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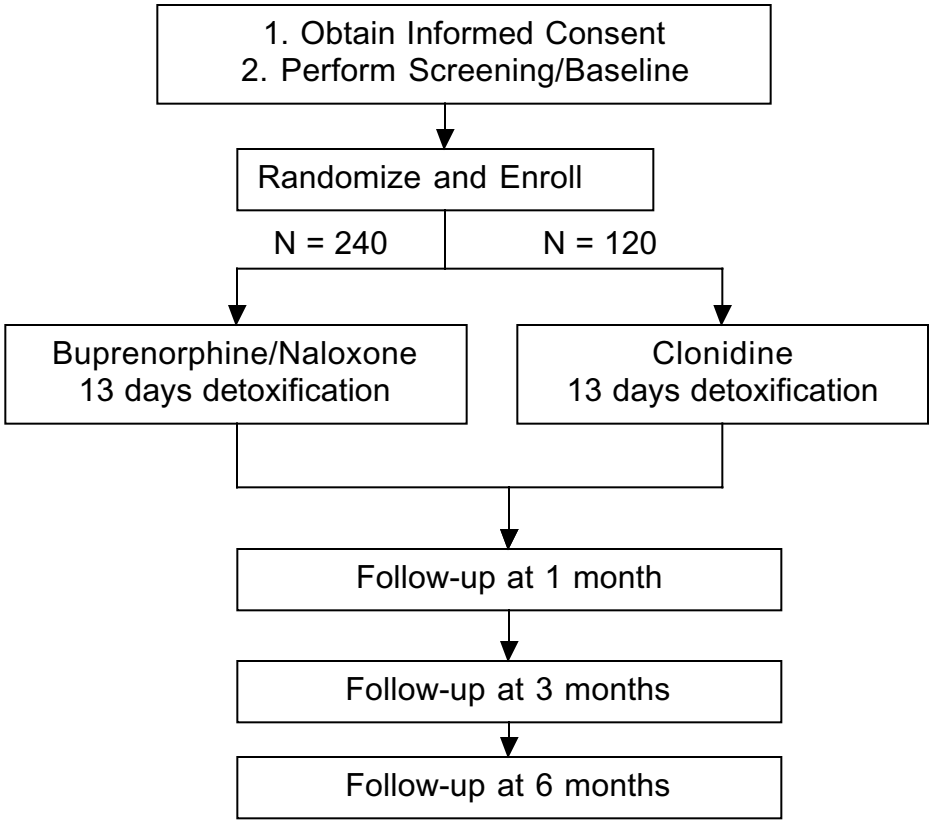
LIST OF ABBREVIATIONS

SYNOPSIS or SCHEMA
(Sample)



STUDY FLOW CHART or TIME AND EVENT TABLE
(sample)

TABLE 1. TIME AND EVENTS SCHEDULE **No data collection on weekends**

Activity	Screening/ Baseline	Induction	Stabilization Phase		Detoxification Phase[b]	Follow-up[c] (months since
Days		1-3	4 - 30		31 - 90	3 and 6
BUP/NX Dosing						
Group 1 (7 day taper)		X	X		Days 31-37	
Group 2 (30 day taper)		X	X		Days 31-60	
Group 3 (60 day taper)		X	X		Days 31-90	
Screening Assessments						
Informed Consent	X					
Demographics	X					
DSM-IV Checklist	X					
Psychiatric eval. (ASI Lite)	X					
Medical History	X					
Prior Medications	X					
HIV Risk (HBRS)	X					
Hepatitis serology	X					
Safety Assessments						
Physical exam/ Vital signs	X					
Hematology/Chemistries	X					
Routine Urinalysis	X					
12-lead ECG[a]	X					
Pregnancy test	X		X (day 30)		Groups 2 and 3 (day 60) Group 3 (day 90)	
Adverse Events		X	2X/week		2X/week	
Concomitant medications		X	2X/week		2X/week	
Efficacy Assessments						
COWS	X	X	2X/week		2X/week	
ARSW	X	X	2X/week		2X/week	
ASI Lite			X (day 30)			X
SF-36	X					X
VAS	X	X	2X/week		2X/week	
SSR		X	2X/week		2X/week	X
CSQ					day 90 or final visit	
Urine Drug screen		X (day 3)	2X/week		2X/week	X
Ancillary medications			-		2X/week as of 4 mg bup/nx	
Program compliance		X	2X/week		2X/week	

RANDOMIZATION

[a]Only in patients over the age of 40 or with a history of cardiovascular disease. [b]If subject terminates early, complete all assessment

1.0 INTRODUCTION

1.1. Background

1.1.1. Description of Drugs (or non-pharmaco treatments)
1.1.2. Preclinical Profile
[if applicable]

1.1.3. Clinical Profile

1.1.3.1. Clinical Efficacy

1.1.3.2 Pharmacokinetics

[if applicable]

2.0 STUDY RATIONALE

3.0 OBJECTIVES

3.1 Primary Objective
3.2 Secondary Objectives

4.0 STUDY DESIGN

5.0 STUDY POPULATION

5.1 Number of Sites and Subjects
5.2 Duration of Study and Visit Schedule
5.3 Informed Consent
5.4 Inclusion Criteria
5.5 Exclusion Criteria
5.6 Subject Discontinuation Criteria

5.6.1 Required Termination
5.6.2 Consideration of Early Termination
5.6.3 Procedures for Discontinuation

5.7 Replacement of Subjects

6.0 STUDY MEDICATIONS AND SUPPLIES (STUDY TREATMENTS)
Alternative section titles for non-pharmaco studies are in parentheses.

- 6.1 Study Treatments (Study Therapies)
- 6.2 Drug Packaging (Selection and Training of Therapists)
- 6.3 Administration of Study Medication (Administration of Study Therapies)
  - 6.3.1 Randomization
  - 6.3.2 Blinding
  - 6.3.3 Quality Control of Therapies Administered
  - 6.3.4 Other Procedures to Minimize Potential Biases in Administration of Therapies
- 6.4 Drug Storage
- 6.5 Drug Accountability

7.0 CONCOMITANT THERAPY

- 7.1 General Considerations
- 7.2 Medications Prohibited During the Trial

Medications Prohibited During the Trial	**Washout Period**

7.3 Medications Allowed During the Trial

8.0 MEASUREMENTS, EVALUATIONS, AND ANALYTICAL METHODS

[insert subsections to describe the study methods]

8.1 Informed Consent
8.2 Inclusion/Exclusion Criteria Review
8.3 Concomitant Medications Review
8.4 DSM-IV Checklist
8.5 HIV Risk
8.6 Medical History
8.7 Vital Signs, Height and Weight
8.8 Physical Examination
8.9 Laboratory Tests
8.10 Urine Drug Screen
8.11 ECG Test
8.12 Pregnancy Test
8.13 Randomization and Treatment Assignment
8.14 Efficacy Evaluation
8.15 Adverse Event Evaluation
8.16 Treatment Compliance

9.0 ASSESSMENT OF SAFETY

9.1 Assessment of Adverse Event Severity and Relationship to Treatment
9.2 Monitoring Adverse Events
9.3 Known Potential Toxicities of Study Drug
9.4 Immediately Reportable Adverse Events
9.5 Definition of Serious Adverse Events
9.6 Reporting of Subject Death
9.7 Known Adverse Events Relating to the Underlying Clinical Condition
9.8 Human Subject Safety
9.9 Data Safety Monitoring Board

An independent CTN Data and Safety Monitoring Board (DSMB) will examine accumulating data to assure protection of subject s safety while study s scientific goals are met.

The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data in accordance with the interim analysis plan or established

procedures. The DSMB will review data independently from the study sponsor, investigator(s), and IRBs, to determine whether the accumulating data support continuing the trial, whether study procedures should be changed, or whether the trial should be halted, for reasons relating to the safety of the study subjects, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment of subjects).

The CTN DSMB consists of approximately 10 to 12 members and meets quarterly in the calendar year. DSMB recommendations will be communicated to the Node PI within 6 weeks of the meeting. It is the responsibility of the Node PI s to convey DSMB recommendations to the appropriate IRB(s).

9.10 Medical Safety Officer

A study medical monitor, or the PI in consultation with a medical monitor, will review all serious adverse events and provide an assessment of its relatedness to the study intervention. In addition, NIDA will appoint a medical safety officer to each study to review the safety data, expedite the DSMB review, and notify all participating IRBs (via Node PI s) with a Safety Letter when necessary.

10.0 DEPARTURES FROM PROTOCOL

11.0 STATISTICAL ANALYSIS

- 11.1 Objectives of Analysis
- 11.2 Primary Efficacy Measure and Statistical Hypotheses
- 11.3 Sample Size and Statistical Power
- 11.4 Study Population
- 11.5 Demographic Profile
- 11.6 Analysis of Primary Efficacy Measure
- 11.7 Analysis of Secondary Efficacy Measures
- 11.8 Analysis of Safety Measures
- 11.9 Interim Analyses

12.0 STUDY TIMETABLE

Estimated study start date	
Estimated date when 50% of subjects will be completed	
Estimated study end date	

13.0 DISCONTINUATION OF STUDY

[Specify the right of the sponsor to discontinue the study and the procedures for discontinuation.]

14.0 DISCLOSURE OF DATA

It is understood by the investigator that the information and data included in this protocol may be disclosed to and used by the investigator s staff and associates as may be necessary to conduct this clinical study.
[Specify the investigator s obligation for provision of study data to the sponsor and the sponsor s plan for disclosure of data.]

15.0 ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

The ethical and regulatory requirements must be observed to comply with NIH policies and guidelines and Principles of Good Clinical Practice for the conduct and monitoring of clinical investigations. By signing this protocol, the investigator agrees to adhere to these requirements. The study should be reviewed by the Institutional Review Board. Written informed consent is required for all subjects.

15.1 Inclusion of Women and Minorities (see Appendix D for references)

15.1.1.1 Description of study population in terms of sex/gender and race/ethnicity.

15.1.1.2 Justification of study design to reflect compliance of NIH policies and guidelines.

15.1.1.3 Description of recruitment plan.

15.1.1.4 Description of plans to conduct valid analysis on study results by sex/gender and race/ethnicity.

15.2 Reporting to Sponsor
15.3 Publications and Other Rights

16.0 DISPOSITION OF DATA

Completed and signed Case Report Forms for all subjects entered into the Study will be submitted to the sponsor or its designee.

17.0 REFERENCES

18.0 AMENDMENTS

[insert changes from previous protocol, if any.]

18.1 Protocol Amendment No. 1
18.2 Protocol Amendment No. 2

APPENDICES

Appendix A. NIDA s Requirements for Clinical Trials
[Discuss general requirements and specific requirements for protection of study subjects, monitoring, recording of data, drug accountability, study documents and record retention, and legal requirements.]

Appendix B. Product Information for Study Drug
[e.g. investigator s brochure]

Appendix C. Training Plan
[A template proposed by the Training Subcommittee is forthcoming}

Appendix D. Inclusion of Women and Minorities as Subjects in Clinical Research

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Women of childbearing potential should not be routinely excluded from participation in clinical research. Nor should cost be a reason to exclude women and minorities from research. Thus, the inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract

proposal appropriate to the scientific objectives of the study/contract.

The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. Based on prior studies, one of the three situations below will apply. Please review the NIH Policy on Inclusion of Women and Minorities, Section IIB. for details http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm:

1. **Prior Studies Support the Existence of Significant Differences**: If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, the primary question(s) to be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this. The Research Plan must include a description of plans to conduct analyses to detect significant differences in intervention effect (see DEFINITIONS - Significant Difference) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable.

2. **Prior Studies Support No Significant Differences**: If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and/or relevant subpopulation comparisons, then sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still be strongly encouraged.

3. **Prior Studies Neither Support nor Negate Significant Differences**: If the data from prior studies neither strongly support nor strongly negate the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, then the NIH-defined Phase III clinical trial will be required to include sufficient and appropriate entry of sex/gender and racial/ethnic participants, so that valid analysis of the intervention effects can be performed. However, the trial will not be required to provide high statistical power for these comparisons. The Research Plan must include a description of plans to conduct valid analysis (see DEFINITIONS - Valid Analysis) by sex/gender, racial/ethnic groups, and relevant subpopulations, if

applicable.

[Add other appendices relevant to measurements and evaluation in the study]