

Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS-MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD)

**National Institute on Drug Abuse
Center for the Clinical Trials Network
NIDA-CTN-0028 Version 3.4 (December 18, 2007)**

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ARCQ	Adolescent Relapse Coping Questionnaire
ADHD	Attention-Deficit/Hyperactivity Disorder
ASRS	Adult ADHD Self Report Rating Scale, Version 1.1 Screener
AE	Adverse Event
CBC	Complete Blood Count
CBT	Cognitive-behavioral therapy
CCC	Clinical Coordinating Center
CD	Conduct Disorder
CGAS	Children's Global Assessment Score
CHQ-CF80	Child Health Questionnaire, 80-item child (self-report) form
CIDI	Composite International Diagnostic Interview
CRF	Case Report Forms
CTN	Clinical Trials Network
CTP	Community Treatment Provider
DSC	Data and Statistics Center
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual-version IV
ECG	Electrocardiogram
FA	Functional Analysis
IDS	Impaired Driving Score
IRB	Institutional Review Board
IR MPH	Immediate release Methylphenidate
ITT	Intent To Treat
K-SADS-E	Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children - -Epidemiological Version, 4 th Edition
LFT	Liver Function Test
LI	Lead Investigator
LT	Lead Team
MAR	Missing at Random
MCAR	Missing Completely at Random
MDD	Major Depressive Disorder
MC	Medical Clinician
MSO	Medical Safety Officer
NIDA	National Institute on Drug Abuse
NIH	National Institute on Health
NP	Nurse Practitioner
OROS-MPH	OROS Methylphenidate
PA	Physician's Assistant
PCP	Primary Care Provider
QA	Quality Assurance
RN	Registered Nurse
RA	Research Assistant
SAE	Serious Adverse Event
SP	Study Physician; can be M.D., O.D.-- or a PA or NP with prescribing privileges AND clinical mental health experience

Abbreviation	Definition
SUD	Substance Use Disorder
TAU	Treatment As Usual
TES	Treatment Effectiveness Score
THC	Tetrahydrocannabinol
THS	Teen Health Survey
TLFB	Timeline Follow-Back

2.0 STUDY SYNOPSIS

STUDY OBJECTIVES. The primary objectives of this study are to evaluate the efficacy of OROS-MPH/Concerta, relative to placebo, in treating ADHD and decreasing substance use in adolescents with ADHD and a substance use disorder (SUD).

Secondary objectives include: evaluating the safety and abuse liability of OROS-MPH in the treatment of adolescents with ADHD and a SUD; and evaluating the impact of treating ADHD with OROS-MPH on substance use treatment outcomes and psychosocial functioning. Tertiary aims include conducting preliminary analyses related to differential treatment response related to participant characteristics (e.g. gender, ethnicity) and program characteristics (e.g. urban, rural).

STUDY DESIGN. This is a 16 Week randomized, controlled trial comparing the efficacy of OROS-MPH vs. placebo in the treatment of adolescents meeting DSM-IV criteria for ADHD and SUD. All study participants will receive standardized treatment for SUD consisting of weekly, manualized Cognitive Behavioral Therapy (CBT).

STUDY POPULATION. Approximately 300 participants, recruited from approximately 10-13 sites, will be randomized into this study. Each site will randomize between approximately 15 and 60 participants, with a target average of 30 randomized participants from each site. The study population will include adolescents (13-18 years old) with ADHD (DSM-IV) and at least one non-nicotine SUD (excluding methamphetamine abuse/dependence or past month use; and opioid dependence).

TREATMENTS. Participants will be randomly assigned to OROS-MPH or matching placebo and titrated to a maximum dose of 72 mg/day (if tolerated) for the duration of the trial. All participants will receive individual, manualized CBT. CBT will consist of approximately one 60-minute session per week during study weeks 1-16 and will focus on the treatment of the adolescent's SUD.

EFFICACY ASSESSMENTS. Efficacy assessments will include ADHD symptom severity, self-report of substance use, urine toxicology screens, and measures of psychosocial functioning and treatment compliance.

SAFETY ASSESSMENTS. Safety measures will include vitals, ECG, adverse events (AEs), and laboratory tests.

ANALYSIS. Each primary and secondary outcome variable will be analyzed using appropriate statistical methods for the intent-to-treat design. Statistical tests will be two-sided at a 5% Type I error rate.

3.0 STUDY FLOW CHART

No

No

No

No

No

4.0 BACKGROUND AND RATIONALE

4.1 Background.

ADHD is one of the most common co-occurring psychiatric disorders in adolescents with substance use disorders (SUD) (30-50%) (Latimer et al., 2003; Tims et al., 2002; Wilens et al., 2003). Several studies indicate that up to one-half of the adolescents in substance treatment programs have ADHD, which is associated with more severe substance abuse, behavior problems, poorer treatment retention and outcomes when compared to substance-dependent adolescents without ADHD (Crowley and Riggs, 1995; Horner and Scheibe, 1997; Latimer et al., 2003; Riggs et al., 2004; Tims et al., 2002; Wise et al., 2001). One reason cited for poorer treatment outcomes is that the majority of adolescents in community-based drug treatment programs do not receive concurrent treatment for ADHD while in treatment for SUD (Grella et al., 2001; Latimer et al., 2003; Wise et al., 2001).

Over the past decade, there has been a growing research and clinical consensus that treatment of co-occurring psychiatric disorders such as ADHD, mood and anxiety disorders should be integrated (concurrent) with treatment for SUD. Since 1999, NIDA has included integrated treatment of co-occurring psychiatric disorders as one of nine core drug treatment principles (Drug Strategies, 2002; National Institute on Drug Abuse, 1999; Riggs and Whitmore, 1999).

While community-based treatment programs (CTPs) across the country have progressed in the delivery of multimodal treatment that effectively addresses many related problem domains, the integration of psychiatric/mental health services has been much slower, due to a number of systemic, clinical, and economic barriers. These barriers include: 1) shortage of psychiatrists/physicians with dual training in the treatment of addiction and psychiatric disorders; 2) poor third-party reimbursement for psychiatric services in substance treatment programs, which results in lack of support for integrated services delivery; 3) lack of dual training in the assessment and treatment of mental health problems for staff/counselors in community drug treatment programs; 4) cultural differences between researchers and practitioners; and 5) insufficient infrastructure and clinical expertise at the local level to support effective translation and implementation (Marinelli-Casey et al., 2002; Mojtabai, 2004; Rawson et al., 2002; Watkins et al., 2004). Despite research indicating that the majority of patients in substance treatment have psychiatric comorbidity, a recent survey (N-SSATS) conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) indicated that less than half of current substance abuse treatment facilities nation wide offered dual-diagnosis treatment programs. Most of these lacked the necessary services required to meet the special needs of dual-diagnosis patients, some of which are considered "critical components" of successful dual-diagnosis treatment programs (Mojtabai, 2004). For example, 43.4% of facilities with dual-diagnosis program and groups did not offer prescription medications, 37.8% did not offer psychiatric or psychological assessment or diagnostic services, and 26.7% were unable to fully implement comprehensive services, especially integrated psychiatric services (Mojtabai, 2004).

4.2 Validity of Psychiatric Diagnosis in Adolescents with SUD.

At least 5 published reports (including the aforementioned studies) have demonstrated that reliable screening and valid psychiatric diagnoses (including ADHD, conduct disorder, and major depressive disorder) can be made in adolescents with concurrent SUD, generally using a combination of screening, structured diagnostic and/or clinical evaluation (Crowley et al., 2001; Geller et al., 1998; Lohman et al., 2002; Riggs et al., 2004; Wilens et al., 2003).

4.3 Rationale for Choosing OROS-MPH as the Study Medication.

Psychostimulants are clearly the mainstay of pharmacologic treatment for ADHD in children, adolescents, and adults. Both MPH and D,L-amphetamine are considered equally effective in the treatment of ADHD (Biederman, 2002). More than 50 randomized controlled trials (Schachter et al., 2001), along with decades of clinical experience, have established the safety and efficacy of MPH in the treatment of ADHD in youth (Greenhill et al., 1999). In fact, the Multimodal Treatment Study of Children with ADHD (MTA) chose Immediate Release (IR)-MPH as the best initial treatment strategy for ADHD for their large clinical trial when given in a 3-times-per-day dosing schedule (Greenhill et al., 1996). The MTA also concluded that optimal treatment for ADHD required approximately 12 hours of medication effect.

Numerous attempts have been made to develop a longer acting formulation of MPH for the treatment of ADHD. Longer acting formulations are desirable for two reasons: (1) medication compliance is improved with once-per-day dosing, and (2) longer acting formulations have lower abuse potential than shorter acting preparations (see section 4.3.1, Abuse Liability). The OROS delivery system has resulted in the longest delivery system of all psychostimulant formulations. The unique delivery system in OROS-MPH consists of an osmotically active tri-layer core surrounded by a semi-permeable membrane with an immediate-release overcoat that allows for controlled drug delivery throughout the day. OROS-MPH/Concerta is the only formulation that results in 12 hours of clinical response with once per day dosing (Biederman et al., 2003; Lopez et al., 2003; Swanson et al., 2004; Wolraich and Doffing, 2004).

Three studies have evaluated the safety and efficacy of OROS-MPH compared to IR-MPH for ADHD in children. These studies demonstrate low placebo response rates and the robust clinical effects of OROS-MPH, which are equivalent to the clinical effects of IR-MPH in reducing ADHD symptoms in children (Pelham et al., 2001; Swanson et al., 2003; Wolraich et al., 2001). In addition, one small trial has demonstrated the superiority of OROS-MPH over IR-MPH on the effect on driving ability in adolescents (Cox et al., 2004). The results of these trials are summarized in Table 1.

Table 1. OROS-MPH Studies in Children and Adolescents

Author	Wolraich et al., 2001	Pelham et al., 2001	Swanson et al., 2003	Cox et al., 2004
Demographics	Age 6-12	Ages 6-12	Ages 6-12	Ages 16-19
Sample Size	N=282	N=68	N=64	N=6
Study Design	Randomized, placebo-controlled comparing OROS-MPH, immediate-release (IR) MPH, and placebo	Within-subject, double-blind comparison of placebo, IR-MPH, and OROS-MPH	Double-blind, randomized, 3-way, crossover trial (placebo vs. IR-MPH vs. OROS-MPH)	Randomized, crossover, single-blind study comparing OROS-MPH to TID IR MPH
Study Length	28 day	21 days	3 weeks	14 days
Primary Outcome Measures	Mean change in teacher and parent IOWA Conners ratings	Mean change in teacher and parent ratings of ADHD symptoms	Mean change in the teacher I/O rating of the IOWA Conners rating scale	Impaired driving Score (IDS)
Initial Outcomes	OROS-MPH and IR MPH (3 times/day) demonstrated significant reductions in ADHD symptoms and did not differ significantly from each other	OROS-MPH and IR MPH (3 times/day) demonstrated significant reductions in ADHD symptoms and did not differ significantly from each other. Parents preferred the OROS-MPH to the IR MPH.	Effect size for OROS-MPH = 1.69, and for IR-MPH = 1.57; OROS-MPH matched 3 times/day dosing of MPH for onset and duration of efficacy	IDS worsened in the evenings in IR-MPH group compared to OROS-MPH group

4.3.1 Abuse Liability of OROS-MPH

Scheduled medications, by definition, have abuse liability (Schedule I > II > III > IV), and have traditionally been considered relatively contraindicated for use in individuals with SUD (Riggs and Davies, 2002; Wilens et al., 2003). Some adolescent substance treatment programs strictly limit the use of *all* scheduled medications. This may be based on the assumption that all psychostimulants possess *the same* abuse liability to patients, as well as to staff and counselors, who may be in recovery. The extent of the abuse liability of immediate release (IR)-MPH is unclear with several recent reviews of the existing literature arriving at conflicting conclusions (Huss and Lehmkuhl, 2002; Klein-Schwartz, 2002; Kollins, 2003; Kollins et al., 2001; Volkow and Swanson, 2003). The most recent *Monitoring the Future* report (Johnston et al., 2004) indicates that

psychostimulants have high rates of abuse and diversion. However, this report refers almost exclusively to the abuse of shorter acting Schedule II psychostimulants. The reinforcing effects of shorter acting formulations of psychostimulants, such as IR-MPH, are largely associated with rapid changes in serum concentrations, as seen in intravenous injection or nasal inhalation, while the therapeutic effects are associated with more gradual changes in serum concentration, as seen in oral administration (Volkow and Swanson, 2003). This is consistent with clinical findings suggesting that the greatest risk of abuse of IR-MPH occurs when it is crushed and taken intranasally or intravenously – not when its taken orally (Babcock and Byrne, 2000; Garland, 1998; Huss and Lehmkuhl, 2002; Jaffe, 1991; Williams et al., 2004).

Although no systematic studies of OROS-MPH abuse liability have yet been performed, preliminary reports indicate that its abuse potential is low compared to that of shorter acting psychostimulant formulations. A recently published case report of an attempt at abusing OROS-MPH showed that snorting the crushed medication failed to bring about the desired “high” (Jaffe, 2002). It is hypothesized that the lack of the expected stimulant “high” results from the fact that even when the OROS-MPH tablet is crushed, the medication is not released from the tablet all at once (Ciccione, 2002). Although clearly not conclusive, the existing evidence supports that OROS-MPH is likely to have a low abuse and diversion risk owing to its unique delivery system.

4.3.2 Non-Scheduled Medication Alternatives.

Two non-scheduled, non-stimulant medications, atomoxetine and bupropion, have received FDA approval for the treatment of ADHD in children and adolescents. However, neither of these medications are as effective in controlling ADHD symptoms as the psychostimulants (they have lower effect sizes; 0.7, 0.5, respectively).

4.4 Previous Research on the Safety and Efficacy of Pharmacotherapy in Non-Abstinent Adolescents with SUD.

Although several medications have been evaluated in open-label studies in adolescents with ADHD and SUD, there is only one published controlled trial (Riggs et al., 2004). This 12-week, randomized, double-blind, placebo-controlled trial, conducted at our center (UCDHSC), evaluated the safety and efficacy of pemoline, a Schedule IV psychostimulant, in 69 non-abstinent, out-of-treatment, community-recruited adolescents with DSM-IV ADHD and SUD. Study participants met DSM-IV criteria for at least one substance dependence diagnosis. Most adolescent participants were current (non-abstinent) polydrug abusers, the majority of whom were cannabis-dependent. Study participants were not in treatment for either ADHD or SUD at the time of study entry and did not receive treatment for SUD during the study. Only pemoline/placebo with brief bimonthly medication follow up visits was provided. Results showed that pemoline was safe and effective for ADHD despite non-abstinence, with approximately equivalent safety and efficacy for ADHD to that reported for adolescents without SUD (Riggs et al., 2004; Schubiner et al., 2002).

Although pemoline was efficacious for ADHD (compared to placebo), there was no difference between pemoline and placebo-treated groups in change in substance use, which neither declined nor increased during the 12-week trial. In other words, pemoline

was safe and effective for ADHD but did not impact substance use in the absence of specific treatment for SUD. These results are consistent with a 12-week placebo controlled trial of methylphenidate for ADHD in 48 non-abstinent cocaine dependent adults, which indicated that methylphenidate had a good safety profile and was effective for ADHD, but did not decrease cocaine use (Schubiner et al., 2002).

Unfortunately, since the pemoline trial was conducted, its use has become more limited due to reports of rare, but potentially serious, pemoline-induced hepatotoxicity. Nonetheless, the relevance of this study to the current proposal is that it is the first controlled trial to show that pharmacotherapy may be used safely and effectively with careful monitoring, even in non-abstinent adolescents with SUD (Riggs et al., 2004). This may have important treatment implications given that one of the barriers to early diagnosis and treatment of co-occurring disorders in adolescents with SUD has been that most adolescents are not abstinent from substances of abuse at admission to substance treatment programs or during the early stages of treatment. Requiring abstinence for inclusion in the proposed study would limit applicability to real-world settings.

Although abstinence is ideal prior to treating comorbidity with pharmacotherapy, achieving complete or sustained abstinence may not be a realistic expectation for many adolescents if they suffer from the impairing symptoms of an untreated Axis I psychiatric illness. The aforementioned pemoline study demonstrated that abstinence may not be necessary for medication to be safe and effective. Unlike participants in the pemoline trial, participants in the proposed trial will be in concurrent treatment for SUD (CBT), enabling even more regular and consistent safety and efficacy monitoring. We could find only two other controlled trials evaluating the safety and efficacy of pharmacotherapy for any other comorbid disorder in adolescents. Geller et al. (1998) showed that lithium was efficacious in reducing mania in substance abusing adolescents with bipolar disorder who were suffering acute manic episodes, but was not an effective treatment for SUD in the absence of substance treatment.

Interim results from another ongoing randomized controlled trial of fluoxetine versus placebo for major depression (MDD) + cognitive behavioral therapy (CBT) for SUD in conduct-disordered (CD) adolescents indicates that fluoxetine has a good safety profile (low rates of adverse side effects) despite non-abstinence in the majority of study participants (Lohman et al., 2002; Riggs, 2004). This trial also demonstrates the availability and feasibility of recruiting and randomizing comorbid adolescents (N=126 randomized at a single site). The study combined a 16-week pharmacotherapy and behavioral intervention (CBT), randomizing an average of 2-4 subjects per month throughout the study enrollment phase. Retention rates (86%) and medication compliance (73%) were high, as was attendance at medication follow-up (87%) and CBT (71%) visits, in a similar, 16-week controlled trial.

Adolescent study participants in the fluoxetine/placebo trial had a similar or greater severity of illness to those admitted to CTPs: all met diagnostic criteria for CD, SUD, and MDD; many met diagnostic criteria for other comorbid disorders including ADHD (>30% of participants).

In summary, this single-site, controlled trial strongly supports the feasibility of recruiting and retaining the target study population for the current trial, especially when considering that the prevalence of ADHD (targeted disorder of proposed trial) is approximately twice that of MDD (targeted disorder of aforementioned trial) in adolescents with SUD: 30-50% compared to 15-25%, respectively (Biederman et al., 1991; Lohman et al., 2002; Riggs et al., 2004).

4.5 Rationale for Standardizing Psychosocial Intervention (CBT) Across Participating CTPs.

Outpatient adolescent treatment services vary broadly across treatment programs (CTPs) in terms of the length of treatment, frequency, intensity, and treatment modalities. In order to address the primary study objectives, it is necessary to standardize the psychosocial treatment for SUD across all participating sites for the 16-week duration of the randomized controlled trial (i.e., replace TAU for this 16-week period only). The manualized CBT that will be implemented as the standardized psychosocial treatment across sites has been shown to have efficacy in adolescents with SUD. Although there are other empirically-supported psychosocial interventions for adolescent SUD, such as family-based or behavioral interventions, individual CBT was chosen because it controls for the dose of individual and family treatment contact and standardizes the length of treatment across sites corresponding to the length of the medication trial (16 weeks). If possible, up to 3 family sessions will be scheduled during the treatment.

Moreover, individual CBT was chosen over a group model of CBT since it is not feasible to schedule an adolescent group cohort that meets at the same time on a weekly basis for 16 weeks, coordinated with individual research visits. The manualized CBT proposed for this study is the same as that used in the aforementioned trial of fluoxetine/placebo + CBT in comorbid substance dependent adolescents (Lohman et al., 2002; Riggs, 2004). The manualized CBT also utilizes a motivational enhancement approach. Drake and colleagues (1998) consider staged, motivational, psychosocially supportive interventions, as well as interventions that promote cognitive and behavioral skills for self-management of illness, as critical components of successful dual-diagnosis programs (Drake et al., 1998). The CBT intervention selected for this protocol appears to be the most appropriate choice in terms of scientific support as well as feasibility of training and implementation for a controlled trial taking place in “real world” community treatment programs within the CTN.

CBT interventionists will be masters' and bachelors' level counselors with a minimum of two years' experience with this population. All counselors at participating CTPs will be trained by the Lead Protocol Team's (UCDHSC) expert trainers, who in turn were originally trained and certified by Holly Waldron, Ph.D. Dr. Waldron developed and authored the manual with her colleagues at the Center for Family Studies at the University of New Mexico. Therapist selection criteria, training, and fidelity monitoring are described in section 9.

4.6 Rationale for Conducting the Study in the CTN.

Treatment of adolescents with addiction and psychiatric comorbidity is among NIDA's top research priorities. This study addresses a key NIDA and NIH Roadmap initiative to increase medical involvement in substance treatment by facilitating formation of an infrastructure linking primary care, mental health, and substance treatment providers at the local level. Given that physicians with subspecialty training are not available to many CTPs (or in many areas of the country), the protocol specifies that study physicians need not have subspecialty training in psychiatry, child and adolescent psychiatry, or addiction psychiatry, but may be local primary care physicians (PCPs) who are widely available in most communities. The feasibility of implementing this protocol is enhanced by the fact that PCPs already treat a large number of cases of ADHD in the U.S. and that cases of childhood ADHD are increasingly being managed by primary care providers, as opposed to subspecialty trained child and adolescent psychiatrists (Brown et al., 2001; Busch et al., 2002). In addition, ADHD is also the most common psychiatric disorder for which PCPs (e.g., pediatricians, family practitioners, counselors) already receive formal clinical training in diagnosis and treatment, and is one of the few pediatric psychiatric disorders for which pharmacotherapy is the first-line treatment standard (American Academy of Child and Adolescent Psychiatry, 1997). The inclusion of local PCPs in this protocol may have a significant impact on public health and bear lasting dissemination fruit of its own by creating integrated treatment and continuing care networks.

4.6.1 Need for Conducting a Multi-Site Trial and Utilizing the CTN's Unique Resources.

Although recruitment of adolescents at 1 or 2 study sites would be adequate to address the safety and efficacy of OROS-MPH on ADHD outcomes, due to its large effect size, a larger multi-site trial is necessary to evaluate the impact of pharmacotherapy for ADHD on substance treatment outcomes. As noted in the "background and significance" no studies have yet been conducted to enable estimates of the potential effect size (of treating ADHD) on substance treatment outcomes. Given that these data do not exist, consideration must be given to the study size and power needed to detect the lower limit of a clinically meaningful effect size, which has been determined to be .4 (low-medium effect size) or above. This will require approximately 300 participants randomized from at least 10 and up to 13 participating sites (CTPs).

4.7 Summary of Study Rationale.

In summary, the current state of the science indicates a small but growing body of research that has thus far consistently demonstrated that pharmacotherapies targeting a variety of common comorbid psychiatric disorders in non-abstinent adolescents with SUD have similar safety and efficacy to that reported for adolescents without SUD (Geller et al., 1998; Lohman et al., 2002; Riggs et al., 2004). Research shows a high prevalence of ADHD in adolescents with SUD and indicates that they have poorer substance treatment outcomes (early drop out; poor treatment completion and compliance; more difficulty achieving abstinence) and poorer prognosis and risk of persistence and progression of drug use and behavior problems into adulthood (Wilens et al., 2003). Although research indicates that the majority are not treated for ADHD while in substance treatment, we do not know whether concurrent pharmacotherapy for

ADHD will improve treatment outcomes. This is an important research and clinical question with significant public health implications. However, this question could not be feasibly addressed in a single site or even smaller multi-site trial because of the lack of feasibility of recruiting an adequate number of participants—which will require a larger multi-site trial. The CTN's resources and national network of “real world” community treatment programs are uniquely well suited to conduct this study addressing these important aims.

5.0 STUDY OBJECTIVES

5.1 Primary Objectives.

- 1) To evaluate the efficacy of OROS-MPH compared to placebo, for treating ADHD in adolescents with ADHD and a SUD
- 2) To evaluate the impact of treating ADHD with OROS-MPH on substance use in adolescents with ADHD and a SUD

5.2 Secondary Objectives.

- 1) To evaluate the safety of OROS-MPH compared to placebo, for treating ADHD in adolescents with ADHD and a SUD
- 2) To evaluate the abuse liability of OROS-MPH
- 3) To evaluate the impact of treating ADHD with OROS-MPH on substance use treatment outcomes (treatment compliance, urine toxicology screens)
- 4) To evaluate the effect of treating ADHD with OROS-MPH on psychosocial functioning

5.3 Tertiary Aims.

Tertiary Aims include conducting preliminary analyses evaluating differential treatment response related to specific participant characteristics (e.g. gender, ethnicity, comorbidity) and program characteristics (e.g. rural, urban). We will also evaluate convergent validity of parent and adolescent self report on the DSM-IV symptom checklist.

6.0 STUDY DESIGN

6.1 Overview of Study Design.

This is a 16-week randomized, placebo-controlled, Phase IV pharmacotherapy trial comparing the acute efficacy of OROS-MPH vs. placebo for ADHD in adolescents with ADHD and a SUD and the impact on substance treatment outcomes. Study participants will also be followed up at approximately one month post-study.

6.2 Number of Sites and Participants.

Approximately 300 participants will be randomized into this study. Approximately 10-13 sites will participate, each site randomizing between approximately 15 and 60 participants, with an average target of 30 randomized per site.

6.3 Duration of Study and Visit Schedule

6.3.1 Start Up.

The start up phase will entail site preparations for study implementation. These preparations include hiring and training of study staff and obtaining IRB approval.

6.3.2 Active Enrollment Phase.

Upon completion of training and IRB approval, and following the NIDA CCC guidelines for endorsement to enroll, participating CTP sites may begin enrolling participants. This study will be implemented in two stages. The first stage will consist of initiating the study at approximately three sites. Initiating the trial in a subset of sites will allow an evaluation of study feasibility and study procedures prior to full-scale implementation. Any study amendments or procedural changes deemed necessary based on the experiences with the first 3 sites will be completed prior to stage two of implementation. It is estimated that initiation of the stage two sites (i.e., the remaining 7-10 sites) will occur approximately four months after the initiation of the wave one sites.

The active enrollment phase of the study will be approximately 36 months for each participating CTP with all participants completing the study within an approximately 36 month period from first randomized participant at each site. We anticipate a 4-month close out phase for each participating site. We anticipate the entire study will be completed within approximately 40 months after initial randomization.

Randomized study participants will be scheduled for weekly medication and research assessment visits (approximately 45 minutes to 1 hour in length; see Table 2 for schedule of assessments). Participants will also attend weekly CBT sessions (approximately 1 hour in length, generally scheduled just before or after the medication and research visits) targeting their drug use. CBT attendance is not required for continued study participation (as participation is a secondary study outcome measure) but will be offered at no cost to all study participants.

Every effort will be made to encourage compliance with all aspects of the 16-week trial. However, if participants are not fully compliant or choose to discontinue the study medication for any reason before completing 16 weeks, every effort will be made to continue to obtain all 16 weeks of assessments plus the follow-up assessments (unless participants withdraw consent/assent) consistent with an intent to treat (ITT) design (no participants will be replaced for study withdrawal or non-compliance). All randomized study participants will therefore be included in primary outcome analyses.

Medication may be discontinued in cases of serious clinical deterioration; emergence of active suicidal ideation; or serious adverse effects clinically deemed related to study medication. Participants will continue to be followed/assessed weekly if possible in all cases for the duration of the 16-week trial and for the one-month follow-up (again, unless consent/assent is withdrawn).

6.3.3 Study Discontinuation.

After the last study participant completes the one month follow-up visit, study close out procedures will begin, including completion of data cleaning and data lock over an approximately 4 month study close out phase.

6.4 Site and Participant Selection

6.4.1 Site Selection

6.4.1.1 CTP Inclusion Criteria.

- 1) Must offer outpatient adolescent substance treatment services.
- 2) Admit at least 50-100 adolescents annually to outpatient treatment services.
- 3) Be willing to implement manualized CBT instead of TAU for the duration of the 16-week controlled trial in order to standardize the psychosocial intervention for SUD across participating sites (rationale previously discussed in section 4.5).
- 4) Be willing to undergo training of staff in:
 - Cognitive Behavioral Therapy
 - Screening, study referral, and diagnostic evaluation of co-occurring ADHD
 - Evaluation and monitoring of medication compliance, adverse effects, treatment response
- 5) Have access to a medical clinician— generally, but not necessarily, an R.N. or P.A. The degree and licensing requirements depend in part upon the regulations of the state in which the site is located. In order to optimize flexibility and feasibility of clinical research staffing, site-specific factors may be taken into account regarding the qualifications and experience necessary for the site's medical clinician. The MC or SP will perform medical assessments (e.g., medical history, concomitant medications, etc.), to determine participant eligibility, to regulate the medication dose appropriately, and to advise about possible untoward interactions between the study medications and other medications the study participant may be taking.
- 6) Have access to a physician (psychiatrist, pediatrician, family practice, etc.) to participate in the baseline screening interview (including administering or observing the K-SADS-E) and to be available to back-up the on-site medical clinician for clinical questions that may arise.

6.4.1.2 Rationale for CTP Inclusion Criteria.

Why outpatient only? In order to evaluate the potential impact of treatment on substance use, patients cannot be in highly restrictive treatment settings such as inpatient or residential treatment facilities where access to substances of abuse are limited/prohibited by the restrictiveness of the environment. Adolescents must be in outpatient treatment settings in order to address the impact of the study intervention on drug use and substance treatment compliance and retention.

Will it be possible for CTPs to implement a medication trial if they do not currently have medical staff/psychiatric services? CTPs do not need to currently have on-site medical or psychiatric services in order to participate in the study. The protocol allows for

assistance from the Lead Team to develop linkage between CTPs and local psychiatric or primary care medical clinicians to provide protocol-related medical/psychiatric services. The study protocol allows for sufficient flexibility across participating sites regarding staffing and procedures for providing the necessary protocol related medical/psychiatric services. However, in general we anticipate that the most common staffing arrangement will include an onsite medical clinician (e.g., RN, M.D., Physician's Assistant (PA), etc.) to perform screening/baseline and weekly medical and psychiatric assessments (e.g. adverse events, vital signs) with physician backup (who will be available by pager or cell phone for emergencies or if consultation is needed).

What qualifications are required for the CBT clinicians? CBT clinicians may be either bachelors' or masters' level therapist/counselors if they have at least 2 years of experience treating adolescents with SUD (see section 9.3 for clinician inclusion criteria).

6.4.2 Participant Selection

6.4.2.1 Inclusion Criteria.

- 1) Adolescents aged 13 through 18
- 2) Meet DSM-IV diagnostic criteria for ADHD as determined by the KSADS-E
- 3) Meet DSM-IV diagnostic criteria for at least one non-nicotine substance use disorder (abuse or dependence) except current opiate dependence or current methamphetamine abuse or dependence AND have used a non-nicotine substance (except methamphetamine) within 28 days prior to signing consent.
- 4) Are willing to participate in concurrent drug treatment (CBT) during the 16 week medication trial
- 5) Are likely to be in the area for 6 months and able to attend weekly outpatient treatment for the 4 month duration of the active study
- 6) Are able to understand and provide written informed consent (or assent if a non-emancipated minor)
- 7) Parent or guardian able to understand and willing to provide written informed consent (if participant is a non-emancipated minor)
- 8) Has a DSM-IV ADHD Symptom Checklist score ≥ 22 derived from the adolescent-completed checklist **and**, if the adolescent is a non-emancipated minor, a score ≥ 22 derived from a joint adolescent and parent/guardian checklist
- 9) If female and of child bearing potential, agrees to use one of the following methods of birth control:
 - Complete abstinence from sexual intercourse
 - Patch
 - Barrier (diaphragm or condom)
 - Intrauterine contraceptive system
 - Levonorgestrel implant
 - Medroxyprogesterone acetate contraceptive injection
 - Hormonal vaginal contraceptive ring
 - Oral contraceptive

6.4.2.2 Exclusion Criteria.

- 1) Serious medical illness or other clinical issues that, in the judgment of the medical clinician (MC) or study physician (SP), would make study participation unsafe, including serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems
- 2) History of tic disorder
- 3) Pregnancy (determined by serum HCG baseline)
- 4) Breastfeeding
- 5) Meet DSM-IV criteria for current or life-time psychotic disorder as determined by the K-SADS-E and confirmed by the SP
- 6) Meet DSM-IV criteria for current or life-time bipolar disorder as determined by the K-SADS-E and confirmed by the SP
- 7) Requires, or is currently taking other concurrent psychotropic medication
- 8) Taking any medications listed in section 8.10 and/or those which, in the judgment of the MC or SP, may produce interactions with OROS-MPH that are sufficiently dangerous so as to exclude the patient from participating in the study. Alternatively, the MC, with consultation with the patient and his or her physician, may elect to withdraw the patient from the problem medications before starting on OROS-MPH, and therefore, would not be exclusionary
- 9) Meet DSM-IV criteria for current opiate dependence as determined by the CIDI
- 10) Meet DSM-IV criteria for current methamphetamine abuse or dependence as determined by the CIDI or reports past 28 day use of methamphetamine, or has a positive urine drug screen for methamphetamine at baseline assessment
- 11) Is a significant suicidal risk, as determined by clinical assessment
- 12) Active participation in substance abuse treatment or mental health treatment (including outpatient, day-treatment, residential, or inpatient) within 28 days prior to signing consent
- 13) If in the judgment of the MC or SP, requires additional or more intensive (e.g. inpatient, residential) treatment as assessed at screening/baseline

6.4.2.3 Rationale for Participant Inclusion/Exclusion Criteria.

Broad inclusion criteria are proposed to allow participation by a diverse patient population representative of “real world patients in real world settings.” For similar reasons participants do not have to have achieved abstinence to participate in the medication trial as they will also be participating in concurrent psychosocial treatment for SUD (CBT). The SP will confirm eligibility for randomization. The generalizability of study results would be highly questionable if study participation required total abstinence, since the majority of adolescents admitted to drug treatment programs are not abstinent when they enter treatment.

6.5 Outcome Measures

6.5.1 Primary Outcome Measures.

This study evaluates the effects of OROS-MPH compared to placebo on two distinct outcomes (i.e., ADHD and substance use). Consequently, the present study requires two primary outcome measures, one for ADHD and one for substance use.

6.5.1.1 ADHD Outcome

6.5.1.1.1 DSM IV ADHD symptom checklist.

The DSM-IV ADHD Symptom Checklist assesses each of 18 individual criteria symptoms using a severity scale (0= “not present”, 3= “severe”; overall minimum score=0, overall maximum score=54). This scale has been shown to be correlated with ADHD and is medication sensitive (Bostic et al., 2000; Prince et al., 2000). The research staff administering this instrument will have completed training and certification by expert trainers to ensure competence and adherence in assessment administration and adequate inter-rater reliability.

During screening/baseline, the DSM-IV ADHD Symptom Checklist will be completed with each adolescent, and, for non-emancipated adolescents, a joint interview with the adolescent and parent/guardian will be completed as well. However, whenever possible, we encourage a joint adolescent/parent/guardian DSM-IV checklist for emancipated and age 18 adolescents as well. Each DSM-IV checklist administered during screening/baseline will reference the past 28 days. The DSM IV ADHD Symptom Checklist score from the adolescent-only interview will serve as the baseline score for the DSM-IV Symptom Checklists completed by the adolescent weekly (referencing past week) during the active study (see Table 2). During weeks 8 and 16, the MC/RA will also complete a DSM IV ADHD Symptom Checklist based on parent report (interviewed either in person or by phone) for non-emancipated minors.

6.5.1.2 Substance Use Self-Report

6.5.1.2.1 Number of Use Days in Past 4 Weeks.

This outcome will be assessed with the Timeline Follow-Back (TLFB), originally developed by Sobell and Sobell (1992) and modified as a Form 90D version by Miller and Del Boca (1994). The Form 90D version has been shown to have a high test-retest reliability (Tonigan et al., 1997), as well as high subject-collateral correlations for total days of drug use. The TLFB will be utilized for analytical purposes as a past-28-day measure of drug use at screening/baseline, for each of the 4 months of the active study. However we will gather TLFB information weekly during the active study to enhance reliability of participant’s recall of drug and alcohol consumption during the previous week (as opposed to requiring recall use over an entire 4-week period). Using the TLFB in this way will also establish a temporal relationship between drug use and adverse side effects that may be due to interactions between drugs of abuse and study medication. An additional TLFB will be completed at the one month follow-up to assess the participant’s substance use between the end of the active phase and the scheduled follow-up.

6.5.2 Safety Measures

6.5.2.1 Adverse Events (AEs).

AEs (see Section 11.6) will be assessed by study staff according to the schedule outlined in Table 2. A MC or well-trained RA with access to medical back-up will be

scheduled to meet face-to-face with the participant to assess all medical and psychiatric AEs since the previous MC visit.

6.5.2.2 Blood Chemistries.

Approximately one tablespoon of blood will be collected at screening/baseline and at the week 16 visit (or at early study termination, if possible). Quantitative analysis will be performed for the following: total protein, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyl transferase (GGT), total bilirubin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and alkaline phosphatase (ALP) blood urea nitrogen (BUN), CO₂, chloride, creatinine, glucose, potassium, and sodium. A prescription topical numbing cream may be offered to all participants prior to the blood draw.

6.5.2.3 Hematology.

A complete blood count (CBC) with differentials and platelet count will be performed (from same blood draw as blood chemistries, above). Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. These labs (blood chemistries/hematology) will be performed at screening/baseline and at the week 16 visit (or at early study termination, if possible).

6.5.2.4 ECG.

Adolescents who are being considered for study participation will have a twelve-lead electrocardiogram and a physical exam to assess for the presence of cardiac abnormalities. A medical history will also be obtained from each potential participant to ascertain if he/she has any pre-existing structural abnormalities of the heart or any other cardiac problems (e.g. cardiomyopathy, arrhythmias, syncope) that would be exclusionary for this study. Additionally, information about family history of serious cardiac problems (e.g., sudden death; ventricular arrhythmias) will be collected. A board-certified cardiologist will review the individual and family cardiac histories, relevant concomitant medications and ECGs. Abnormal results determined to be clinically significant would be reason to exclude the candidate from study participation. In some cases, the cardiologist may request that a candidate be referred for additional cardiac evaluation to determine whether borderline abnormal findings on ECG are a normal variant versus exclusionary pathology.

If a participant develops symptoms suggestive of cardiac problems such as exertional chest pain, unexplained syncope, or arrhythmia during the active study, study medication will be discontinued and the participant will be referred for further cardiac evaluation.

6.5.2.5 Urinalysis.

Urine will be collected and analyzed at screening/baseline and study exit for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, nitrite, bilirubin and urobilinogen.

6.5.2.6 Vital Signs and Weight.

Vital signs including blood pressure and heart rate will be assessed at each visit during the medication trial. In addition, the participant's weight will be recorded during screening, and at monthly intervals during participation in the study.

6.5.3 Secondary Outcome Measures

6.5.3.1 OROS-MPH Abuse Liability

6.5.3.1.1 The MGH Liking Scale.

This scale was developed by Timothy Wilens MD and colleagues at Massachusetts General Hospital (MGH) to distinguish reports of "liking" the medication for treating ADHD symptoms vs. "liking" the medication because it "makes me feel high." The liking scale will be administered at the week 4 visit, after participants have been titrated up to maximum study medication dose, and monthly thereafter, ending at the week 16 visit.

6.5.3.1.2 MGH Diversion Questionnaire.

The likelihood of medication diversion, or distribution of medication to individuals other than for whom the medication is intended, will be evaluated monthly by self-report beginning at the week 4 visit and ending at the week 16 visit. The MGH Diversion questionnaire developed by Wilens and associates will be used.

6.5.3.2 Substance Use Treatment Outcomes

6.5.3.2.1 Frequency of Drug Use.

The TLFB (see description in section 6.5.1.2.1) will be used to assess the participant's frequency of drug use. The TLFB will be administered by the MC or RA at screening/baseline (past 28 day report) and completed weekly during medication follow up visits but utilized as a past 28 day measure of drug use. The TLFB will also be administered at the one month follow-up visit.

6.5.3.2.2 Urine Toxicology

Urine toxicology (Urine Drug Screen) will be collected at screening/baseline, weekly throughout the 16-week trial, and at the one month follow-up visit (see Table 2). A rapid urine screen system that screens for amphetamine, barbiturates, benzodiazepines, cocaine, methamphetamine, opiates, and THC will be used to analyze the urine samples. The validity of urine samples will be checked with the use of a commercially available adulterant test.

Urine toxicology results will be analyzed based on the proportion that are negative for drugs of abuse rather than the proportion that are positive out of a standard number of samples scheduled for collection across the study (weekly in this case). This method, also denoted as the Treatment Effectiveness Score (TES), has been recommended by Ling et al. (1997) as a more accurate measure of urine toxicology data because it eliminates problems associated with imputation of "positive" urine toxicology results if a scheduled sample collection is missed.

6.5.3.3 Compliance

This study includes three measures of compliance:

1. Research Visit Attendance.

Weekly research assessment and medication follow up visits will be scheduled to coordinate with weekly scheduled CBT sessions (either before or after CBT sessions). Compliance will be assessed by recording the number of scheduled visits attended and whether the participant completes weekly assessments as specified in Table 2, including the DSM-IV ADHD Symptom Checklist and evaluation of AEs.

2. Medication compliance will be also be assessed at each of these weekly visits by performing tablet counts and eliciting adolescent self report of daily compliance. Tablet counts will be conducted and reconciled with the participant's medication diary and self-report. If the participant forgets his/her medication bottle and any remaining medication, the self report will be recorded in the progress notes and the tablet count will be reconciled with the self report when the bottle/medication is returned (generally the following week). Counseling regarding the importance of medication compliance will be included in each visit, and particularly emphasized with those participants who have had difficulty with full compliance. Participants will be able to receive an additional 5 dollars for remembering to bring their medication bottle and diary (20 dollars for visit; 5 dollars for remembering to bring medication bottles and diary) to provide augmented incentives for medication compliance and the reliability of weekly tablet counts.

3. CBT Attendance.

CBT compliance will be evaluated by attendance at each of the 16 weekly sessions. If the participant's therapist is unable to schedule a weekly session (e.g. due to vacation or illness) and if there is no opportunity for the participant to do a makeup session, this will be deducted from the number of opportunities for attendance and will not be counted as participant "non-compliance." CBT attendance is not required for continued study participation (as compliance/attendance is a secondary outcome measure) but must be strongly encouraged both during the consent/assent process and throughout the 16 week trial.

6.5.3.4 Psychosocial Functioning

6.5.3.4.1 Children's Global Assessment Score (CGAS).

The CGAS is an adaptation for children of the Global Assessment Score (GAS), used throughout psychiatry to assess general global functioning of adults. The CGAS will generally be administered by the MC or SP at baseline, week 8, week 16, and at the one-month follow-up visit (See Table 2).

6.5.3.4.2 Child Health Questionnaire (CHQ-87).

The CHQ, a generic measure of adolescent health and well-being (Langford et al., 1996), is an 87-item questionnaire with 12 subscales assessing such domains as social roles, self-esteem, mental health, family cohesion and activities, and physical

functioning. The CHQ-87 will be administered by the MC or RA at the screening/baseline, week 8, and week 16 visits (see Table 2).

6.5.4 Other Measures

6.5.4.1 Adult ADHD Self-Report Rating Scale V1.1 Screener (ASRS-V1.1).

The ASRS-V1.1 Screener (Copyright © 2003 World Health Organization; Kessler et al., in press) is a 6-item questionnaire that has been shown to have concurrent validity with DSM-IV criteria for ADHD in adult studies. This scale, while not formally validated in adolescents, has been used in previous research studies with adolescents. It was chosen for use in the present study since there is no validated, accepted standard self-report screening assessment for ADHD in adolescents. The ASRS-V1.1 will be administered by clinical research staff (MC, RA) incorporated in the prescreening interview, or by clinical staff at the participating community treatment program (CTP) as part of their outpatient admission packet. Adolescents who appear to meet pre-screening criteria for ADHD in addition to other pre-screening criteria will be invited to make an appointment for more extensive baseline screening and assessment. The ASRS-V1.1 will be re-administered to adolescents after consent/assent as part of the screening/baseline assessment battery.

6.5.4.2 Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children - Epidemiological Version, 4th Edition (K-SADS-E).

At baseline, the diagnosis of ADHD will be established by administration of the (K-SADS-E) (Orvaschel and Puig-Antich, 1987). The K-SADS-E is a widely used, psychiatric diagnostic interview with known psychometric properties (Geller et al., 2000). The ADHD module of the K-SADS-E will be administered **jointly** to both the parent/guardian (for adolescents who are non-emancipated minors, and strongly encouraged for parent/guardian of emancipated minors and age 18 adolescents) and adolescent, preferably by the study physician, or a clinician with, at minimum, a master's degree who has been trained in its administration. If the master's level clinician administers the K-SADS-E, the study physician will be present during administration. Following the joint administration of the ADHD module, parent/guardian will leave the room. The following K-SADS-E modules, Affective Disorders (Depression and Mania modules), Psychotic Disorders (Psychosis module), and Behavioral Disorders (Conduct Disorder module), will be administered to the adolescent only. However, if clinically indicated, additional information may be obtained from the parent/guardian in order to clarify the diagnosis on these modules.

6.5.4.3 University of Rhode Island Stage of Change (URICA).

The University of Rhode Island Change Assessment (URICA) (DiClemente and Hughes, 1990) will be used to assess the participants' motivation to change their substance use behavior at baseline and at week 16.

6.5.4.4 Composite International Diagnostic Interview (CIDI).

The expanded substance abuse and dependence sections of the CIDI will be administered to establish DSM-IV diagnoses of substance abuse and dependence for

10 drug classes. The CIDI is a structured 30-60 minute interview designed for lay interviewer administration and is part of the CTN's Common Assessment Battery (CAB). It is a descendant of the NIMH Diagnostic Interview Schedule. The reliability and validity of the CIDI (Cottler et al., 1989; Robins, 1988) made it the main assessment for DSM-IV substance field trials and for the National Comorbidity Study (Kessler et al., 1994). The authors of the CIDI now have a computer-administered version for making DSM-IV diagnoses, which we have used extensively. The ability of the CIDI to discriminate adolescent patients with SUD from controls in terms of abuse and dependence diagnoses has also been demonstrated to be excellent (Crowley et al., 2001). The CIDI will be administered by a RA or MC who has been trained and certified in the proper administration of this instrument.

6.5.4.5 Teen Health Survey (THS).

The Teen Health Survey (THS) assesses participants' levels of HIV risk reduction information, motivation, behavioral skills, and HIV-risk and HIV-preventive behavior (Misovich et al., 1998). The THS was developed by researchers at the Center for Health Information/HIV Intervention and Prevention and has been psychometrically validated and used widely in HIV risk reduction research. Its use in this study will provide a screening/baseline measure of both cognitions and behavior related to safe sexual practice. Information gained from the THS will increase the efficacy of teaching and practicing skills for safe sexual practices which takes place during CBT (HIV module). It is a self-administered questionnaire which takes approximately 30 minutes to complete. It will be administered by the MC or RA at screening/baseline and week 16.

6.5.4.6 Demographics Form.

The Demographics Form was developed by the CTN (CAB) to capture data about participants who participate in CTN studies regardless of whether they go on to randomize in the study. The Demographics form captures basic race and ethnicity information about each potential study participant in a standard format and is administered at screening/baseline.

6.5.4.7 Medical History.

A medical history, including cardiovascular history, will be performed by a certified MC or SP at screening/baseline, based on information from adolescent and parent/guardian (if applicable).

6.5.4.8 Physical Exam.

A brief physical exam will be performed by a certified MC or SP at screening/baseline.

6.5.4.9 Clinician Global Impression of Improvement (CGI-I) Rating Scale.

The CGI-I is a widely used standard assessment of the overall degree of clinical improvement (or worsening) of the targeted disorder since treatment initiation (Connors et al., 1985). The scale consists of 7 possible scores: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse. The CGI-I ideally will be completed at visits during weeks 4, 8, 12, and 16 by the MC or SP.

6.5.4.10 Pregnancy Test.

A serum pregnancy test will be completed on female participants during screening/baseline. A urine pregnancy test, designed to measure human chorionic gonadotropin, will be assessed at weeks 4, 8, 12, 16. If the participant misses one of these visits, a urine pregnancy test will be performed at the next visit attended. All female participants will be tested regardless of their likely child-bearing capacity.

6.5.4.11 Prior/Concomitant Medications.

All medications taken by the participant for the 30 days prior to screening/baseline and during the screening/baseline period will be documented on a Prior/Concomitant Medications CRF. All concomitant medications taken by the participant while on study medication will be reviewed by the MC as outlined in Table 2 and will be recorded on a Prior/Concomitant Medications CRF.

6.5.4.12 Check on Blind.

A check on the medication blind will be completed for both the adolescent and a MC who completed assessments for the adolescent. In this assessment the respondent (i.e., the adolescent, MC) is asked which medication the adolescent was taking (OROS-MPH or placebo). This assessment is scheduled to be completed during the week 16 visit.

6.5.4.13 Participant Status at the End of the Active Study Phase.

This is a brief assessment that is completed by the MC or RA in conjunction with study week 16 OR upon confirmation of early termination/participant drop-out.

6.5.4.14 Treatment Status.

At the one-month follow-up visit, the participant's treatment status in terms of: 1) pursuing pharmacological treatment for ADHD and 2) participating in substance abuse treatment will be assessed.

6.5.4.15 Adolescent Relapse Coping Questionnaire (ARCQ).

This self report evaluates adolescent skills for coping with temptations to use alcohol and/or other drugs and provides a cognitive appraisal of relapse risk situations including motivation and confidence for abstinence (Myers and Brown, 1996). The ARCQ will be administered at screening/baseline and study week 16 to measure changes in coping skills over the course of treatment.

Table 2. Schedule of Assessments and Procedures

Abbrevia tion	Assessment/ Procedure	Ideally Completed by	Completed with	Time Est. (Min)	Scrn/ Base	Acute Phase (Weekly Visits)															Final Acute Visit	FU	
						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			16**
Visit Study Week						1	8- 14	15- 21	22- 28	29- 35	36- 42	43- 49	50- 56	57- 63	64- 70	71- 77	78- 84	85- 91	92- 98	99- 105	106- 112	134- 161	
Visit Study Day[†]						1	8- 14	15- 21	22- 28	29- 35	36- 42	43- 49	50- 56	57- 63	64- 70	71- 77	78- 84	85- 91	92- 98	99- 105	106- 112	134- 161	
Approximate Length of Visit (Hours)						5.7	1.9	1.8	1.8	1.9	1.8	1.8	1.8	2.4	1.8	1.8	1.8	1.8	1.8	1.8	1.8	3.5	0.7
	Treatment																						
	OROS-MPH/placebo	MC	Adolescent	5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Individual CBT	CBT Clinician	Adolescent	60		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Screening Assessments																						
ASRS	ASRS (ADHD Pre- screen)	MC or RA	Adolescent	5	X																		
	Informed consent/assent	MC or RA	Guardian/ Adolescent	40	X																		
DEMO	Demographics	MC or RA	Adolescent	10	X																		
	Physical	MC	Adolescent	20	X																		
	Medical history	MC	Guardian/ Adolescent	10	X																		
PRIOR	Prior/Concom Meds	MC	Guardian/ Adolescent	5	X																		
K- SADS-E (ADHD module)	Kiddie-SADS- Epidemiology (ADHD module)	SP, MC or Master's level RA	Jointly with Guardian and Adolescent	30	X																		
K- SADS-E (MDD, Mania, Psychosis, CD)	Kiddie-SADS- Epidemiology (MDD, Mania, Psych., CD modules)	SP, MC or Master's level RA	Adolescent ONLY and separately with Guardian if needed	30	X																		
CIDI	Composite International Diagnostic Interview	MC or RA	Adolescent	50	X																		

Abbreviation	Assessment/Procedure	Ideally Completed by	Completed with	Time Est. (Min)	Scrn/Base	Acute Phase (Weekly Visits)															Final Acute Visit	FU		
						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			16**	20
Visit Study Week						1	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91	92-98	99-105	106-112	134-161		
Visit Study Day⁺						1	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91	92-98	99-105	106-112	134-161		
Approximate Length of Visit (Hours)						5.7	1.9	1.8	1.8	1.9	1.8	1.8	1.8	1.8	2.4	1.8	1.8	1.8	1.8	1.8	1.8	1.8	3.5	0.7
Treatment																								
SE	Study Eligibility form	MC or RA	Adolescent	2		X																		
RAN	Randomization form	MC or RA	Adolescent	1		X																		
Safety Assessments																								
CONMED	Prior/Concomitant Meds	MC	Adolescent	5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
VS	Vital Signs	MC	Adolescent	5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG	ECG	MC	Adolescent	10	X																			
LAB	Lab values (Hematology, LFTs)	MC or RA	Adolescent	5	X																	X		
UA	Urinalysis	MC or RA	Adolescent	1	X																	X		
UPT	Urine Pregnancy test	MC or RA	Adolescent	1				X					X				X					X		
SPT	Serum Pregnancy test	MC	Adolescent	5	X																			
AEs	Adverse Events	MC	Adolescent	5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Efficacy Assessments																								
DSM-IV checklist	DSM-IV ADHD symptom checklist	SP, MC, RA	Adolescent	10	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
DSM-IV checklist	DSM-IV ADHD symptom checklist	SP, MC, RA	Jointly Guardian/Adolescent*	10	X																			
DSM-IV checklist	DSM-IV ADHD symptom checklist	SP, MC, RA	Guardian	10									X									X		
CGAS	Children's Global Assessment Score	MC, RA, or SP	Adolescent	1	X								X									X		

Abbreviation	Assessment/ Procedure	Ideally Completed by	Completed with	Time Est. (Min)	Scrn/ Base	Acute Phase (Weekly Visits)															Final Acute Visit	FU		
						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			16**	20
Visit Study Week						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16**	20		
Visit Study Day⁺						1	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91	92-98	99-105	106-112	134-161		
Approximate Length of Visit (Hours)						5.7	1.9	1.8	1.8	1.9	1.8	1.8	1.8	2.4	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	3.5	0.7
	Treatment																							
CGI-I	Clinician Global Impression of Improvement Rating	MC, RA, or SP	Adolescent	1					X				X				X				X			
CHQ-87	Child Health Questionnaire	MC or RA	Adolescent	25	X								X								X			
UDS	Urine Drug Screen	MC or RA	Adolescent	5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
TLFB	Timeline Follow-Back	MC or RA	Adolescent	5	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Other Assessments																							
THS	Teen Health Survey	MC or RA	Adolescent	30	X																X			
URICA	University of Rhode Island Change Assessment Scale	MC or RA	Adolescent	5	X																X			
MEDL	Medication Liking	MC or RA	Adolescent	5					X				X				X				X			
MGHD	MGH Diversion Questionnaire	MC or RA	Adolescent	2					X				X				X				X			
CBT-AF	CBT Attendance Form	Clinician	Adolescent	1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
RVC	Research Visit Compliance	MC or RA	Adolescent	1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MEDC-PC	Medication Compliance (PC)	MC or RA	Adolescent	5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MEDC-SR	Medication Compliance-SR	MC or RA	Adolescent	5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
BLIND	Check on Blind	MC or RA	MC/Adolescent	1																	X			
ARCQ	ARCQ	MC or RA	Adolescent	10	X																X			

Abbrevia tion	Assessment/ Procedure	Ideally Completed by	Completed with	Time Est. (Min)	Scrn/ Base	Acute Phase (Weekly Visits)															Final Acute Visit	FU	
						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			16**
Visit Study Week						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16**	20	
Visit Study Day⁺						1	8- 14	15- 21	22- 28	29- 35	36- 42	43- 49	50- 56	57- 63	64- 70	71- 77	78- 84	85- 91	92- 98	99- 105	106- 112	134- 161	
Approximate Length of Visit (Hours)						5.7	1.9	1.8	1.8	1.9	1.8	1.8	2.4	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	3.5	0.7
	Treatment																						
TXS	Treatment Status	MC or RA	Adolescent	5																		X	

⁺ The study days on which a particular visit can be completed.

*This DSM-IV ADHD Symptom Checklist completed at screening/baseline is completed jointly with both the adolescent and the parent/guardian and again separately with the adolescent.

++ If this visit is missed, complete urine pregnancy test at next attended visit.

**If a participant discontinues the study early, for any reason, a concerted attempt will be made to obtain all of the measures listed for study week 16.

7.0 STUDY PROCEDURES

7.1 Overview of Study Assessments and Procedures.

Table 2 provides an overview of the study assessments and procedures.

7.2 Recruitment Plan.

The recruitment plan is based on the recruitment strategies proved successful in previous single site studies conducted by the PI and the Lead Team (Lohman et al., 2002; Riggs, 2004). This strategy applies only to participants qualified and willing to enter substance treatment concurrent with treatment for ADHD per the protocol. This process will significantly augment the recruitment capability of the CTP and is also designed to enhance the patient referral network for the individual CTPs.

Recruitment resources: A primary source of participants will be the pool of new admissions to participating outpatient CTPs. Our comprehensive recruitment strategy involves several proven techniques for this population, including advertisements, promotional materials, word-of-mouth, networking within the community at local churches, schools, and primary care providers, email communication, and referrals with other research studies within the local area. Study participants will also be recruited from the community by placing notices in newspapers, as well as other public media such as radio, television, movie theaters, and public transportation. Study brochures will be sent to local schools, mental health and substance abuse agencies, as well as juvenile justice and social services. These contacts will target those who have direct contact with this at-risk population such as nurses, social workers, mental health, substance abuse counselors, and primary care providers. Contacts will be followed up by phone calls and on-site informational meetings whenever possible. Where available, study notices will also be placed in local professional newsletters for disciplines including nursing, social work, and pediatric psychiatry. Recruitment may also include email announcements at local universities or colleges, flyers in local libraries, grocery stores, and medical clinics. In academic communities, contracts may be made with local IRB's to obtain contact information for other adolescent ADHD research studies to collaborate on cross-referrals when there are different inclusion and exclusion criteria between the studies.

To maintain a successful recruitment strategy, study staff should respond to study-related inquiries within a 24-hour period whenever possible. It may be necessary for staff to return phone calls on nights and weekends, in order to reach working parents of potential study subjects. A prescreening template will be used to assess the eligibility of potential participants who respond to community advertisements or referrals via telephone. The template is scripted to ensure that the necessary information is exchanged, but will be flexibly applied in a conversational manner. It is essential for recruiting staff members to be flexible and to use a motivational enhancement approach when communicating with adolescents and their families. This includes showing empathy and being non-judgmental and positive at all times.

7.2.1 Minority Recruitment.

Usual CTP referral sources often under-represent ethnic minorities due to national health care disparities in treatment access. The community based recruitment strategy utilized in this protocol to augment usual CTP referral sources will enable over-recruitment of ethnic minority participation. Individual CTPs will also make efforts to over recruit minority subject participants from the community by using the above recruitment strategies. These efforts will be augmented through special recruitment efforts from local alternative schools servicing special populations, schools in lower income areas, Boys' and Girls' clubs, African American and other ethnic churches, and public health clinics. Additional effort will be made to recruit study participants from inner city schools, local alternative schools servicing special populations, schools in lower income areas, Boy's and Girl's clubs, African American and other ethnic churches and to establish recruitment relationships/linkages with local churches and primary care providers that specifically serve minority populations. The goal will be to recruit a sample of study participants that reflect the proportion of minorities in the community where the CTP is located.

7.3 Screening, Baseline Assessments, Informed Consent Procedures.

Preliminary eligibility will be assessed with a brief pre-screening interview. Assessment of ADHD symptoms described in the ASRS will be utilized to identify potential candidates for the study. Research staff will provide further study information and pre-screening assessment to those adolescents endorsing ADHD symptoms. Adolescents who indicate ADHD symptoms and Substance abuse or dependence and show interest in the study will be offered the opportunity to provide informed assent/consent and further screening for study eligibility.

Following informed assent/consent, ideally, the screening/baseline procedures will be completed in two visits but they can be completed in fewer visits or more visits if necessary. Typically, the screening/baseline procedures will be completed within a one-week time-frame. Participants who meet study criteria and complete baseline assessments will be eligible for randomization to either OROS-MPH/Concerta or matching placebo. The allowable time for completion of screening/baseline procedures and randomization is within 30 days of signing consent.

7.4 Randomization.

OROS-MPH and matching placebo will be provided by McNeil Consumer and Specialty Pharmaceuticals and delivered to the NIDA contractor. A permuted block within CTP randomization scheme will be utilized. The NIDA contractor will be responsible for randomizing successive study participants within CTP to either OROS-MPH or placebo. Blinded study medication supplies will be provided to each participating CTP.

7.5 16-Week Study Phase.

During the 16-week placebo-controlled phase, participants will participate in weekly research visits to assess adverse side effects and target symptom response (see Table 2 for schedule of assessments). After randomization, visits will be scheduled as outlined in Table 2. CBT sessions and research visits will be scheduled to run within the visit window. Research visits will be scheduled to coincide with adolescents' weekly

CBT sessions, if at all possible, and performed by a qualified MC or RA. Although medication and research assessment visits and CBT sessions are closely coordinated in terms of scheduling to enhance study feasibility by requiring only one weekly clinic visit, care should be taken to avoid overlap of therapy content/process with research assessments. For example, the DSM IV checklist should never be administered in the context of a CBT session and questions regarding medication (e.g. dosing; adverse side effects) that might arise in the context of a CBT session should be referred to the MC or SP for response).

7.6 One Month Follow-Up.

The follow-up visit will be conducted at approximately one month after the final medication visit (week 16 visit). The measures to be collected during this visit are delineated in Table 2. There will be a 28-day timeframe in which to complete the follow-up visit. The primary purpose of the follow-up visit is to obtain safety measures and to assess the participant's treatment and substance use status. Participants are paid 25 dollars for completing the follow up visit.

7.7 Participant Reimbursement.

Participants will be reimbursed for their transportation, inconvenience, and time. Study participants will be reimbursed a total of \$50 for the screening/baseline assessment procedures; \$25 (\$20 for the visit; \$5 additional for remembering to bring in the medication diary and bottle/medication for tablet counts) for completing the research visits during weeks 1-15 of the study; \$35 (\$30 for the visit; \$5 additional for remembering to bring in the medication diary and bottle for tablet counts) for completing the final research visit (week 16), due to the increased length of the visit; and \$25 for completing the follow-up visit.

7.8 Medication and Trial Discontinuation

7.8.1 Medication Discontinuation.

An investigator may discontinue a participant's medication (without breaking the blind unless the conditions stated in section 8.4 are met) if he or she deems it clinically appropriate or, at the discretion of the investigator, for any of the reasons listed below.

1. significant side effects from the investigational agents
2. serious or unexpected AEs which would make further study medication dosing dangerous and/or otherwise not in the participant's best interest
3. inability or unwillingness of the participant to comply with the study protocol
4. serious inter-current illness
5. clinically significant out of range laboratory values
6. development of symptoms of cardiac disease

Unless consent /assent is withdrawn by the participant and/or their parent guardian, participants will be strongly encouraged to continue attending CBT sessions and weekly scheduled visits at which safety and outcome measures are assessed. If the study medication is discontinued by the study physician for safety reasons, participants will be

similarly encouraged to continue participation in CBT and weekly scheduled research assessment visits.

Whenever a study participant stops coming to the clinic without notification, staff will make a concerted effort to contact the participant (or the designated contact person if the participant cannot be contacted) to assure that they have had no untoward effects from study participation and to encourage ongoing study participation.

Table 3: Concerta Dose Escalation

DAY	OROS-MPH Dose	# of Pills (OROS-MPH or Placebo QAM)
1	0	0
2	18	1
3	18	1
4	18	1
5	36	2
6	36	2
7	36	2
8	54	3
9	54	3
10	54	3
11	54	3
12	54	3
13	54	3
14	54	3
15	72	4
16	72	4
17	72	4
18	72	4
19	72	4
20	72	4
21	72	4
22	72	4

Study participants withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Clinical information may be released to the referred health care providers or other agents with (and only with) specific written participant consent to release the information. Study staff may request transportation for emergency treatment of a participant if medically appropriate (e.g., for acutely psychotic or suicidal participants).

7.8.2 Trial Discontinuation.

The study sponsor, NIDA, has the right to discontinue the investigation at any time.

8.0 INVESTIGATIONAL AGENT

8.1 Active Medication Group.

OROS-MPH is an extended-release tablet for once-a-day oral administration designed to have a 12-hour duration of effect. Tablets containing 18 mg of methylphenidate HCl USP will be used for this study. Chemically, methylphenidate HCl is d,l (racemic) methyl α -phenyl-2-piperidineacetate hydrochloride. Its empirical formula is C₁₄H₁₉NO₂•HCl.

Methylphenidate HCl USP is a white, odorless crystalline powder. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Concerta™ is the marketed trade name of OROS-MPH and is manufactured by the Alza Corporation and marketed by McNeil Consumer and Specialty Pharmaceuticals. The medication will be **titrated** to therapeutic dose over the first month of study participation. The participant will be instructed to begin taking the medication in the morning of the day after randomization. A forced titration dosing strategy will be used starting with 18 mg/day OROS-MPH/placebo for 3 days, increasing to 36mg/day for the next three days; increasing to 54 mg/day in week two, and to 72 mg/day in week three through the remainder of the study (as tolerated) (see Table 3). Dosage may be

decreased to the previous dosing level at the discretion of the SP in consultation with the MC, if the participant is not tolerating the target dose.

8.2 Placebo Control.

As previously described, matching placebo will be titrated and monitored in the same way that the active medication group is monitored.

8.3 Dispensing Investigational Agents.

During the week 1 visit, a two-week supply of OROS-MPH or matching placebo will be prescribed and dispensed for daily self-administration during weeks 1 and 2; each week's supply will be packaged separately. In the week 2 visit, and each successive visit through the week 15 visit, the following week's OROS-MPH will be dispensed. This procedure will provide the participant with enough extra medication at all times to account for holidays or missed visits, while keeping waste and confusion to a minimum.

8.4 Blinding & Breaking the Blind.

With the sole exception of the NIDA contract research pharmacist, all other study personnel and participants will remain blinded to medication status until completion of the trial, nationwide.

In rare cases it may be necessary to break the blind for a particular study participant before completion of the trial (e.g. medical emergency). The decision to break the study blind for an individual participant should be made by the site PI or site SP after consultation with the Lead Investigator if possible, and should be resorted to only in cases of life-threatening emergency when knowledge of the treatment group investigational agent may be important to good clinical management and decision making. Instances of breaking the blind must be communicated to the Lead Investigator/Co-lead Investigator within 24 hours of the break.

8.5 Packaging and Labeling.

The product will be supplied in pre-randomized kits, containing individual bottles. Each kit and bottle will be labeled with the protocol number and treatment/randomization number. Labeling will protect the study blind and indicate that the medication is investigational.

8.6 Storage.

Investigational agents will be stored in compliance with federal law, state law and institutional policy.

8.7 Record of Administration.

Inventory will be maintained on a per participant basis until the participant has completed or terminated from the study. Each site will identify those persons responsible for handling, dispensing and accounting for the medications. That/Those person(s) will record the number of tablets dispensed to an individual and accurately account for the remaining tablets. If the drug is dispensed to the MC or designee, that individual will verify the number of tablets received and record the date received in the

study documentation. Accurate recording of all investigational agents dispensed/administered will be made in the appropriate sections of the Drug Accountability Log.

8.8 Used/Unused Supplies.

Empty, partially used, and unused bottles of investigational agent will be recorded on the participant drug accountability logs. Partially used and unused bottles will be returned to the pharmacy (or other appropriately licensed entity). Inventory will be maintained by participant until the participant has completed or terminated from the study.

8.9 Side Effects of OROS-MPH

The most frequent adverse effects of methylphenidate appear to be dose related and include nervousness and insomnia. Other adverse effects include anorexia, nausea, abdominal pain, dryness of the throat, dizziness, syncope, palpitation, headache, akathisia, dyskinesia and drowsiness, and insomnia. Angina, tachycardia, cardiac arrhythmias, and changes in blood pressure or pulse may also occur.

Hypersensitivity reactions including rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme and thrombocytopenic purpura.

Toxic psychosis and Tourette's disorder have been reported rarely. Neuroleptic malignant syndrome (NMS) has been reported rarely and it is usually when methylphenidate is used in combination with other drugs associated with NMS.

Treatment emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses.

Sudden death has been reported in association with CNS stimulant treatment as usual in children and adolescents with structural cardiac abnormalities or other serious heart problems.

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. Other rare adverse events include hepatotoxicity, thrombocytopenia, epistaxis, gingival bleeding, leukopenia, anemia, eosinophilia, transiently depressed mood and hair loss.

Adverse side effects will be monitored on a weekly basis by the MC. In rare instances when the MC is not available to perform weekly medication follow up visits, the RA may perform these assessments with alternate MC (either provided locally or by the national team) back up by teleconference to oversee and provide real time supervision during the visit.

8.10 Concomitant Medications.

Any medication (including prescription, over-the-counter medications, herbal supplements and health store products) taken the month prior to study entry, at screening/baseline or to be started/taken during the study ideally must be approved by a qualified onsite MC and will be recorded at screening/baseline and all research visits.

Participants may not participate in the study (exclusion criteria) if they require other medications with psychoactive properties and/or including the following:

- Monoamine oxidase inhibitors (isocarboxazid, phenelzine, selegiline, tranylcypromine) which may increase plasma concentrations of methylphenidate.
- Centrally acting antihypertensive agent (guanadrel, methyldopa, clonidine) effects may be diminished by methylphenidate.
- Inhibitors of CYP2D6—amiodarone, chlorpheniramine, cimetidine, clomipramine, fluoxetine, haloperidol, methadone, paroxetine, quinidine and ritanovir.
- Antibiotics with MAO-inhibiting activity—linezolid.
- Neuroleptic malignant syndrome (NMS) has been reported in patients receiving methylphenidate and venlafaxine.
- Phenytoin, phenobarbital, tricyclic antidepressants, and warfarin—levels of which can be increased by methylphenidate
- Sympathomimetics, including yohimbine, sibutramine, and pseudoephedrine.

9.0 Cognitive Behavioral Therapy (CBT)

9.1 Introduction.

For the duration of the 16-week controlled medication trial study participants will receive manualized weekly CBT as the standardized psychosocial treatment for substance use disorders to enable the study to determine the impact of pharmacotherapy for ADHD on drug treatment outcomes. The CBT manual that will be used in this study is based on the work of Dr. Holly Waldron and colleagues at the University of New Mexico Center for Family Studies. Dr. Waldron's manual was developmentally adapted for adolescents from a standard, published, empirically supported adult CBT manual (Kadden et al., 1995; Monti et al., 1989). This version is empirically supported by published results from several studies (Lohman et al., 2002; Riggs, 2004; Waldron et al., 2001). In addition, Dr. Waldron consulted on the adaptation of the manual as a 16-week intervention to correspond with the length of a recently completed randomized controlled trial of fluoxetine vs. placebo in depressed substance dependent adolescents (N=126) (Riggs, 2004).

The use of CBT as a background treatment in this study is designed to sufficiently standardize psychosocial treatment across CTPs to enable internal validity of drug treatment outcomes measures and to allow for meaningful interpretation of results. Just prior to completing the 16-week trial, study participants will be evaluated by CTP clinical staff at the CTP and referred to ongoing TAU or continuing care/community treatment services as is clinically indicated.

9.2 Overview of the Manualized CBT.

The therapy begins with a goal setting exercise during which the participant identifies short-term goals and specific objectives to meet these. In addition, the participant is asked to identify who can support the completion of these goals as well as potential barriers. During this session, the therapist works to increase engagement through motivational enhancement strategies. These interventions will be guided by the participant's readiness to change. Participants will complete the University of Rhode Island Change Assessment Scale (URICA) at screening/baseline and at the final visit.

Following goal setting, the therapist leads a *functional analysis (FA)* during which the participant identifies external and internal triggers for their use and examines the short-term positive consequences and long-term negative consequences of using each substance. This is done carefully over the course of one to two sessions in order to promote full engagement with the participant. (A separate FA is done for each substance for which there is dependence). The process establishes a baseline for stage of change and, in some cases, enhances readiness to change providing an open dialogue for decisional balance exercises (Velasquez et al., 2001). By identifying past, current and future reinforcers, patients become "experts" about their own problem enhancing self efficacy from the beginning.

After the FA, in individual CBT sessions/modules, adolescents are taught skills to manage cravings, to avoid high risk situations, to use refusal methods, and to find peers and activities incompatible with drug use. Life skills such as communication, problem solving, job seeking and education, and social support networks are taught and practiced so that they can be applied to different domains, i.e. home, school/work, and interpersonal relationships.

A module on HIV prevention incorporates a functional analysis on risk behaviors associated with HIV/AIDS and other STD's. During this session, participants will identify their triggers for unsafe practices and develop plans for safe behavior in high-risk situations.

Sessions are approximately 45 minutes to an hour in length. Following the 20/20/20 or Thirds Rule, the sessions are ideally structured such that the first third of the session includes a "check in" with a thorough review of the skills taught in the previous session and discussion of the homework assignment, the second third is the introduction and teaching of a new skill providing a rationale for why it was chosen and the final third involves the clinician and participant practicing the new skill together, typically role plays, and then assigning a homework practice. The in-session and at-home practice are central to the skills-training program as these are the main strategies by which the clients acquire new skills. Adherence to these critical elements in each session will be monitored closely during the supervision process (see section 9.4.4 below).

9.3 CBT Clinician Selection.

The educational background, credentials, and experience of the clinical staff implementing the intervention will vary between CTPs. The term "clinician" as used in the present protocol does not imply a particular educational background or

credentialing. Rather, it is used as a short-hand term to refer to the clinical staff members administering the treatment.

Clinician Inclusion Criteria:

- Masters or Bachelors level therapist/counselors with at least 2 years' experience working with adolescents with substance abuse
- Willingness/commitment to learn CBT and comply with supervision requirements and adherence to competency ratings as per the protocol.
- Willingness to be audio recorded for supervision purposes and to participate in all aspects of supervision and remediation of skills as per protocol, if necessary.

9.4 CBT Clinician Training and Supervision

9.4.1 Training Model.

The present study will utilize a centralized training and supervision model.

9.4.2 Clinician Training.

An expert, certified CBT Trainer/Supervisors, will train CTP clinicians. This training will be completed using one of two forums:

9.4.2.1 Initial Training.

A CBT Trainer will conduct the approximately 3.5 day clinician training, followed by approximately 1.5 days for certification (Section 9.4.3.1). At least two clinicians from each participating CTP will ideally complete this training. Goals for this training include: 1) ensure the consistency of training protocols across Nodes and CTPs; 2) develop local CBT expertise within the CTPs; 3) prepare to complete certification requirements for CBT therapists; and 4) provide accessible training resources in the event that CTP therapist turnover requires training of new staff. The centralized training will focus on the review of the CBT Training Manual and implementation of a common training curriculum.

9.4.2.2 Training Replacement CBT Clinicians.

Power point presentation(s) will be given during the initial training. Replacement CBT Clinicians will be provided with the power point presentation(s) and manuals from the training. These materials will be supplemented with training provided by a CBT Trainer via teleconference. The success of the training will be reflected by the ability of the CBT Clinician to meet certification requirements (see below). Should a CBT clinician fail to meet certification requirements, face-to-face training could be provided as needed.

9.4.3 Clinician Certification.

As noted in section 9.4.2, training will be completed using one of two forums. The certification process utilized for a given clinician depends upon the forum in which s/he was trained.

9.4.3.1 Certification Associated with Initial Training.

Clinicians trained during initial training will ideally complete the certification immediately following training. Following the training, clinicians will participate in approximately 1.5

days of live interviews with “mock” patients to evaluate delivery of particular modules. Trainers will provide written feedback on strengths and areas for continued practice with specific ratings on key training objectives (approximately 15 items, using a 1-5 Likert scale, “not at all” to “extensively”). In addition, clinicians will be given a post-training test to demonstrate knowledge of key cognitive and behavioral principles and how to integrate these in a substance use treatment as well as familiarity with the skills modules. To be certified, clinicians need to pass the post-training test ($\geq 80\%$ accuracy) and receive, at minimum, an average rating of 3 across all training objectives. If these criteria are achieved then the clinician is certified as CBT proficient after which s/he may accept randomized participants.

Clinicians who do not meet certification requirements during the centralized training will participate by phone in a remedial training period with the CBT Trainer to take place immediately following the training and certification program. Specific areas of deficiency will be addressed through additional follow-up phone sessions with targeted learning objectives assigned by the supervisor. This remedial period will last until the clinician has demonstrated a thorough understanding of the deficient components by obtaining the required rating of 3 across all training objectives and passing the post-training test $\geq 80\%$. After that time the clinician will be ready to accept CBT cases.

9.4.3.2 Certification Associated with Training Replacement Clinicians.

Clinicians who join the study after the initial training will be certified by the CBT Protocol supervisor through the following process. After completing the training requirements onsite at the CTP (see section 9.4.2), the clinician will perform goal setting and functional analysis sessions (each approximately 45 minutes) with a “mock” patient (ideally an adolescent, but could be a staff member) at the CTP. These sessions will be audio recorded and then sent to a CBT Trainer/Supervisor for review. The CBT Trainer/Supervisor will rate and provide written feedback using the same training objectives and rating scale (approximately 15 items) used in the centralized training (see section 9.4.2). At a minimum, the clinician needs to obtain an average rating of 3 across all training objectives. They will also be expected to take the post-training test and obtain $\geq 80\%$ accuracy on this test. If these criteria are achieved then the clinician is certified as CBT proficient after which they may accept randomized participants. If proficiency is not obtained, the CBT Supervisor will continue to provide phone supervision addressing the specific areas of deficiency as indicated by the tape reviews. Supervisees will be asked to listen and/or view training tapes and to produce an additional audio recorded session with a mock patient covering skills in that area of deficiency.

9.4.4 Ongoing Clinician Supervision and Training.

Consistent with a centralized model of training and supervision, the Lead Team expert CBT trainers/supervisors will have primary responsibility for supervising the clinicians' implementation of the CBT manual. It is expected that the CBT Trainer/Supervisors typically will have a teleconference with the clinicians for group supervision on a monthly basis, contingent upon the clinicians having active cases to discuss. The Trainer/Supervisor may provide individual supervision at his/her discretion. The supervision

sessions will include a review of audio recorded sessions including strengths and deficits of the sessions.

Within each site, local CBT clinicians will meet up to 4 times per month for peer supervision. During peer supervision the clinicians will review the status of their cases, discuss specific issues related to the manualized treatment, and prepare agenda items for teleconferences with the Protocol CBT supervisor.

An attempt will be made to audio record every CBT session. Audio recordings will be randomly selected to be rated by a Trainer/supervisor (see section 9.4.5).

9.4.5 Quality Control of CBT Administered.

To ensure fidelity with the manualized treatment, a CBT Trainer/Supervisor will rate randomly-selected audio records throughout the study. An algorithm for tape selection will be followed to simplify this process and to prevent overburdening clinical staff. Ratings should be done concurrent with treatment whenever possible in order to catch any serious drifting from the manualized therapy so that specific problems can be addressed. If a clinician falls below minimum criteria, additional supervision will be provided to the CBT clinician by the CBT Trainer/Supervisor, which will include the review of extra audio records. The supervisor and CBT clinician would together determine a suitable plan and schedule for extra supervision giving attention to the specific problems identified. This one-to-one supervision would continue until the clinician is at or above criteria on all specified problem areas.

10.0 ANALYTICAL PLAN

10.1 Statistical Hypotheses

10.1.1 Primary Hypotheses.

There are two hypotheses associated with the primary study objectives:

- 1) In adolescents with ADHD and SUD, OROS-MPH treatment, compared to placebo, will result in greater reduction of ADHD symptoms, as measured by the DSM-IV ADHD Symptom Checklist (continuous variable).
- 2) In adolescents with ADHD and SUD, OROS-MPH treatment, compared to placebo, will result in greater reduction in number of days of substance use, as measured with the TLFB (continuous variable).

10.1.2 Secondary Hypotheses.

It is hypothesized that:

- 1) OROS-MPH will be safe for treating ADHD in adolescents with SUD as determined by the lack of clinically significant differences in vital signs and AE/SAE frequency between the OROS-MPH and placebo groups.

- 2) In adolescents with ADHD and SUD, participant ratings of liking the study medication for the high, as measured by the MGH liking scale (continuous variable), will not differ significantly between the OROS-MPH and placebo groups.
- 3) In adolescents with ADHD and SUD, OROS-MPH treatment, compared to placebo, will result in greater treatment compliance, as measured by the proportion of CBT and research visits attended (continuous variables).
- 4) In adolescents with ADHD and SUD, those treated with OROS-MPH compared to placebo, will have less drug use, as determined by having a greater proportion of negative urine drug screens (continuous variable)
- 5) In adolescents with ADHD and SUD, OROS-MPH treatment, compared to placebo, will result in improved psychosocial functioning, as measured by the CGAS and CHQ-CF80 (both continuous variables).

10.1.3 Tertiary Analyses.

1. Exploratory analyses will be conducted to assess whether specific participant characteristics are predictors of treatment response (differential treatment (e.g. gender; ethnicity; substance severity; comorbidity; court-mandated vs non-court mandated)
2. Exploratory analyses will be conducted to determine whether treatment outcomes differ across participating sites based on specific CTP characteristics (e.g., rural vs. urban; private vs. public, etc.).
3. Exploratory analyses will be conducted to evaluate the convergent validity between the parent and adolescent reports of ADHD symptoms.

10.2 ANALYTIC OVERVIEW

10.2.1 Testing of Distributional Assumptions.

Empirical distributions of all variables will be visually inspected. Prior to performing analyses addressing the primary and secondary hypotheses, data will be screened for (1) entry errors, (2) outliers, (3) the extent and pattern of missingness. The underlying proposed statistical methods for each analysis will be examined, primarily through inspection of graphical displays, standardized residuals, and influence diagnostics. Where appropriate, transformations will be utilized to account for extreme values or analyses will be performed utilizing more appropriate non-normal data distribution assumptions such as the Poisson, or zero inflated Poisson (Muthén and Muthén, 1998-2004). Although a trial should not be unduly influenced by a single observation, deleting data violates the intent to treat principle and makes it difficult to generalize and interpret trial results. Should the aforementioned measures not be sufficient to minimize the influence of particular observations, a sensitivity analysis assessing results of redoing the primary analysis after deleting each participant one at a time will be conducted. If results differ when outlying values are deleted, this will be reported as a secondary analysis and implications for the trial interpretation will be discussed.

10.2.2 Randomization.

Preliminary analyses will validate that our permuted block within CTP randomization scheme (i.e. CTP is the only stratification factor) is successful, i.e. there are no baseline differences in ADHD severity, drug use, and demographics between the placebo and OROS-MPH groups and across CTPs. Although we expect that baseline differences will be accounted for by randomization, some differences may remain. Due to potential interpretation problems that may occur when inclusion of covariates are based on a test of baseline balance (Beach and Meier, 1989), seven potentially important covariates will be used as control variables on an a-priori basis for all hypotheses: (i) gender; (ii) age; (iii) meet DSM-IV criteria for conduct disorder (CD) vs. no CD; (iv) severity of substance abuse/dependence; (v) court-ordered vs. not-court mandated; (vi) initial ADHD symptom level; and (vii) site of recruitment.

10.2.3 Missing Data and Attrition.

Missing data are a serious problem with no adequate statistical solutions. The problem with all of the statistical approaches to missing data is that they require assumptions about the reasons why the data are missing which are not testable. It is difficult to know how to handle missing data and whether or not it threatens trial validity because the true causes of missing data are unknown.

Missing data will be managed in a variety of ways and sensitivity analyses will be performed to determine the effects of missing data on the inferences regarding the outcome of the primary hypotheses. These sensitivity analyses are secondary to the planned intention-to-treat analysis as described below in section 10.3. The pattern of participant dropout will be examined to ensure a reasonably equal distribution of participants lost to follow-up across a variety of baseline measures including clinic site, ADHD and substance use severity, and demographic variables. Primary analyses on the intent-to-treat sample will evaluate results utilizing various strategies for handling missing data. The linear mixed effects models proposed in Section 10.3.1 employ maximum likelihood techniques of parameter estimation that can utilize participants with incomplete data, avoiding the potential bias caused by list wise deletion. These techniques are robust under conditions of missing completely at random (MCAR) and missing at random (MAR) and therefore, the comparisons of experimental groups will not be biased as long as missing data is ignorable (Laird, 1988). To allow for the possibility of non-ignorable dropout, pattern-mixture models will be evaluated (Little, 1993). Secondly, analyses of participants who complete the study will be conducted and compared with the principal intent-to-treat results.

10.3 Analytic Strategy.

The primary analytic strategy will be intent-to-treat (ITT), including all randomized participants in analyses of primary and secondary outcome measures.

10.3.1 Linear Mixed Model Growth Curve Analyses.

All of the primary and secondary outcome measures, with the exception of the safety measures, will be assessed with the same general design: a two group (OROS-MPH and placebo) mixed-model growth curve analysis where baseline characteristics

including clinic site and a clinic site by treatment interaction will be included in the model as covariates. Note that if the clinic site by treatment interaction is not significant at the .05 level, this term will be dropped from the analysis and the test of the main hypothesis will be from a model not including this interaction. Two-tailed tests with alpha level of 0.05 are conservatively proposed in order to detect differences between groups in either direction. The method proposed by Hochberg (1988) will be used to adjust for multiple comparisons. Initial blinded examination of the data will determine the appropriate functional form (the number of polynomial terms in time) and the importance of including the control covariates (see section 10.2.2). In addition, in the blinded analysis phase it will be determined if the individual outcome variable or a suitable transformation is sufficiently approximated by the normal distribution. If it is not, appropriate modifications to the analysis strategy will be made (e.g. Poisson, zero-inflated Poisson or non-parametric methods).

Mixed model growth curves, also frequently called hierarchical linear modeling by some (Raudenbush and Bryk, 2002) conceptualize the growth curve as separate equations for the intercept and another equation or other equations (if more than linear change is examined) for the slope, though both (all) are estimated jointly. As noted above, prior to testing hypotheses, in an analysis blind to condition, we will fit this model with additional polynomial terms for measures with more than 3 post-baseline observations such as urine toxicology or ADHD symptoms. If any of the random components, or polynomial terms is not significantly different from zero, we will drop them from the model. To facilitate interpretation of the growth curve, time will be centered on the 4-month post-randomization assessment (T4). Thus, the intercept term represents the difference between the two conditions immediately post intervention. If the expected ordinal nature of the outcome measure results in sufficient deviation from normality a log transformation or Poisson link function will be used.

10.3.1.1 Level 1.

For each hypothesis, the outcome measure will be estimated for the appropriate time period (based on frequency of assessment) and the growth trajectory will be parameterized to be a function of OROS-MPH intervention status. Additional predictors will be effect-coded indicators for the participating sites, the site by treatment interaction and the six control variables, described under the heading randomization (see section 10.2.2). The growth curve analysis will include the times after screening/baseline only, and baseline value of the dependent measure will be included as a covariate (i.e. an analysis of covariance parameterization). The presentation below uses vector notation for the Site, Site by Treatment interaction and Control variable effects to simplify the equations. We will use the multi-level model approach to presenting the equations to be estimated in this model:

Level 1:

$$y_{it} = \pi_{i0} + \pi_{i1} \cdot a_{it} + \varepsilon_{it} ,$$

where y_{ijt} , a_{ijt} , and ε_{ijt} , are the outcome measure, time, and a random (or error) term, respectively, for person i , in CTP j , at observation occasion t . The variable a_{ijt} will be

measured as time from assessment point (T4), which occurs four months post randomization. The variables π_{ij0} and π_{ij1} are the intercept and slope of the outcome measure, respectively for person i , in CTP j . Note that by centering the time variable, a_{ijt} , at the last time point, the intercept parameter refers to level of the outcome measure at the end of the intervention.

10.3.1.2 Level 2.

The Level 2 model describes the individual intercept, π_{ij0} , and the individual slope term, π_{ij1} as a function of *OROS-MPH*:

Level 2:

$$\pi_{i0} = \beta_{00} + \beta_{10}(\text{OROS} - \text{MPH}) + \beta_{20}\text{Sites} + \beta_{30}(\text{Site X OROS}) + \beta_{40}\text{Controls} + r_{i0},$$

$$\pi_{i1} = \beta_{01} + \beta_{11}(\text{OROS} - \text{MPH}) + \beta_{21}\text{Sites} + \beta_{31}(\text{Site X OROS}) + \beta_{41}\text{Controls} + r_{i1}.$$

The *OROS-MPH* variable is a 0-1 or dummy-coded variable that is coded 1 if the participant is receiving *OROS-MPH*, and 0 otherwise. Given this coding of the *OROS-MPH* variables, β_{00} and β_{01} are the intercept and slope, respectively, for participants who are in the placebo condition. The parameters, β_{10} and β_{11} , are the increments to the intercept and slope of the placebo participants, (β_{00} and β_{01} , respectively), for participants receiving *OROS-MPH* (i.e. intercept for *OROS-MPH* = $\beta_{00} + \beta_{10}$ and slope for *OROS-MPH* = $\beta_{01} + \beta_{11}$). Finally, r_{i0} and r_{i1} are person-specific random terms for the intercept and slope.

10.3.1.3 Test of Hypothesis.

The primary test of a given hypothesis is a test of the significance on the coefficients on the *OROS-MPH* term alone from the intercept equation— β_{10} . Recall that because of the centering of the time term at the end of the study, the intercept term is the level of an outcome measure post-intervention, so β_{10} is the decrement (or increment) in the outcome measure for participants who were randomized to *OROS-MPH* relative to those randomized to placebo. Please note that this model may be estimated twice per hypothesis. In the first form, the Site by Treatment interaction will be examined for statistical significance. If the interaction is not significant at the .05 level, this term will be dropped and the model re-estimated. The estimate of β_{10} from this second specification will be used for the test of the hypothesis. Please note that the primary test of the hypotheses is from the covariate adjusted analyses.

10.3.1.4 Advantages of the Statistical Model.

There are several advantages to this approach. First, in the test here, a_{ijt} is the time since T4 (approximately 4 months post-randomization). Thus, assessments are not required to be at the same or at equally spaced intervals across individuals. Second, these equations, as presented, assume a linear growth curve, if there is evidence of quadratic trends in the outcome, these will also be modeled, but they are omitted here

for ease of exposition. Third, all available data will be included in the test of the hypothesis. It is not necessary to drop any participant just because they missed a particular assessment. The within subjects growth curve model will incorporate all available data for each participant to facilitate the intent-to-treat analyses.

10.3.2 Other Analyses

10.3.2.1 Safety Analyses.

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group. The incidence of adverse events and serious adverse events by type will be compared between treatment arms using either Fisher's Exact Test or Chi-Square analysis as appropriate; and (2) a table displaying the total number of each event will be given overall and by treatment group. Similar summary tables of serious adverse events will also be provided. Listings of serious adverse events will be given, sorted by body system, preferred term, and treatment. Detail in these listings will include severity, relationship to study drug, and action taken as available.

10.3.2.2 Exploratory Analysis of Differential Treatment Response.

In addition to the planned tests of hypotheses, exploratory analyses of **differential treatment response** based on specific participant characteristics (e.g. gender; ethnicity; substance severity; comorbidity) and/or CTP characteristics (e.g. rural; inner city)) will be conducted. These analyses are easily conducted within the study's analytic strategy by including these variables as well as the interaction of these variables and treatment assignment as predictors in the intercept and slope equations described in Section 10.3.1.2 Level 2.

10.4 Sample Size Estimate.

The number of participants targeted for randomization nationally- across all participating sites- is 300 participants (150 per treatment arm). These numbers provide more than adequate power (>99%) to evaluate the safety and efficacy of OROS-MPH/Concerta compared to placebo on ADHD but are necessary to evaluate the impact of pharmacotherapy (for ADHD) on substance treatment outcomes. The effect size of OROS-MPH/Concerta on ADHD has consistently been shown to be large (>.8), but the effect size on substance treatment outcomes is unknown. Since the potential effect size of pharmacotherapy for ADHD on substance treatment outcomes is not known, we powered the study to detect the lower limit of a clinically meaningful effect size, deemed to be .4 (low to medium effect size). Power is calculated using a procedure and computer program described in Hedecker, Gibbons & Waternaux (1999). Assuming as much as 10% attrition per month (which is much higher than anticipated given prior studies), there will be over 90% power to uncover a treatment difference at treatment termination of .40. To get an idea of the changes these effect sizes imply, consider that a recent estimate of the mean of pre-treatment DSM IV ADHD symptom score was 31.6 with an S.D. of 9.4. Thus, with an effect size of .8 we would expect a decline in ADHD

score to approximately 24, or very near the clinical cut-off of 22 for scores indicative of a diagnosis. Note that the observed effect size in prior trials has been much greater than this and we anticipate the realized mean change in this trial to be larger and reflect a movement below the clinical cutoff. For days of drug use, a recent estimate of the mean pre-treatment number of days of drug use (out of 30) for a non-ADHD sample was 6.5 with a .4 effect size implying a mean decrease to 3.5 drug use days.

10.5 Descriptive Statistics.

Summaries of the characteristics of the participant population in both treatment arms at screening/baseline will be prepared. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatments and for major subgroups. Weekly treatment compliance of each group will be summarized. All adverse events will be reported in tabular form indicating the frequency and severity of each type of event.

10.6 Interim Analyses.

An interim analysis to examine whether there is overwhelming evidence that one treatment is better or worse than the other (e.g., OROS-MPH/Concerta is significantly better than placebo) is determined to be unnecessary for the present protocol. This determination is primarily based on the fact that the outcome of interest, substance use, will be indirectly impacted by the experimental treatment (i.e., OROS-MPH/Concerta will treat ADHD and the relief of ADHD symptoms should make substance use reduction easier). Consequently, whereas we expect to find a significant and clinically meaningful effect for OROS-MPH in reducing substance use, we do not expect to find overwhelming evidence of OROS-MPH's benefits in this regard. Furthermore, because of the relatively short duration of the protocol over 3/4 of the proposed sample size would have accrued before the data could be prepared and the interim analyses completed.

10.7 Post-hoc Analyses.

In addition to the analyses described above, a number of post-hoc analyses will be completed. Some examples of possible analyses include an exploration of participant screening/baseline variables that are predictive of treatment outcome and of site characteristics associated with treatment outcome.

11.0 REGULATORY AND REPORTING REQUIREMENTS

11.1 IRB Approval.

Prior to initiating the study, the Investigator at each study site will obtain written Institutional Review Board (IRB) approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to each IRB for approval prior to implementation. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

11.2 Informed Consent/Assent.

Each study site must have the study informed consent/assent approved by their local IRB(s). A copy of the IRB approved consent/assent along with the IRB study approval must be sent to NIDA and the Lead Team (LT) prior to the site initiation visit. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent/assent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent/assent for every participant in a locked, secure location that is in compliance with their IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent/assent form.

Prior to signing the informed consent/assent form, research staff knowledgeable about the study and trained in properly obtaining informed consent will explain the study to the potential participant. If the potential participant is interested in participating in the study, a researcher (who is authorized to obtain informed consent/assent by the PI and, if applicable, by the IRB) will review each section of the informed consent/assent form in detail, and answer any of the participant's questions.

A study specific Comprehension Tool will be administered to the potential participant to further insure and document understanding of study components and procedures. Potential participants must score 100% to be eligible for the study. Any item missed on the quiz will be reviewed and explained until it is understood. If the person explaining the consent determines that the potential participant is not competent to provide informed consent, the consent process stops.

Informed assent will be obtained from adolescents (ages 13 to 17 inclusive) and consent from a parent or legally authorized parent figure/guardian for that adolescent to participate in the study. Informed consent will be obtained from adolescents age 18 and from legally emancipated adolescents under age 18.

The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document. The consent /assent must be properly executed and complete to be valid. The protocol PI or qualified designee will review the consent/assent after it is signed to ensure that the consent/assent is properly executed and complete. Adolescents (age 13 to 17 inclusive) will only be included in the study if they assent and their parent/legal guardian consent. Adolescents (age 13 to 17 inclusive) who do not wish to assent will not be included in the study, regardless of their parent/legal guardians wishes. Persons delegated by the PI to obtain informed consent/assent must be listed on the Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

11.3 Clinical Monitoring

11.3.1 Study Medical Monitors.

Each of the CTPs participating in this study has established agency practices for managing medical and psychiatric emergencies, and the study staff will be trained to utilize these procedures. Study Clinicians as designated by the Local Protocol Principal Investigator for each participating site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for recommending appropriate responses.

The LI has appointed a medical monitor for this study, who will review or provide consultation for each SAE. These reviews will include an assessment of the seriousness and possible relatedness of the Event to the study intervention or other study procedures. The medical monitor will also provide consultation for decisions to exclude, refer, or withdraw participants for medical reasons. For any adverse event that is related to the study, a designated study clinician will ensure that adequate medical care is provided to the participant until the event is resolved. In addition, NIDA will appoint a medical safety officer (MSO) to this study to independently review the safety data, present it to the DSMB for periodic review, and provide LIs with summary reports of SAEs, or a Safety Letter when necessary. The study staff will be trained to identify, assess, document and report adverse events and SAEs.

11.3.2 Node Protocol Managers.

Protocol Management visits will be conducted at each site by qualified node personnel before, during, and at the close of the trial. These visits will take place at least as frequently as specified in the Protocol Management and Oversight Plan for this protocol and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Protocol Managers will assist the site in preparations of all regulatory documentation per CTN guidelines as needed, assure that study procedures are properly followed and that data CRFs are complete, accurate, and in agreement with source documentation. Protocol Managers will also ensure that all essential documentation required by Good Clinical Practice guidelines is present and appropriately filed. If the manager's review of study documentation or procedures indicates that additional training of study personnel is needed, node managers will undertake or arrange for that training. A report on each protocol management visit will be written and distributed in a timely manner according to the Protocol Management and Oversight Plan.

11.3.3 NIDA Contract Monitors.

Investigators will host periodic visits by NIDA contract monitors to audit regulatory documentation, consent/assents, data quality, protocol adherence, and audit and evaluate the study safety and progress. These monitoring visits allow for independent evaluation of study progress and identification of potential problems at the study sites.

11.3.4 Data and Safety Monitoring Board (DSMB).

NIDA has appointed a CCTN DSMB in accordance with NIH requirements to provide independent oversight of this trial. The DSMB will review the research protocol and plans and make recommendations to assure that participant safety, trial validity, and data integrity are appropriately addressed. Throughout this trial the DSMB will

periodically assess at regularly scheduled meetings trial progress, factors that can affect study outcome, safety and outcome data, critical efficacy endpoints, and factors or scientific discoveries external to the study that may have ethical considerations or may affect the risk-benefit analysis of this study. After review of the trial data and other factors, the DSMB will make recommendations to NIDA on whether to continue, stop, or modify the trial or an individual participant's participation in the trial.

11.4 Study Documentation.

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms, and all regulatory documentation for conduct of the protocol at the site.

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. 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.

11.5 Confidentiality

11.5.1 Confidentiality of Data.

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

11.5.2 Confidentiality of Participant Records.

To maintain participant confidentiality, all CRFs, reports and other records will be identified by a coded study participant number only. Research records will be stored in a locked cabinet. Participant information will not be released without written permission, except as necessary for monitoring.

11.5.3 Certificate of Confidentiality.

To further ensure confidentiality, the Lead Team will obtain a Federal Certificate of Confidentiality for the conduct of this trial.

11.6 Safety Reporting

11.6.1 Definition of Adverse Event/Serious Adverse Event.

An adverse event (AE) is defined as any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have a

causal relationship with this treatment (ICH GCP). An AE can therefore be any new sign (including an abnormal laboratory finding), symptom, or disease or a worsening in frequency or severity of a preexisting condition that occurs during the course of the study. For this study, changes including physical, psychological or behavioral that occur in a study participant during the course of the trial are adverse events and will be reported. The relationship between self-reported drug use and reported AEs/SAEs will be closely monitored. Admissions for detoxification in a freestanding facility (not affiliated with a licensed hospital) will be reported as 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.

Serious Adverse Event (SAE)

Any adverse therapy experience that suggests a significant hazard, contraindication, side effect, or precaution will be defined as an SAE. This includes, but may 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 or prolongation of existing hospitalization
4. Persistent or significant disability or incapacity
5. Congenital anomaly/birth defect
6. An event that required intervention to prevent one of the above outcomes

Admissions for detoxification, substance abuse treatment in a freestanding facility (not affiliated with a licensed hospital), and preplanned/elective surgeries will not be considered SAEs for this study and will not require expedited reporting. These events will be captured as AEs and will be documented on the AE CRF. All AEs and SAEs will need to be reported to the local IRB(s) per local IRB requirements.

All SAEs as defined in this section will be reported to the LI and NIDA as defined in section 11.6.2.2.

Unexpected Adverse Event

Any adverse therapeutic experience, the specificity or severity of which is not consistent with the investigator brochure.

11.6.2 Monitoring Adverse Events.

The research staff (medical, RAs and CBT clinicians) will elicit AEs/SAEs at each visit (starting the day after consent) during the study by asking a standard, general question, such as *“How have you been feeling since I saw you last?”* The research staff will obtain as much information as possible about the AE/SAE to complete the AE/SAE forms and will consult with the study nurse or medical clinician as warranted. SAEs will be reported as indicated in section 11.6.2.2. The study nurse, other medical clinician, or a well-trained RA with real-time access to medical back-up (including consultation with Lead Team if necessary) will review AEs for seriousness, severity, and relatedness weekly. The medical clinician will review all adverse event (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.

The Medication Liking Scale and Diversion Questionnaire will be reviewed by the MC for indications of abuse and diversion potential. Any worsening drug use will be evaluated in relation to the self-reported use of the study medication.

NIDA contracted monitors and local node Protocol Managers will monitor the study sites and study data on a regular basis and will promptly report any previously unreported safety issues. Local Protocol Managers and NIDA Contract monitors will review 100% of all SAEs and related documentation and ensure that the SAE is followed appropriately by the research staff. The Protocol Manager will ensure that any unreported or unidentified SAEs discovered during visits are promptly reported. Staff re-training or appropriate corrective action plan will be implemented at the participating site when unreported, unidentified AEs or SAEs are discovered, to ensure future identification and timely reporting by the site. NIDA CTN DSMB will also review data related to safety monitoring for this trial periodically at regularly scheduled meetings.

11.6.2.1 Assessment of Severity and Relatedness.

The study nurse, other medical clinician, or a well-trained RA with real-time access to medical back-up (including consultation with Lead Team if necessary) 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 nurse and other research personnel as needed. The severity of the experience indicates the intensity of the event. 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.

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

Relationship to therapy is defined as follows:

Associated: There is a reasonable possibility that the adverse event may have been caused by the test product and/or procedure. This definition applies to those adverse events that are considered definitely, probably or possibly related to the test article.

- **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 participants clinical state or by other therapies.

Not associated: An adverse event for which sufficient information exists to indicate that the etiology is not related to the test product and/or therapy.

- **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.

11.6.2.2 SAE Reporting 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 LT and the NIDA appointed Medical Safety Officer (MSO) of SAEs within 24 hours of learning of the event. The SAE form and summary and any other relevant documentation should be submitted 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 forms. 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 LT and MSO. This form must be signed and dated by the medical clinician, i.e. study physician, 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 their 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 Medical 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.

The MSO is responsible for reviewing all serious adverse event reports. The MSO will also make recommendations regarding the reportability of events to the sponsor and the Data & Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events for all scheduled meetings.

Serious events will be followed until resolved or considered stable, with reporting to the CCC 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 LT 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 Medical Monitor, local ethics Committee/IRBs or regulatory authorities.

Figure 1: AE/SAE Reporting Schema.

NO

YES

12.0 DATA MANAGEMENT AND PROCEDURES

12.1 Design and Development.

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

12.1.1 Site Responsibilities.

The data management responsibilities of each individual CTP will be specified in the manual of operations.

12.1.2 Data Center Responsibilities.

The DSC will 1) develop a data management plan and will conduct data management activities, 2) provide final CRF specifications for the collection of all data required by the study, 3) provide 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.

12.2 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. Corrections to electronic CRFs shall be tracked electronically with time, date, individual making the change, and what was changed. 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 paper CRFs.

12.3 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 forwarded to the 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.

12.4 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.

12.5 Data 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.

12.6 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 LT 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.

13.0 QUALITY ASSURANCE MONITORING

A monitoring plan will be developed to ensure all study procedures are conducted and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. Investigators will host periodic visits by NIDA contract monitors to audit, at mutually agreed upon times, all case report forms (CRFs) and corresponding source documents for each participant.

Qualified node personnel will provide site management for each site during the trial, according to the Protocol Management and Oversight Plan developed by the Lead Team. This will take place as specified by the protocol team or node PI and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will verify that study procedures are properly followed and that site staffs are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training.

14.0 PUBLICATIONS AND OTHER RIGHTS

Protocol development and implementation in the NIDA CTN is a collaborative process. The publication plan for the current protocol will comply with the CTN Publications Subcommittee's guidance on publications. Individuals making substantive contributions to the protocol development and implementation will have opportunities to participate in publications. Other contributors will also be acknowledged.

15.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____

INVESTIGATOR (S)

- I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of participants.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.
- I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.
- I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human participants.
- I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

Typed Name	Signature	Date
_____	_____	_____

Principal Investigator

Sub-Investigator

Sub-Investigator

16.0 REFERENCES

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