blind to treatment assignment) and will depend on the individual outlying values.

11.2.3 Intent to Treat (ITT) and Completer Samples

The primary analyses will be on the ITT samples; i.e., on all participants randomized in Phase 1 and all randomized subjects in Phase 2.

11.2.4 Missing Data and Dropouts

Every possible effort will be made to assess all patients in both Phase 1 and Phase 2. Despite our thorough and proactive approach to taking complete measurements on all randomized study patients at all time points, it is expected that there will be cases when assessments will be incomplete or missing.

Accounting for dropout in the analysis. The primary qualitative outcome measures, success/failure in Phase 1 and substantial improvement (yes/no) in Phase 2 will be determined for all study patients, regardless of whether they completed the treatment in these phases or not (see *Treatment Success/Failure for Dropout and Missing Data* on page 11-7 and *Substantial Improvement Status for Dropout and Missing data* on page 11-10). The analysis of the quantitative outcomes, measuring severity of symptoms and positive/negative weekly urines will be based on generalized linear models and Generalized Estimating Equations (GEE) models [Diggle, PJ, Liang K-Y, and Zeger, SL (1994) *Analysis of Longitudinal Data*, Oxford University Press, Oxford]. The GEE methodology requires no parametric distribution assumption, provides robust inference with respect to misspecification of the covariance, and allows analysis of continuous, categorical, and count data which may be missing for some patients either because of a missed week or due to drop-out. Thus, complete information for all patients is not needed. PROC GENMOD in SAS (2003) will be used to carry out these analyses.

The inferences from incomplete or missing data are valid provided that the missing data are missing at random (Little and Rubin, 1987). “Missing at random” means that the missing mechanism does not depend on the value of the unobserved outcome. Unfortunately, this assumption is untestable in most medical research, as in this study.

Sensitivity analyses will be used to address the impact of missingness on conclusions. One approach to this problem is to assume a model for the missingness mechanism that does depend on the unobserved outcome value and to do the analysis (i.e., estimate the treatment effect) incorporating the assumed model for the missingness. There are parametric and semi-parametric methods for doing so (Diggle and Kenward, 1994; Kenward 1998; Rotnitzky et al., 1998; Scharfstein et al., 1999; Lu et al., 1999). Comparison of the inferences from assuming various models for the missingness provide a measure of the validity of the efficacy estimate from the model that assumes missing “at random.” Another approach to sensitivity analysis is based on computation of a local sensitivity index, which measures the change in the estimated treatment effect in a neighborhood of the “missing at random” model for missingness (Ma and Heitman, 2005; Liu and Liang, 1997).

In the analysis of the secondary outcome measure status (positive/negative) of weekly urines over time, when urines are missing but a piece of “hard” data is available that the participant has used drugs, a positive urine status will be imputed. Examples of “hard” data indicating use include self-report of use or knowing that the participant entered an opiate treatment program or an inpatient detoxification program.

11.2.5 Demographic and Baseline Characteristics

The number of patients enrolled into the study (both Phase 1 and Phase 2) will be summarized by CTP sites and overall. Treatment groups will be described in terms of demographics and baseline diagnostic and clinical characteristics. The description of categorical and ordinal variables will be in terms of proportions; the description of continuous variables will be in terms of means and standard deviations, medians, quartiles, and minimum and maximum values. Variables found to be different between the groups at baseline will NOT be automatically included in the analyses; the effect of such imbalance on the inferences about the study hypotheses will be assessed only as an exploratory analysis.

To assess the prognostic power and potentially differential effect of gender and ethnicity on treatment outcome, the hypotheses and all exploratory questions will be repeated adjusting for these factors, including both main effects and interactions (with treatment) terms.

11.2.6 Adjusting for Covariates

There are no known factors that affect treatment outcome both in Phase 1 and Phase 2. Therefore the primary analysis of the study hypotheses will be performed without adjusting for any covariates. Secondary analysis will be performed adjusting for the a priori identified covariates. Adjusting for factors found to differ between treatment groups at randomization is a data-driven analysis and will be considered exploratory.

11.2.7 Modeling of Site Effects

The outcomes of subjects from the same site are expected to be correlated. To account for these correlations in the analysis, all tests will be based on Generalized Estimating Equations (GEE) models [Diggle, PJ, Liang K-Y, and Zeger, SL (1994) Analysis of Longitudinal Data, Oxford University Press, Oxford]. GEE approach allows modeling of correlated data that is not necessarily normal, such as the primary outcomes for both Phase 1 and Phase 2. This method is generally robust with respect to misspecification of the correlation structure of the outcome in the sense that it produces unbiased estimates of the parameters in the model for the mean.

The goal of this study is to estimate an overall effect of EMM vs. SMM, rather than to study efficacy in individual sites. There is no evidence that the relative efficacy will differ between sites or that overall efficacy of EMM and SMM will be different in different sites, either for Phase 1 or for Phase 2 study. Therefore, main effects for sites and interaction between sites and treatment will be investigated only as an exploratory analysis.

The GEE approach also allows specification of more than one clustering factor. In this study, in addition to site, repeated measurements over time would constitute another clustering factor. GEE will be used to account for the correlation due to repeated measurements over time and the correlation due to correlation within site.

11.3 Phase 1: Initial Treatment Study

11.3.1 Overview

Phase 1 is an initial treatment study for subjects meeting DSM-IV criteria for opioid analgesic dependence who do not require an ongoing opioid treatment for pain. Initial treatment consists of BUP/NX for one month plus a random assignment to SMM or EMM. Participants are followed for two more months and treatment failure is assessed continuously. Phase 1 treatment failures are immediately eligible for treatment in Phase 2, although they can elect to remain in Phase 1 through Week 12 follow-up and can transition to Phase 2 at any time up until the conclusion of Phase 1. The maximum duration of patients in Phase 1 is three months but can be as short as one week.

11.3.2 Outcome Measures and Predictors of Response

11.3.2.1 Primary Outcome Measures

The primary outcome measure is the status of treatment: success or failure. Definition of failure/success: A participant is a *Phase 1 success* if all of the following four criteria are satisfied from Week 3 to the end of Phase 1 (Week 12):

1. Use of opioids on four or fewer days per month (beginning after the end of Week 2) as evidenced by self-report.
2. Urine screen for opioids are never positive on two consecutive weeks (beginning after the end of Week 2).
3. Completion of the 4-week medication regimen and 8-week follow-up period (including Week 6 and Week 8 SMM or EMM booster visits) without participating in other formal substance abuse treatment (e.g., methadone maintenance, drug counseling, etc. Self-help groups such as Narcotics Anonymous and treatment for other issues such as medical or psychiatric problems do not count here).
4. Absence of needle use.
5. Absence of no more than one urine sample after Week 2.

A subject who fails one or more of these four criteria at any time from Week 2 to Week 12 is considered a *Phase 1 failure* and is given the option to make the transition immediately to Phase 2. Failures can elect to remain in Phase 1 through Week 12 follow-up and can make the transition to Phase 2 at any time up until the conclusion of Phase 1.

11.3.2.2 Secondary Outcome Measures

Efficacy of initial treatment will also be assessed with respect to the following domains:

- Craving scores – assessed by Visual Analog Scales (VAS)
- Pain – only for patients who meet criteria for chronic pain at baseline

- Pain intensity as assessed by the Brief Pain Inventory (BPI)
- Functional limitations due to pain as assessed by BPI
- Depression, assessed by the Beck Depression Inventory (BDI)
- “Quality of Life” as assessed by the SF-36.

11.3.2.3 Covariates and Predictors of Outcome

- Demographics-- age, gender, ethnicity
- Clinical characteristics:
 - pain status (no chronic pain, current chronic pain)
 - whether opioids were first used for pain treatment
 - withdrawal - assessed by Clinical Opiate Withdrawal Scale (COWS)
 - Brief Pain Inventory score at baseline
 - baseline Beck Depression Inventory score
 - prior heroin use - assessed by self-report at the baseline (Yes/no)
 - presence/absence of major depressive disorder or PTSD
 - family history of substance use disorder
 - current presence/absence of other substance use disorder in the patient

11.3.3 Statistical Considerations

11.3.3.1 Randomization

The randomization for Phase 1 will be within site and will be stratified with respect to two factors: 1) whether or not the patient has ever used heroin, and 2) whether or not the patient currently has chronic pain. Presence of ‘chronic pain’ will be operationalized by a ‘yes’ answer to the first question of the Brief Pain Inventory (whether you have pain beyond usual aches and pains) AND a duration of pain of at least three months.

11.3.3.2 Sample size

Approximately 648 subjects will enter Phase 1. Starting after the second week, they will be monitored for meeting the treatment failure criteria (see *Primary Outcome Measures* on page 11-5) (needle use would indicate failure prior to Week 2). At any time of meeting failure criteria, participants will be given the option to transition from Phase 1 to Phase 2. However, failures can elect to remain in Phase 1 through Week 12 follow-up and can transition to Phase 2 at any time up until the conclusion of Phase

1. Approximately 20% (average over EMM and SMM) are expected to be treatment successes, and about 30% are expected to drop out or refuse entry into Phase 2.

11.3.3.3 Treatment Success/Failure for Dropout and Missing Data

Dropouts in Phase 1 will be defined as the patients who voluntarily discontinue the study prior to Week 12. Subjects who discontinue the study before Week 12 will be considered treatment failures (these subjects will be eligible for Phase 2). For the patients who miss an assessment visit the self-report drug use will be obtained retrospectively; urines will not be obtained. If the patient has all data except the urines, and satisfies the criteria for success then s/he is a success, unless two or more urines are missing.

11.3.4 Hypotheses Testing

Primary Hypothesis 1.1. There will be a higher rate of treatment success among subjects receiving EMM than among patients receiving BUP/NX and SMM alone.

The following model will be used to test this hypothesis:

(1)

$$(2) \quad \text{logit}(Y_{ij}) = \beta_0 + \beta_1 \text{txt}_{ij} ,$$

where Y_{ij} is a dichotomous measure indicating whether the j^{th} patient of the i^{th} site meets the Phase 1 criteria for success or not, with $Y_{ij}=1$ for success and $Y_{ij}=0$ for failure; txt_{ij} is an indicator variable for treatments, with $\text{txt}_{ij}=1$ for EMM group and $\text{txt}_{ij}=0$ for SMM group. The model parameters will be estimated by GEE (see *Modeling of Site Effects* on page 11-4). Testing the hypothesis is equivalent to testing for significance of \hat{a}_1 .

The success rates for EMM and SMM as well as the overall success rate will be estimated with point estimate and 95% confidence intervals.

11.3.4.1 Exploratory Analyses

The following topics will be addressed in the exploratory analysis:

1. Issues related to pain:
 - a. The prevalence and characteristics of chronic pain among individuals presenting for treatment of prescription opioid dependence.
 - b. The role of pain in the addiction and treatment outcome for the study population.
 - c. The effect of treatment on pain.
2. The prevalence of various clinical characteristics of use and dependence in the study population and their role on the outcome of the standard treatment in Phase 1. In addition to pain, clinical

characteristics of interest include: use of heroin, presence of other substance use disorders, PTSD, and major depressive disorder.

3. Effect of craving and withdrawal symptoms:
 - a. Association between craving and withdrawal symptoms at baseline of Phase 1 and the primary outcome (treatment success/failure)
 - b. Effect of craving and withdrawal symptoms on time to failure
 - c. Effect of treatment on craving and withdrawal symptoms
4. The effect of treatment on quality of life measures.
5. The association between specific demographic characteristics and treatment outcome. The demographic characteristics of potential importance include: age, gender, and ethnicity.
6. The potential interaction effect of clinical and demographic characteristics on treatment outcome will also be assessed.
7. Site effect on treatment outcome, including potential interaction between treatment and site (11 d.f. test).
8. Compare time to failure in EMM and SMM.
9. Prevalence of each of the four criteria for treatment success (see *Primary Outcome Measures* on page 11-5) that were failed by treatment failures.
10. Patterns of drug use during Phase 1 among treatment failures.

11.4 Phase 2: Stabilization Treatment Study

11.4.1 Overview

Phase 2 is a stabilization treatment study for failures to initial treatment (Phase 1). Stabilization treatment consists of BUP/NX for three months plus a random assignment to SMM or EMM. The three months of treatment are followed by one month of taper and two months of follow up. The total duration of Phase 2 is six months. The primary endpoint is the end of the three months of treatment.

11.4.2 Outcome Measures and Predictors of Response

11.4.2.1 Primary Outcomes

The primary outcome measure in Phase 2 is substantial improvement at the end of the three months of treatment (yes/no). A patient has *substantial improvement* at three months if she/he is abstaining from opioids during the last week AND for at least two of the previous three weeks of the third month of BUP/NX treatment. Abstinence is determined by self-reports of opioid abstinence (missing urines will be considered positive for opioids).

11.4.2.2 Secondary Outcomes

Treatment efficacy will be assessed with respect to the following additional outcome measures:

- Substantial improvement at six months: A patient has substantial improvement at six months if she/he is abstinent from opioids during the last week AND for at least two of the previous three weeks of the third month of BUP/NX treatment. Abstinence is determined by self-reports of opioid abstinence (missing urines will be considered positive for opioids).
- Positive/negative (for opioids) status of urines over time in Phase 2
- Craving self-report – assessed by Visual Analog Scales (VAS)
- Pain – only for patients who meet criteria for chronic pain at baseline:
 - Pain intensity as assessed by the Brief Pain Inventory
 - Functional limitations due to pain as assessed by BPI
 - Depression, assessed by the Beck Depression Inventory
- “Quality of Life” as assessed by the SF-36

11.4.2.3 Covariates/Predictors of Response

- Demographics-- age, gender, ethnicity
- Clinical characteristics (at time of entry in Phase 2):
 - pain status (no pain, current pain)
 - whether opioids were first used for pain treatment
 - BPI score – only for those patients with current pain
 - prior heroin use---assessed by self-report at baseline (yes/no)
 - presence/absence of major depressive disorder or PTSD
 - family history of substance use disorder
 - current presence/absence of other substance use disorder in the patient
- Characteristics of treatment and outcome in Phase 1:
 - Treatment assignment in Phase 1
 - Time to failure in Phase 1
 - Reason for failure in Phase 1 (criteria 1-4 in *Primary Outcome Measures* on page 11-5)

- Patterns of drug use in Phase 1

11.4.3 Statistical considerations

11.4.3.1 Randomization

The randomization to SMM vs. EMM will be within site and will be stratified by whether patients received SMM or EMM in Phase 1. Block randomization will be employed.

11.4.3.2 Sample size

A total of 324 subjects will be randomized in Phase 2. Participants in Phase 2 are Phase 1 treatment failures. About 50% of patients enrolled in Phase 1 are expected to be eligible, willing, and to actually enroll in Phase 2. The treatment dropout rate in Phase 2 is expected to be lower than that in Phase 1, since participants in Phase 2 have had experience with the study and have agreed to continue, and because dropout from a stabilization dose of BUP/NX is typically lower than that from a tapering dose. In Phase 2 a rate of about 5% treatment dropout per month is expected, resulting in 15% treatment dropout during the three months of treatment and total of 30% treatment dropout for the entire study (10% treatment dropout per month is expected in Phase 1, or about 30% during the three months of Phase 1).

11.4.3.3 Substantial Improvement Status for Dropout and Missing data

If a patient fails to provide a urine sample on the last week of the 12-week treatment period OR fails to provide data on two or more of the preceding three weeks, he/she will be considered NOT substantially improved (even if he/she provided negative urines on all other assessment occasions).

Definition of substantial improvement when patient discontinues the study prior to Week 12 in Phase 2. The substantial improvement status for patients who complete all 12 weeks of treatment in Phase 2 will be determined based on whether they satisfy the criteria. For patients who discontinue the study before Week 12 (due to non-compliance, being less than minimally improved after the early treatment, or dropouts) will be considered as NOT substantially improved. (Alternative definitions of substantial improvement status of dropouts will be considered to assess the sensitivity of the inferences about treatment efficacy.)

11.4.4 Hypotheses Testing

11.4.4.1 Primary Hypotheses

Hypothesis 2.1: Among Phase 1 treatment failures on stabilizing BUP/NX treatment, those who received EMM will have higher substantial improvement rate than those who received SMM.

The following model will be used to test this hypothesis:

(1)

$$(2) \quad \text{logit}(Y_{ij}) = \beta_0 + \beta_1 \text{txt}_{ij}$$

Here Y_{ij} is a dichotomous measure indicating whether the j^{th} patient of the i^{th} site meets the criteria for Phase 2 ‘continuous substantial improvement’ or not, with $Y_{ij}=1$ for substantial improvement and $Y_{ij}=0$ for no substantial improvement; txt_{ij} is an indicator variable for treatments, with $\text{txt}_{ij}=1$ for EMM group and $\text{txt}_{ij}=0$ for SMM group. The model parameters will be estimated by GEE (see 13.2.7). Testing this hypothesis is equivalent to testing for significance of \hat{a}_1 .

11.4.4.2 Secondary Hypotheses

Hypothesis 2.2: During the 3 months of treatment, the decrease of probability for positive weekly urines will be faster in the EMM group than in the SMM group.

The course of opiate-free urines over the 12 weeks of the acute treatment will be studied using model (1) below.

(1)

$$(2) \quad \text{logit}(Y_{ijt}) = \beta_0 + \beta_1 \text{txt}_{ij} + \beta_2 t + \beta_{12} t * \text{txt}_{ij}$$

Here Y_{ijt} is a dichotomous measure indicating whether the urine of j^{th} patient in the i^{th} site at time t is opiate-free, with $Y_{ijt}=1$ for opiate-free and $Y_{ijt}=0$ for opiate, t is as in model (1) and t is time, $t=1,2,\dots,12$. Testing the hypothesis is equivalent to testing for significance of \hat{a}_{12} . Presence of a significant interaction between time and treatment would indicate that the reduction of the proportion of opiate positive urines is different for the patients who received the BUP/NX plus EMM than for those in BUP/NX plus SMM group during the active treatment period. If the interaction term is not significant, a model with no interaction term between treatment and time will be fit. In this case, inference about Hypothesis 2.2 will be based on the model with main effects only and testing Hypothesis 2.2 will be equivalent to testing for significance of $\hat{a}_1 = 0$. The presence of a significant treatment effect indicates that EMM group has on average a higher proportion of patients providing opiate-free urines during the treatment period than does the SMM group. GEE will be used to fit this model.

Hypothesis 2.3: EMM will be more effective than SMM with respect to substantial improvement at the end of the follow up period (i.e., at six months post-randomization in Phase 2).

This hypothesis will be tested along the lines of testing the primary Hypothesis 2.1 using model (1).

As a part of this secondary hypothesis, the change in substantial improvement rates during the follow up will be estimated separately for each of the two treatment conditions and overall. The rates will be estimated with point estimates and 95% confidence intervals. Testing will be based on

(1)

$$(2) \quad \text{logit}(Y_{ijt}) = \beta_0 + \beta_1 \text{txt}_{ij} + \beta_2 t + \beta_{12} t * \text{txt}_{ij},$$

where Y_{ijt} is a dichotomous measure indicating whether the j^{th} patient in the i^{th} site at time t meets criteria for substantial improvement, with $Y_{ijt}=1$ for substantial improvement and $Y_{ijt}=0$ for not

substantial improvement, t_{rt} is as in model (2), and t is time, $t=3$ or 6 months post randomization. Testing the hypothesis is equivalent to testing $\hat{a}_{12} = 0$ vs. $\hat{a}_{12} \neq 0$. The presence of a significant interaction between time and treatment would indicate that the effect of EMM versus SMM is different at three months post randomization versus at 6 months post randomization. The hypothesis that overall, the percentage of patients who are substantially improved is the same at three months post-randomization versus at 6 months randomization is a hypothesis about \hat{a}_2 . The model parameters will be estimated and tested by GEE approach.

11.4.5 Exploratory Analysis

This study provides the opportunity to explore important research questions. The quality of evidence from these analyses will be considered inferior to the evidence that results from the analysis of primary and secondary objectives. The following issues will be investigated:

1. The effect of treatment on pain and the relationship between pain and treatment efficacy.
 - a. The relative efficacy of EMM vs. SMM depending the patient's pain status at baseline (interaction between chronic pain and treatment) will be studied. If the relative efficacy does not depend on baseline chronic pain (lack of significant interaction effect), whether pain during the treatment period affects the efficacy of the treatments will be investigated (test for main effect of pain in a model with main effects only). Appropriate logistic regression models using GEE to account for within site correlation will be used. The probabilities for substantial improvement at three and six months will be modeled as functions of treatment, pain status, and their interaction. A significant interaction effect would indicate that the relative efficacy of EMM vs. SMM depends on pain status. If the interaction effect is not statistically significant at level $\alpha=0.05$, a model with main effects of pain and treatment will be fit and the effect of pain will be estimated from this model.
 - b. For patients with chronic pain at baseline, the course of pain during the three months of treatment and during the follow up will be studied. This will be done using an approach similar to a) above and shown by Model 1.
2. A history of any heroin use: whether the history of any heroin use moderates the effect of treatment on the rate of substantial improvement will be studied.
3. The reason for addiction to prescription opioids: how the patient became addicted to prescription opioids will be explored; whether through illicit use unrelated to pain or due to an initial legitimate prescription to pain. Whether this factor moderates the effect of EMM on substantial improvement will be examined.
4. Coexisting psychiatric illness: Whether a history of PTSD or major depressive disorder, both common in this population, moderate the effect of treatment on the rate of substantial improvement will be studied.
5. Craving during treatment and its relationship to treatment outcome.
 - a. Effect of treatment on craving: The weekly craving measures will be studied to assess whether the two treatments affect the course of craving symptoms differently. The following model will be used:

(1)

$$(2) E(Y_{ijt}) = \beta_0 + \beta_1 txt_{ij} + \beta_2 t + \beta_{12} t^* txt_{ij} + \beta_{2t} I_{ij}^s + \beta_{12} I_{ij}^s txt_{ij} ,$$

where Y_{ijt} is mean craving scores, measured by VAS, of j^{th} patient in the i^{th} site at time t , ($t=1$ to 12). Testing the hypothesis is equivalent to testing for significance of \hat{a}_{12} . The presence of a significant interaction of treatment and time would indicate that the decrease of self-reported craving will be faster in the EMM groups than in the SMM group. If the interaction term is not significant, the significance of \hat{a}_1 from a model with main effects only will be tested. The presence of a significant treatment effect would indicate that the EMM group has different mean self-report craving scores than the SMM group during the treatment phase. The GEE approach with identical link function will be used to fit this hypothesis.

In addition, the efficacy of the BUP/NX with EMM on the mean craving scores during the follow up period using a similar model will be explored.

- b. Effect of craving on treatment outcome: The effect of craving on outcome will be studied by modeling the probability for substantial improvement as a function of treatment, and a measure representing the course of craving during treatment, and their interaction. As measures of craving during treatment, the average craving over the 12 weeks of treatment and the average craving in the last month of treatment or the patient's craving slope from model (1) above will be considered. A significant interaction effect between treatment and the measure of craving would indicate that the level of craving during the treatment period has a different effect on abstinence depending on the treatment. For instance, EMM might be equivalent to SMM among patients without craving, but might be more effective than SMM among patients with a severe course of craving. If the interaction term is not significant, a model with main effects (treatment and course of craving) will be considered and the estimated treatment effect from this model will be compared with the treatment effect estimated from model (1). If the latter is larger (in magnitude) than the former, this would indicate that the course of craving mediates treatment effect and is at least a partial mediator. If the treatment effect from the model with main effect and treatment and course of craving is not significant, this would indicate that craving is a complete mediator of treatment effect.

In addition, the association between the weekly craving and the weekly probability for negative urine will be studied. Appropriate logistic regression models with GEE method of estimation will be used to account for the correlation between the repeated weekly measures and the correlations between patients from the same site.

6. Withdrawal symptoms: the effect of the withdrawal symptoms at baseline in Phase 1 on the outcome of the treatment will be studied. In addition, the signs and symptoms of withdrawal change at the end of the taper period, and at 4- and 8-week followups, will be studied.
7. The relationship between the treatment at Phase 1 and the outcome in Phase 2: the EMM or SMM assignment in Phase 1 is not expected to affect outcome in Phase 2. However, that eventuality will be formally tested. For example, in an exploratory analysis of primary hypothesis 2.1 the following model will be fit:

(1)

$$(2) \text{logit}(Y_{it}) = \beta_0 + \beta_1 txt_{ij} + \beta_2 t I_{ij}^s + \beta_{12} I_{ij}^s txt_{ij} ,$$

where I_{ij}^S is an indicator variable, $I_{ij}^S = 1$ if the subject is in EMM at Phase 1 and $I_{ij}^S = 0$ if the subject is in SMM group at Phase 1. A significant interaction term β_{12} would indicate that the relative efficacy of EMM in Phase 2 depends on the treatment assignment in Phase 1. If β_{12} is not significantly different from 0, the data will be refit with a model without interaction term. GEE approach will be used to fit this model. Similar exploratory analysis will be performed for the secondary hypotheses.

8. Effect of time to failure and pattern of drug use in Phase 1 on the treatment outcome in Phase 2.
9. Age, gender and ethnic differences: the relationship of gender, ethnicity, and age to outcome will be explored.

11.5 Rationale for Sample Size and Statistical Power

11.5.1 Overview

The sample size for this study is selected to ensure sufficient power (at least 80%) of a two-sided significance test with level of significance $\alpha=0.05$ to detect clinically meaningful differences between EMM and SMM in Phase 2 with respect to the primary outcome. It is shown in *Phase 1: Detectable effects* on page 11-14 that under the proposed study design and under realistic assumptions about the parameters that affect the power of the test for the primary hypothesis in Phase 1, 324 subjects need to be randomized in Phase 2.

Conservative assumptions have been made that about 50% of subjects randomized in Phase 1 will meet the criteria for Phase 1 treatment failure (i.e., will be eligible for Phase 2) and will agree to be randomized in Phase 2. This assumption is based on expecting about 20% overall (average of EMM and SMM) success rate in Phase 1 and expecting about 40% of the treatment failures (about 30% of all randomized subjects) to be unreachable or to refuse to participate in Phase 2. With this conservative estimate of 50% rate of transition from Phase 1 to Phase 2, it is projected that about $2 \times 324 = 648$ subjects will be entered in Phase 1. Therefore, the sample size for Phase 1 is considered pre-determined and the computations below estimate the relative treatment effect (EMM vs. SMM) that can be detected with $n=648$ subjects randomized in Phase 1.

Of note, since the treatment success rate and the Phase 2 refusal rate are unknown, a feasibility phase will be conducted to refine the estimate of this number (refer to Data and Safety Monitoring Plan). If the actual success and refusal rates are such that less than 50% of Phase 1 participants become randomized in Phase 2, recruitment in Phase 1 will continue until sufficient number of subjects ($n=324$) are entered in Phase 2.

11.5.2 Phase 1: Detectable effects

The success rates for SMM and EMM is expected to be 10%-20% (P_{SMM}) and 20%~30% (P_{EMM}), respectively, and the within site correlation will be small ($0 \sim 0.1$). Table 11.1 shows the power for different combination of P_{SMM} and P_{EMM} based on Model 1. The rightmost three columns represent the percentage of subjects enrolled in Phase 1 who will be eligible for Phase 2, drop out in Phase 1 or refuse to enter in Phase 2, and actually enter in Phase 2. Assume the difference between the success

rate between SMM and EMM is about 10%. The proposed sample size (648) gives sufficient power (>80%) to detect the difference with a two-sided test at $\alpha = 0.05$.

Table 11.1 Power for detecting EMM vs. SMM effects in Phase 1 with n=648, and percent of subjects eligible for Phase 2 and percent entering Phase 2 out of the total n=648.

P_{SM} M	P_{EM} M	Difference $P_{EMM} - P_{SMM}$	Odds Ratio ^a	Power	Drop/Ref Rate Phase 1	Eligible for Phase 2 ^b	Entering Phase 2 ^c
0.1	0.15	0.05	1.59	49%	25%	88%	63%
	0.18	0.08	1.98	84%	25%	86%	61%
	0.2	0.1	2.25	95%	25%	85%	60%
0.15	0.2	0.05	1.42	39%	25%	83%	58%
	0.23	0.08	1.69	74%	25%	81%	56%
	0.25	0.1	1.89	89%	25%	80%	55%
0.2	0.25	0.05	1.33	33%	25%	78%	53%
	0.28	0.08	1.56	67%	25%	76%	51%
	0.3	0.1	1.71	84%	25%	75%	50%
0.25	0.3	0.05	1.29	30%	15%	73%	58%
	0.33	0.08	1.48	62%	15%	71%	56%
	0.35	0.1	1.62	80%	15%	70%	55%
0.3	0.35	0.05	1.26	27%	15%	68%	53%
	0.38	0.08	1.43	58%	15%	66%	51%
	0.4	0.1	1.58	80%	15%	65%	50%

a) Odds Ratio = $[P_{EMM}/(1-P_{EMM})]/[P_{SMM}/(1-P_{SMM})]$

b) Eligible for Phase 2 = 1 - overall success rate in Phase 1 = 1 - $(P_{SMM} + P_{EMM})/2$

c) Entering Rate for Phase 2 = Eligible for Phase 2 – Dropout/Refusal Rate in Phase 1.

The table shows that the sample size planned for Phase 1 affords sufficient power to detect differences in success rate between EMM and SMM as small as 10%. It also shows the range of realistic assumptions about success rate in Phase 1 and dropout (unable to locate or refusal to enter Phase 2) in Phase 1 that result in at least 50% of subjects in Phase 1 going into Phase 2.

11.5.3 Phase 2: Sample Size Determination

The power analysis is based on a test statistic proposed by Liu & Liang (1997). The test statistic is based on generalized estimating equation. The power analysis takes into account the fact that data are

correlated (the measurements of patients from the same site) and that the outcome follows a non-normal distribution.

The test statistic is actually a quasi-score statistic based on the generalized estimating equation. The asymptotic distributions of the test statistic under H0 and H1 are both known. In the analysis, the outcome (the substantial improvement rate) has been assumed to follow a binomial distribution with the marginal mean being a function of the intervention. In this case, under the null hypothesis the test statistic converges to Chi-square distribution with 1 degree of freedom. Under the H1, the test statistic converges to non-central Chi-square distribution with 1 degree of freedom. After the parameters in the linear predictor for the mean and in the covariance matrix of the outcome (the working correlation matrix which does not have to be necessarily exactly correct) are specified, the non-central parameter can be computed and thus the power of the test determined.

Power of the test for difference between the two interventions with respect to their substantial improvement rates is computed for a range of values of the difference and the associated covariance parameters. Based on the model (1), the odds of the substantial improvement, depends on the effect of BUP/NX treatment plus SMM (β_0), the efficacy of the BUP/NX with EMM, and the correlation of responses between sites and within sites (ρ). Usually the correlation between sites is very small, and in our case it is reasonable to assume that it is zero (0). To illustrate the efficacy (of EMM vs. SMM) in different familiar terms, Table 11.2 shows the relationship between substantial improvement rates in SMM and EMM group for fixed odds ratios (1.8, 1.9 and 2.0) and change in the substantial improvement rate in the SMM group (P_{SMM}) from 20% to 50%. The higher the odds ratio, the greater the difference (Diff) and relative risk.

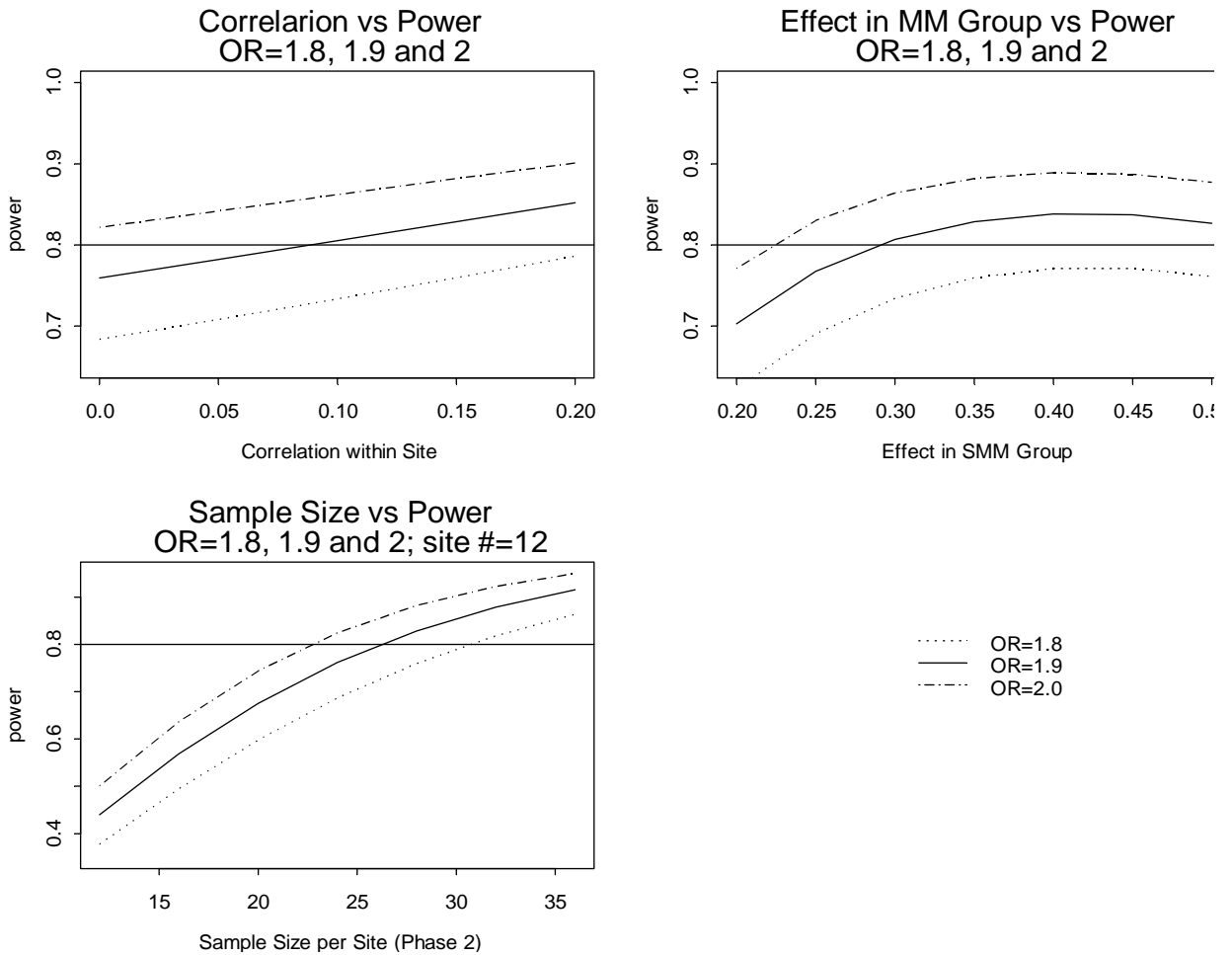
Table 11.2 Relationship between Substantial Improvement Rates in SMM and EMM Groups for Fixed Odds Ratio

Odds Ratio	P_{SMM}	P_{EMM}	Diff = $P_{EMM} - P_{SMM}$	Relative Risk (P_{EMM}/P_{SMM})
1.80	0.20	0.31	0.11	1.55
	0.25	0.38	0.13	1.50
	0.30	0.44	0.14	1.45
	0.35	0.49	0.14	1.41
	0.40	0.55	0.15	1.36
	0.45	0.60	0.15	1.32
	0.50	0.64	0.14	1.29
1.90	0.20	0.32	0.12	1.61
	0.25	0.39	0.14	1.55
	0.30	0.45	0.15	1.50
	0.35	0.51	0.16	1.44
	0.40	0.56	0.16	1.40
	0.45	0.61	0.16	1.35
	0.50	0.66	0.16	1.31
2.00	0.20	0.33	0.13	1.67
	0.25	0.40	0.15	1.60
	0.30	0.46	0.16	1.54
	0.35	0.52	0.17	1.48
	0.40	0.57	0.17	1.43
	0.45	0.62	0.17	1.38
	0.50	0.67	0.17	1.33

Figure 11.2, page 18 shows how the P_{SMM} , odds ratio, total sample size, and correlation within site (ρ) affect the power. Here, the following assumptions were conservatively made:

- The substantial improvement rate in the SMM group is between 30% and 50%.
- The correlation for each pair of responses (substantial improvement) from the same site is about 0.1.
- Between 20 and 30 patients are recruited from each site.

Figure 11.2 Odds Ratios



Top left: Power vs. the correlation for each pair of the substantial improvement rate from the same site (ρ) given site # = 12, sample size per site = 27, $P_{SMM} = 0.30$ and odds ratio = 1.8, 1.9 and 2.0.

Top right: Power vs. P_{SMM} given site # = 12, sample size per site (Phase 2) = 27, $\rho = 0.1$ and odds ratio = 1.8, 1.9 and 2.0.

Bottom left: Total sample size vs. Power given site # = 12, $P_{SMM} = 0.30$, $\rho = 0.1$, and odds ratio = 1.8, 1.9 and 2.0.

This figure conveys at least 80% power to detect an odds ratio of 1.9 between EMM and SMM group or to detect that the difference in substantial improvement rate between two groups is greater than 16% with $324 = 12 \times 27$ total patients enrolled in Phase 2. If the conservative assumption is made that about 50% subjects enrolled in Phase 1 will actually enroll in Phase 2, then the required sample size in Phase 2 is equivalent to a total sample size 648 in Phase 1.

11.5.4 Projected Number of Sites and Participants Per Site

Based on the simulation results, given the total sample size of 648, variation in the number of site from five to 20 only affects power slightly. Thus, the projected number of sites and patients per site are based on how many sites are willing to join the study and how many patients each site can recruit. It is assumed that 12 sites will enroll in our study, and each site will be able to recruit 54 patients.

12.0 Safety Monitoring

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12-1	<i>Data and Safety Monitoring Board (DSMB)</i>
12-1	<i>Safety Monitoring</i>

12.1 Data and Safety Monitoring Board (DSMB)

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

12.2 Safety Monitoring

12.2.1 Adverse Event Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the protocol. The occurrence of AEs and SAEs will be assessed at each visit during the study.

12.2.1.1 Known Potential Toxicities of Study Drug/Intervention

Potential toxicities of BUP include: deaths, which have been reported among people who abuse BUP in combination with benzodiazepines; withdrawal, if BUP/NX is taken within 24 hours of using methadone; increased risk of opiate dependence or death with continued use of heroin or other opiates; and possible impairment of mental or physical abilities for at least 6 hours after taking BUP/NX.

12.2.1.2 Known Potential Adverse Events Related to the Underlying Clinical Condition and/or Study Population

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

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

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

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

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

12.2.1.3 Definition of Adverse Event/Serious Adverse Event

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication- or study-related or clinically significant. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. A thorough history during the screening/baseline phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant to avoid reporting false AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits. Each AE will be classified by the study investigator as serious or non-serious and appropriate reporting procedures followed. For the purpose of this study, the symptoms associated with withdrawal are not defined as AEs.

12.2.1.3.1 Serious Adverse Event (SAE)

Any adverse therapy experience occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution will be defined as an SAE. Admission to a hospital or free-standing residential facility for drug detoxification or rehabilitation will *not* be considered an SAE.

SAE qualifying events include, but are not be limited to any of the following events:

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported.
2. Life-threatening: Any adverse therapy experience that places the subject or subjects, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death).
3. In-patient hospitalization (other than drug detoxification or rehabilitation) or prolongation of existing hospitalization.
4. Persistent or significant disability or incapacity.

5. Congenital anomaly/birth defect.
6. Any event that required intervention to prevent one of the above outcomes.

This terminology is from Section B.2 on the FDA MedWatch form. For a copy of the current MedWatch Form 3500, see the list of PDF forms at:

<http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>

12.2.1.3.2 Unexpected Adverse Event

An “unexpected adverse event” is any adverse therapeutic experience, the specificity or severity of which is not consistent with the investigator brochure.

For the purposes of this study, admission to a hospital or free-standing residential facility for the treatment of drug dependence, e.g., for detoxification or rehabilitation, is not defined as an SAE, but the event will be recorded on the concomitant treatment CRF.

12.2.1.4 Eliciting and Monitoring Adverse Events

The research staff will elicit AEs/SAEs at each visit. The research staff will obtain as much information as possible about the AE/SAE to complete the AE/SAE CRFs and will consult with the study medical clinician as warranted. SAEs will be reported as indicated in *SAE Reporting and Management Procedures* on page 12-5. The study medical clinician will review AEs for seriousness, severity, and relatedness weekly. The medical clinician will review all adverse events (AE) documentation and verify accuracy of assessments during each clinician visit with the participant to ensure that all AEs are appropriately reported and to identify any unreported SAEs. The research staff and medical clinician will follow any elicited AEs/SAEs until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization even beyond the end of the study. Each participating site’s Protocol PI is responsible for study oversight, including ensuring human subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

NIDA contracted quality assurance (QA) monitors from the Clinical Coordinating Center (CCC) will monitor the study sites and study data on a regular basis and will promptly report any previously unreported safety issues. The CCC monitors will review 100% of all SAEs and related documentation and ensure that the SAEs are followed appropriately by the research staff. The CCC monitors will ensure that any unreported or unidentified SAEs discovered during monitoring visits are promptly reported by the site to NIDA, the LN, Node or Protocol PI or designee, and the IRB per local IRB requirements and will be reported on the CCC monitoring report. Staff re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified AEs or SAEs are discovered, to ensure future identification and timely reporting by the site. The NIDA DSMB will also review data related to safety monitoring for this trial at regularly scheduled meetings.

12.2.1.5 Assessment of Severity

12.2.1.5.1 Severity

The study medical clinician will review each AE for seriousness, relatedness, and severity. An experienced medical clinician and/or protocol PI will review all AEs and SAEs for severity and relatedness during each clinician visit with the participant, and will consult with the study medical clinician and other research personnel as needed. The severity of the experience refers to the intensity of the event.

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

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

12.2.1.5.2 Relatedness

The relatedness of the event refers to causality of the event to the study. Relatedness requires an assessment of temporal relationships, underlying diseases or other causative factors, medication challenge/re-challenge and plausibility.

Relatedness to Therapy is defined as:

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

- **Probably related:** An adverse event that follows a reasonable temporal sequence from administration of the test product and/or procedure; follows a known response pattern to the test product and/or procedure, is confirmed by improvement after dechallenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.
- **Possibly related:** An adverse event that follows a reasonable temporal sequence from administration of the test product and/or procedure and follows a known response pattern to the test product and/or procedure, but could have been produced by the participant's clinical state or by other therapies.
- **Unrelated:** An adverse event that does not follow a reasonable temporal sequence after administration of the test product and/or procedure; and most likely is explained by the participant's clinical disease state or by other therapies. In addition, a negative dechallenge and/or rechallenge to the test article and/or procedure would support an unrelated relationship.

12.2.1.6 SAE Reporting and Management Procedures

Standard reporting (with 5-7 business days) is permitted for adverse events. Rapid reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for *serious* adverse events (including death and life-threatening events). A participating site must alert the LN and the NIDA-assigned Safety Monitor of SAEs within 24 hours of learning of the event. Details on reporting procedures are located in the Operations Manual. The completed AE CRF for the SAE should be submitted to the LN and NIDA within 24 hours or the next business day of learning of the event. The SAE CRF and any other relevant documentation should also be submitted with the AE CRF if adequate information is available at the time of the initial report to evaluate the event and provide a complete report. The following attributes must be assigned:

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

Additional information may need to be gathered to evaluate the SAE and to complete the AE and SAE CRFs. This process may include obtaining hospital discharge reports, physician records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event. Within 14 days of learning of the event, an SAE form and related documents must be completed and sent to the LN and NIDA-assigned Safety Monitor. This form must be signed and dated by the medical clinician, Protocol PI (PPI), or other qualified clinician as delegated by the PPI. If the SAE is not resolved or stabilized at this time or if new information becomes available after the SAE form and summary is submitted, an updated SAE report must be submitted as soon as possible, but at least within 14 days after the site learns the information.

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

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

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

For any death, unexpected or study related SAE, the site should bring the case to the attention of the LI and NIDA assigned Safety Monitor and NIDA as soon as possible, to discuss the event, and to discuss the measures, if any, that may need to be taken. The NIDA assigned Safety Monitor will recommend to NIDA whether or not the SAE should be presented to the DSMB via phone or e-mail, or if an urgent meeting with DSMB members must be called, to address any emergent safety concern.

Figure 12.1 AE/SAE Reporting Procedure Flowchart

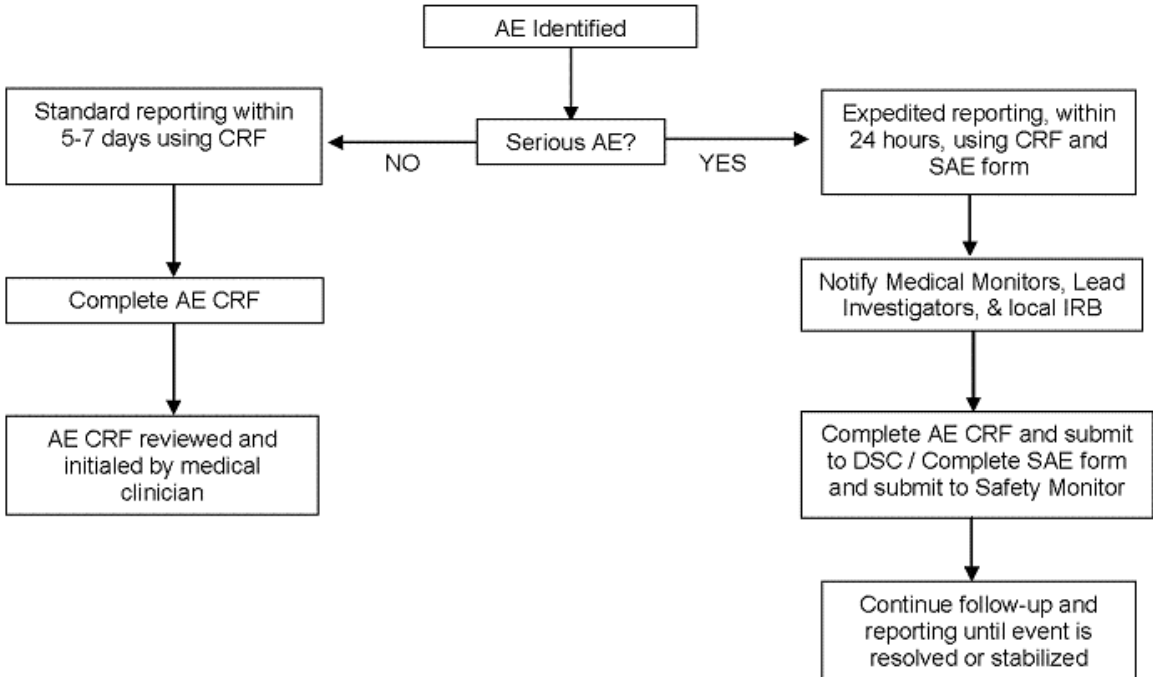
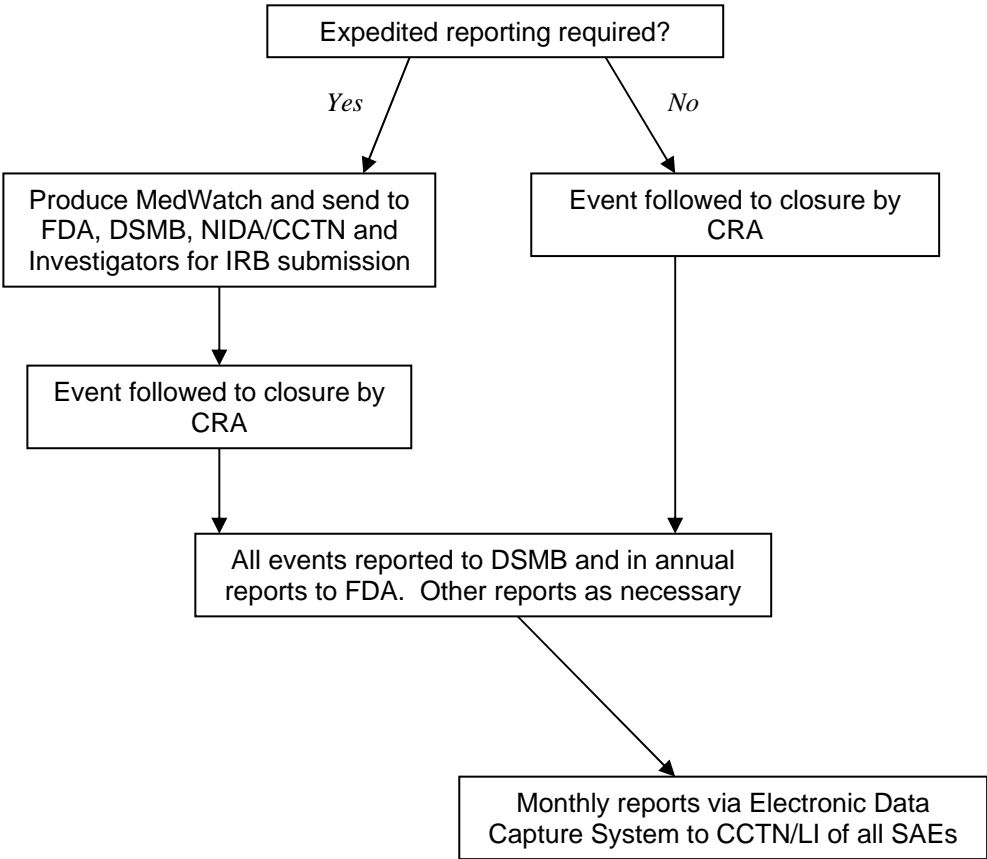


Figure 12.2 FDA Reporting Process Flowchart



13.0 Data Management and Procedures

Page	Section
13-1	<i>Design and Development</i>
13-1	<i>Data Collection Forms</i>
13-1	<i>Data Acquisition and Entry</i>
13-2	<i>Data Editing</i>
13-2	<i>Data Transfer</i>
13-2	<i>Documentation</i>
13-3	<i>Training</i>
13-3	<i>Data QA</i>

13.1 Design and Development

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

13.2 Data Collection Forms

Data will be collected at the study sites on either electronic or paper CRFs. The DSC will provide sites with a final set of standardized CRFs and CRF completion instructions. The CRFs will be distributed to the node's CTPs by the DSC. These forms are to be completed on an ongoing basis during the study. Forms should be completed according to the instructions provided and as discussed during training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for tracking the completion of CRFs for each research participant. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

13.3 Data Acquisition and Entry

For paper CRFs, all CRFs must be completed legibly in ink. Data entered into electronic CRFs shall be performed by authorized individuals. Selected CRFs also require the investigator's written

signature or electronic signature, as appropriate. CRFs will be monitored for completeness, accuracy, legibility and attention to detail during the study. The investigator must retain a copy of all CRFs.

13.3.1 Site Responsibilities

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

13.3.2 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities, 2) provide final CRFs for the collection of all data required by the study, 3) develop data dictionaries for each CRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating CTPs, 5) monitor any preliminary analysis data clean up activities, and 6) rigorously monitor final study data clean up.

13.4 Data Editing

Completed forms/electronic data will be entered into the DSC automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated and distributed to sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the DSC automated data acquisition and management system.

13.5 Data Transfer

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

13.6 Documentation

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

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

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

13.7 Training

The training plan for CTP staff includes provisions for training on assessments, CRF completion guidelines, data management procedures and the use of computerized systems.

13.8 Data QA

To address the issue of data entry quality, a random sample of CRFs will be selected from each CTP for a CRF-to-database audit according to the DSC's Internal Audit SOP. The random selection process should occur as a regular part of the data management process, but the frequency of sampling can remain flexible during data capture. The results of the audits should be made available to the study executive group at any time during the study, and a final summary report will be required as part of the pre-lock procedures. An acceptable quality level will be established as a part of the data management plan.

14.0 Quality Assurance

Page	Section
14-1	<i>Monitoring Roles</i>
14-1	<i>Monitoring Schedule</i>
14-1	<i>Protocol Compliance</i>
14-2	<i>Adverse Event Monitoring</i>
14-2	<i>Regulatory Compliance</i>

14.1 Monitoring Roles

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

14.2 Monitoring Schedule

Monitors will conduct a site initiation visit prior to start of the study. At this visit the monitor will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study. Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals, more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol. At the end of the study the monitors will advise on storage of study records and return of unused study medication. All sites should anticipate visits by NIDA and the FDA.

14.3 Protocol Compliance

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals during the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol.

Deviations from the recommended session length, e.g. 15-20 minute SMM session, will not be reported as a protocol violations but will be monitored by the lead node throughout the trial using reports generated by the data and statistics center.

14.4 Adverse Event Monitoring

14.4.1 Reporting Compliance

In accordance with FDA reporting requirements, all AEs occurring during the course of the study will be collected, documented and reported by the Investigator or sub-investigators according to the specific instructions detailed in *Safety Monitoring* on page 12-1.

14.5 Regulatory Compliance

Verbal and written details about the study protocol will be provided to each participant, and participants will be required to give signed, informed consent to participate. This study will be conducted according to the guidelines for good clinical practice, and the applicable laws and regulations of the various states where the study will be conducted. Required regulatory documentation must be maintained and available to the monitor for review throughout the study.

15.0 Human Subjects Protection

Page	Section
15-1	<i>Informed Consent</i>
15-1	<i>Subject Confidentiality/Privacy</i>
15-2	<i>Compensation for Treatment of Study-Related Adverse Events</i>
15-2	<i>Plans to Inform Subjects of Study Results</i>
15-2	<i>Foreseen Future Uses of Personal Data or Biological Materials</i>

15.1 Informed Consent

The basic elements of informed consent as specified by the FDA (21 CFR 50.25) will be followed. Written consent will be obtained from each participant using the IRB approved Informed Consent Form. A witness will verify consent. Each participant will be given a copy of the signed Informed Consent Form, and this will be noted in the source record.

Designated trained study site personnel will ensure that all aspects of the study are explained to the participant and will answer any questions related to the study. Participants will be informed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice.

15.2 Subject Confidentiality/Privacy

Participant medical information obtained during the study is confidential and disclosure to third parties is prohibited. This study is part of a large, national project in which data will be collected. The study executive group and authorized staff from sites associated with the Node, the National Institute on Drug Abuse Clinical Trials Network, NIDA and its contracted agents, monitors or auditors or other agencies such as the Department of Health and Human Services (DHHS), and the study site's IRB will have access and may inspect these research records.

Data obtained from this study that are sent by mail and electronically to data repositories will be coded with initials and/or a number, and not the participants' names. No identifying participant information, including names, will be disclosed in reports, publications or presentations.

At the participant's written request, medical information may be given to his/her personal physician.

15.3 Compensation for Treatment of Study-Related Adverse Events

Participants will be provided with specific information about any financial costs associated with their participation in the study that are not covered by the sponsor, investigators or the institutions involved. Participants participating in the study will be provided with an explanation about the extent to which they will be responsible for any costs for medical treatment incurred as a result of a study-related injury.

15.4 Plans to Inform Subjects of Study Results

During the course of the study, participants may be informed of any significant new findings (either good or bad), which a reasonable person might consider material to deciding whether to continue participation. These new findings will include changes in the risks or benefits resulting from participation in the research or new alternatives to participation.

15.5 Foreseen Future Uses of Personal Data or Biological Materials

The rights and privacy of participants who participate in research must be protected at all times. The data and associated documentation will be available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes, and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning data after data analysis is completed.

16.0 Regulatory and Administration Considerations

Page	Section
16-1	<i>IRB Approvals</i>
16-1	<i>Investigator Assurances</i>
16-2	<i>Conflict of Interest</i>
16-2	<i>Certificate of Confidentiality</i>
16-2	<i>DEA Registration</i>
16-2	<i>Participant Reimbursement</i>
16-2	<i>Inclusion of Women and Minorities</i>
16-3	<i>Records Retention and Requirements</i>
16-3	<i>Audits</i>
16-3	<i>Reporting to Sponsor</i>

16.1 IRB Approvals

Prior to study initiation, the investigator at each site will obtain written IRB approval to conduct the study. Written IRB approval must be obtained for the study protocol and the Informed Consent Form as well as other documents as required by the reviewing IRB. Any changes to the study protocol and/or Informed Consent Form or other IRB approved documents will be submitted in writing to the IRB by the investigator prior to implementation. The IRB will also approve any advertising materials used for participant recruitment and any educational materials (Self-Help detoxification handbooks) provided to the participant.

16.2 Investigator Assurances

Each community treatment program/site must file (or have previously filed) a written assurance (FWA, MPA, CPA) with the Office of Human Research Protection (OHRP) setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human participants. Prior to study implementation this documentation/assurance will be sent to NIDA or its designee. Under no condition shall research covered by the regulations be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB.

Prior to study initiation, the investigator at each study site will sign an Investigator Agreement form and the protocol signature page of the currently IRB approved protocol providing assurances that the study will be performed according to standards stipulated therein.

16.3 Conflict of Interest

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

16.4 Certificate of Confidentiality

To further ensure confidentiality, the NIDA designee will obtain a Certificate of Confidentiality for the conduct of this trial. Certificates of Confidentiality are issued by the NIH to protect identifiable research information from forced disclosure. Data obtained by research staff, including urine or breathe test for drugs of abuse or alcohol, will not be shared and will be protected by the Certificate of Confidentiality. A certificate of confidentiality does not protect a participant against disclosure of information required by mandatory reporting laws.

16.5 DEA Registration

The Lead Investigator and Sponsor, or its designee must ensure that the DEA requirements, including registration, inspection, and certification, as applicable, are met. Every person who dispenses any controlled substance shall obtain a registration unless exempt by law or pursuant to CFR Sections 1301.22-1301.26. A separate registration is required for each principal place of business or professional practice at one general physical location where controlled substances are distributed or dispensed by a person.

16.6 Participant Reimbursement

Individual Nodes may determine the amount and type (cash, script or voucher) or financial incentive as reimbursement for transportation, inconvenience and time. The local IRB and study executive group must be informed of any and all incentive level changes.

16.7 Inclusion of Women and Minorities

16.7.1 Description of Study Population in Terms of Sex/Gender and Race/Ethnicity

Adult males and females seeking treatment for prescription opioid dependence, in the absence of chronic pain severe enough to require ongoing opioid therapy will be included in the study population. Women and minorities will be included, proportionate to the population base.

16.7.2 Description of Recruitment Plan

Attaining an adequate number of women participants is anticipated because of the relatively high representation of women among those dependent on prescription opioids. Regarding the recruitment

of minorities, first it will be attempted that an adequate number of minority participants be achieved by choosing sites that typically treat minority patients. It is hoped that a diverse group of study sites will be involved and that these sites can attract a diverse patient population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites that treat a large number of women or minorities, advertising in newspapers or radio stations with a high female or minority readership/listening audience, etc.

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

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

16.8 Records Retention and Requirements

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

16.9 Audits

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

16.10 Reporting to Sponsor

The principal investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event reporting and Serious Adverse Event reporting requirements are listed in *Adverse Event Reporting* on page 12-1. At the completion of the trial, the Principal Investigator will provide a final report to the Sponsor.

17.0 Publications and Other Rights

Page	Section
17-1	<i>Publications And Other Rights</i>

17.1 Publications And Other Rights

Per NIH policy, the results of the proposed trial are to be made available to the research community and to the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN, *CTN Policy 010, Publication and Authorship*.

18.0 Signatures

18.1 Sponsor's Representative

_____ Typed Name	_____ Signature	_____ Date
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18.2 Investigators

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 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 events as defined in *Definition of Adverse Event/Serious Adverse Event* on page 12-2 of this protocol.

_____ Typed Name <i>Primary Investigator</i>	_____ Signature	_____ Date
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_____ Typed Name <i>Sub-Investigator</i>	_____ Signature	_____ Date
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_____ Typed Name <i>Sub-Investigator</i>	_____ Signature	_____ Date
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Appendix A ~ Sample Informed Consent

See attachment.

Appendix B ~ Sample Comprehension Tool

See attachment.

Appendix C ~ Therapy Manuals

Appendix D ~ Modification Package Insert

Appendix E ~

Recruitment Plan and Strategy

Recruitment Plan

Early in the development of this project, Community Treatment Program representatives working with the local Regional Research Training Center (RRTC) and the protocol development team selected specific criteria that a community treatment program would have had to meet in order to be eligible to participate this project. If you are reading this protocol, you are in the process of deciding whether your facility is suitable to participate, or you have been selected as one of 12 sites to participate in this nationwide project to determine an effective treatment for prescription opioid dependence.

The participant recruitment expectation for this study is 648 which breaks down to 54 study participants per CTP at 12 sites. Each CTP is required to develop, implement, and maintain a well-tailored, local IRB approved recruitment plan. In the next few pages are some suggestions to maximize your recruitment capabilities.

“Open House” events can be helpful in announcing the start of a study within a facility. IRB approved flyers and or brochures should be posted well in advance of the event to ensure a good turnout and subsequently quick start to recruitment. It is recommended that refreshments be served at recruiting events. Food and drink tend to attract individuals to an event they otherwise would not attend. To state the obvious, the timing of the open house should correspond with the start of the project. It may be necessary to enhance recruitment by going outside the immediate community treatment program. Outreach to pain centers, medical centers/facilities, public health centers, general practitioners and NA/AA meetings are encouraged, should be scheduled, coordinated and professional. Ideas for recruitment events at the CTPs can include, but are not limited to coffee and doughnuts or pizza information meetings for potential participants.

Participant recruitment can vary depending upon several factors including site selection, geographical location, potential participant pool, and the nature of the study however, the recruitment process can be greatly enhanced by the research and clinical teams working closely. One means to facilitate this process is weekly, onsite, team meetings to strategize, review and update study operations. The site investigator and the clinic director should show a united front at this meeting and attend on a regular basis. Any disputes between the clinical and research director as to the implementation of this project should be resolved outside the staff meeting in an effort to not polarize the treatment and research teams. The success of any research project hinges upon these individuals and their respective teams working in concert. Critical to a smooth operating project and adherence to the established recruitment schedule are the melding of these two program disciplines.

During the weekly meeting the “in house” potential participant pool should be reviewed and tracked. A record should be kept of the participants who have been informed of the study and of their level of interest in participating. Generally participant interest will fall into one of three categories: “definitely not interested”, “interested but not ready” and “interested, where do I sign”. Those participants having stated she/he is “definitely not” interested in participating, “not now, not ever” should not be contacted a second time, but rather informed that if they have a change of heart, they should contact study staff. A direct phone number is useful to allow participating and potential participants to contact study staff when information is needed or in the event of an emergency. Potential participants who are

“interested but not ready” should be provided with information regarding the next step, including the IRB approved study brochure, contact information for the research and clinical staff as well as days and times of eligibility screening. Those persons who are “ready to sign” should be seen immediately or scheduled for the next available screening appointment.

It is important that there be several staff members capable of and willing to consent and screen potential participants for eligibility. The hours of operation in many facilities restrict or limit potential participant contact, thereby minimizing the opportunity for screening potential participants. The greater the access potential participants have to the recruitment/study, the less likely participant recruitment will be bottlenecked early in the process. A day-timer should be used with times blocked out for screening and follow-up appointments (Follow-up procedures will be discussed in another section of this protocol). The potential participant’s name and phone number should be kept in this book with access restricted to authorized research staff. Quite frequently potential participants forget that an appointment has been scheduled consequently it can be helpful to provide an appointment card and to place a phone call a day prior to the appointment as a reminder. Please note that it is important to let the potential participant know that you will be calling, just in case there are other individuals in the home the potential participant would rather not be made aware of her/his participation. Maintaining confidentiality is critical.

Research and clinical staff should be flexible in their scheduling philosophy to allow for and welcome walk-ins. The more accommodating the study staff is, the easier it will be to recruit participants and create a sense of goodwill within the facility. Once a study gets rolling, word of mouth can be a tremendous recruitment strategy which should be capitalized upon. Staff flexibility goes a long way to enhance a participant’s willingness to finish what she/he has started.

Once the potential participant has presented for consent and screening, it is important to attend to she/he as quickly as possible. Participants are generally ambivalent about participating in treatment, let alone a “research project” where they are the “guinea pig”, so to keep she/he waiting simply compounds the anxiety. Be prompt, cordial and grateful for their participation.

Recruitment Strategies

Recruitment ideas for the protocol (but not limited to):

1. Free Local/Area (Event) Newspapers (note regional variations)
 - a. LA Weekly
 - b. OC Weekly
2. Radio Airtime (cost vary per station) (note regional variations)
 - a. Geographical (Urban, Suburban, & Rural)
 - i. KOST
 - ii. The Wave
 - iii. KROQ

- iv. KIIS FM
 - b. Public Service Announcements (Cannot Pick & Choose Airtime Slot. Very cost effective).
3. Pamphlets/Flyers
- a. Community Outreach
 - b. Pain Centers
 - c. Hospitals
 - ER & Staff
 - d. Laundromats
 - e. Community Health Centers
 - f. Colleges & University's
4. Billboards
- a. Bus/Subway (Interior/Exterior)
 - b. Bus/Subway Bench Ads (Can be costly)
5. Posters
- a. Hospitals
 - b. Local stores
 - c. Community Health Centers
 - d. Treatment Centers
 - i. Pain Centers
 - ii. Hospitals ER & Staff
6. PBS Commercial (approx. 2k per ad and run)
7. Professional Magazines
8. Craigslist.org

Appendix F ~ Jamison Patient Self-Help Materials