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A Pilot Study of Osmotic-Release Methylphenidate (OROS-MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD)

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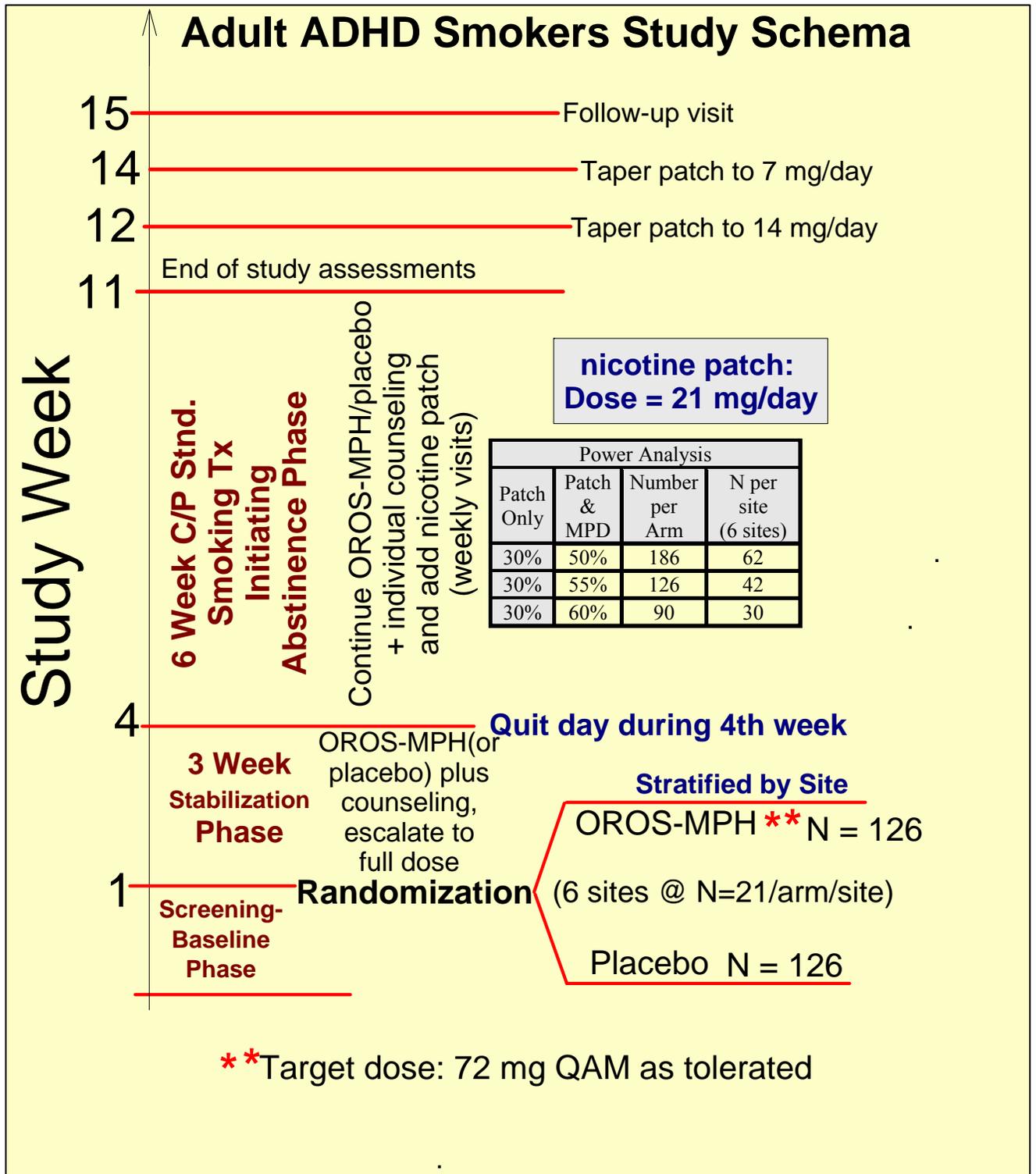
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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACDS	Adult Clinician Diagnostic Scale
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS	ADHD Rating Scale
AE	Adverse Event
ASRS	ADHD Self-Report Scale
ASRS-V1.1	Adult Self-Report Scale – V1.1 Screener
CGI	Clinical Global Impression
CO	Carbon Monoxide
cpd	Cigarettes per day
CRF	Case report form
CCC	Clinical Coordinating Center
CTN	Clinical Trials Network
CTP	Community treatment program
DMAS	Data Management and Analysis Subcommittee
DMC	Data Management Center
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
FTND	Fagerström Test for Nicotine Dependence
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HIV	Human immunodeficiency virus
IMC	Information Management Consultants
IR-MPH	Immediate-Release Methylphenidate
IRB	Institutional review board
ITT	Intent-to-Treat
LI	Lead Investigator
LN	Lead Node
MC	Medical Clinician
MSO	Medical safety officer
NIDA	National Institute on Drug Abuse
NRT	Nicotine Replacement Therapy
O-MPH/P-Stnd Smoking Tx	OROS-MPH/Placebo with Standard Smoking Treatment
OVN	Ohio Valley Node
OROS-MPH	Osmotic-Release Methylphenidate
QA	Quality Assurance
PI	Principal Investigator
RA	Research assistant
SCID	Structured Clinical Interview for DSM-IV
SRNT	Society for Research on Nicotine and Tobacco
TLFB	Time-line follow-back
TOT	Training of Trainers
USPHS	U.S. Public Health Service

2.0 STUDY SCHEMA

Figure 1: Study Schema



3.0 STUDY SYNOPSIS

STUDY OBJECTIVES. The primary objective of this study is to evaluate whether OROS-MPH, relative to placebo, increases the effectiveness of standard smoking treatment (i.e., nicotine patch and individual smoking cessation counseling) in obtaining prolonged abstinence for smokers with ADHD. Secondary objectives include: 1) evaluating the efficacy of OROS-MPH, relative to placebo, in treating ADHD in smokers with ADHD; 2) evaluating the safety of using OROS-MPH in the treatment of smokers with ADHD; 3) determining the effects of OROS-MPH combined with individual smoking cessation counseling, compared to placebo combined with individual smoking cessation counseling, on smoking behavior. An additional objective is to gather information upon which to base the design of a full-scale clinical trial of OROS-MPH (e.g., retention rates, effect size, etc.).

STUDY DESIGN. This is a randomized, intent-to-treat, parallel, two-group study comparing the efficacy of OROS-MPH vs. placebo in the treatment of smokers meeting DSM-IV criteria for ADHD. The study consists of two primary phases: the OROS-MPH/Placebo Stabilization phase and the OROS-MPH/Placebo with Standard Smoking Treatment phase.

STUDY POPULATION. Approximately 252 participants, recruited from approximately 6 sites, will be randomized into this pilot study. Each site will enroll between approximately 15 and 100 participants, with a target of 42. The study population will include smokers (smoking at least 10 cigarettes per day) who wish to stop smoking and who meet DSM-IV criteria for ADHD and have a DSM-IV ADHD Symptom Score > 22 as measured by the DSM-IV checklist.

TREATMENTS. Participants will be randomly assigned to OROS-MPH or matching placebo and will initiate weekly individual smoking cessation counseling. This smoking cessation counseling will consist of approximately one ten-minute counseling session per week during study weeks 1 through 11. Following a three-week OROS-MPH/Placebo Stabilization phase, the participant will enter the 6-week OROS-MPH/Placebo with Standard Smoking Treatment phase, in which he or she will be treated with the nicotine patch in addition to individual smoking cessation counseling. All participants will be tapered from the nicotine patch and discontinued from OROS-MPH/placebo after the final OROS-MPH/Placebo with Standard Smoking Treatment phase assessment, which will occur approximately at the beginning of study week 11.

EFFICACY ASSESSMENTS. Efficacy assessments will include prolonged abstinence rate, point prevalence smoking abstinence rate, urine cotinine levels, breath carbon monoxide (CO) levels, ADHD symptom severity, tobacco withdrawal symptoms, and cigarettes per day.

SAFETY ASSESSMENTS. Safety measures will include vitals, adverse events (AEs), and mood measures.

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

4.0 BACKGROUND AND RATIONALE

4.1 Background

Adult ADHD is a common and impairing neuro-psychiatric disorder, affecting approximately seven to eight million adults in the United States [Adler and Chua, 2002; Adler and Cohen, 2004; Wilens et al., 2004]. A recent re-examination of adults in the National Co-Morbidity Survey found a prevalence rate of adult ADHD of 4.4%, making it the second most common mental health disorder of adulthood (after depressive disorders) [Kessler, 2004]. The symptoms of ADHD include difficulty sustaining attention, distractibility, procrastination, difficulty organizing and completing tasks, misplacing items, restlessness, impulsivity, talking out of turn and interrupting others when busy (DSM-IV, American Psychiatric Association). Critical elements in making the diagnosis of adult ADHD include: 1) Sufficient current symptoms ($\geq 6/9$ inattentive and/or $6/9$ hyperactive-impulsive symptoms), 2) Significant impairment in at least 2/3 realms of an individual's life (home, school/work or social settings), 3) A childhood onset of the disorder, and 4) Ascertaining that the symptoms are best explained by ADHD and not another mental health disorder. ADHD adults are vastly under-diagnosed and under-treated (only 20% identified and treated) [Biederman and Faraone, 2004]. Additionally, there is significant under-recognition of adult ADHD by psychiatrists and primary care physicians. The re-examination of the National Co-Morbidity Survey cohort found that $> 40\%$ of un-diagnosed adults had seen a healthcare professional in the last year. A recent survey of 400 primary care physicians found that they felt that they were three times less knowledgeable and comfortable in making a diagnosis of adult ADHD, as compared to anxiety or depressive disorders [Expert Roundtable Highlight, 2004].

There are significant impairments resulting from adult ADHD in numerous domains, including educational (fewer years of education, higher rates of repeating a grade, lower GPAs, and lower college graduation rates), occupational (more frequent job changes, higher rates of unemployment, more ADHD symptoms on the job, more frequently being fired from the job and working lower paying jobs), driving (more speeding tickets, accidents, severe accidents, driving without a license, and when placed on a driving simulator higher rates of accidents, speeding, and false braking and steering), and social (higher rates of divorce/separation and family discord) functioning [Adler and Chua, 1992; Borland and Heckman, 1976; Morrison, 1980A; Morrison, 1980B; Murphy and Barkley, 1996; Biederman et al., 1994; Murphy et al., 2002; Biederman and Faraone, 2004].

Substance use disorders, including cigarette smoking and nicotine dependence, are some of the more common co-morbid disorders with adult ADHD. Two independent studies have found that adults with ADHD have overall rates of substance use disorders two to three times greater than controls [Kessler, 2004; Biederman, 1995]. Several studies have also found that cigarette smoking and nicotine dependence are twice as common in adults with ADHD as compared to controls [Biederman and Faraone, 2004; Wilens et al., 1999]. Additionally, studies have shown that adolescents with ADHD are more likely to smoke, smoke at an earlier age, and smoke more than control participants [Milberger et al., 1997; Pomerleau et al., 1996]. Even though ADHD is generally posited to result from dysregulation of dopaminergic and noradrenergic pathways, the important interplay of ADHD and cigarette smoking/nicotine dependence is supported by studies in the neuro-psychology, pharmacology, and pathophysiology of the disorders. A variety of neuro-psychological measures shown to be impaired in ADHD, including the stop signal reaction time and the Stroop task, were shown to be significantly improved in adults with ADHD after nicotine administration [Potter and Newhouse, 2004]. Nicotine administration and a novel cholinergic agonist have also been shown in

independent studies to have efficacy on ADHD symptoms in adults with the disorder [Levin et al., 1996; Wilens et al. 1999]. Nicotine has also been shown to stimulate dopamine neurons, induce dopamine release or increase dopamine transporter activity [Mereu et al., 1987; Westfall et al., 1983; Krause et al., 2003]. These lines of investigation support the concept that adults with ADHD and cigarette smoking/nicotine abuse are using nicotine in part to self-medicate ADHD symptoms.

4.2 Rationale for Selecting OROS-MPH as the Study Medication

Psychostimulants are clearly the mainstay of pharmacologic treatment for ADHD in children, adolescents, and adults. Both methylphenidate (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, has established the safety and efficacy of MPH in the treatment of ADHD [Greenhill et al., 1999]. The Multimodal Treatment Study of Children with ADHD (MTA), in fact, chose immediate-release methylphenidate (IR-MPH) given in a 3 times/day dosing schedule as the best initial treatment strategy for ADHD for their large clinical trial [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/day dosing, and 2. longer acting formulations have lower abuse potential than shorter acting preparations. The OROS delivery system used in OROS-MPH 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 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. These studies demonstrate low placebo response rates and robust clinical effects of OROS-MPH, 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].

Two non-scheduled, non-stimulant medications, atomoxetine and bupropion, have received FDA approval for the treatment of ADHD. However, neither of these medications is as effective in controlling ADHD symptoms as the psychostimulants (they have lower effect sizes; 0.7, 0.5, respectively, compared to the >.8 effect size that has been consistently found for OROS-MPH).

4.3 Rationale for a Pilot Study

Long-acting stimulants, such as sustained release methylphenidate (OROS-Methylphenidate (OROS-MPH)) are a mainstay of the treatment of adult ADHD [Adler and Chua, 2002; Wilens et al., 2004]. As it is posited that the increased use/dependence on nicotine seen in adult ADHD is related to self-medication, it is likely that successful treatment of ADHD symptomatology will result in decreased cigarette abuse. The possible public health benefits of such a reduction in cigarette use are significant, as cigarette smoking is the leading cause of preventable death in the United States, and data from 1995-1999 indicate that the annual cost of cigarette smoking is over \$150,000,000 per annum [Center

for Disease Control, 2002]. However, to our knowledge, a clinical trial of OROS-MPH for initiating and maintaining abstinence in smokers with ADHD has not been conducted previously. Consequently, there is little evidence that OROS-MPH will be effective in reducing smoking in smokers with ADHD, and there is little empirical data upon which to base the design of a full-scale clinical trial (e.g., effect size estimates, attrition rate, etc.). The present study will provide an initial evaluation of the efficacy and safety of OROS-MPH in the treatment of smokers with ADHD and will yield the information needed to design a full-scale clinical trial. If the study shows that it is feasible to conduct a multi-site evaluation of OROS-MPH, and if there is evidence to suggest positive effects and safety of OROS-MPH compared to placebo, the information gathered from the present pilot study would provide a solid foundation on which to base the design of a large-scale clinical trial of OROS-MPH.

5.0 STUDY OBJECTIVES

5.1 Primary Objective

1. To evaluate the efficacy of OROS-MPH and standard smoking treatment (i.e., nicotine patch and individual smoking cessation counseling), relative to placebo and standard smoking treatment, in achieving prolonged abstinence in smokers with ADHD.

5.2 Secondary Objectives

1. To evaluate the efficacy of OROS-MPH, relative to placebo, in reducing ADHD symptoms in smokers with ADHD.
2. To evaluate the effect of OROS-MPH, with individual smoking-cessation counseling, compared to placebo, with individual smoking cessation counseling, on cigarettes per day (cpd) and cotinine levels in smokers with ADHD.
3. To evaluate the efficacy of OROS-MPH and standard smoking treatment, relative to placebo and standard smoking treatment, in achieving an initial quit, point-prevalence abstinence, complete abstinence, and in reducing the number of smoking days in smokers with ADHD.
4. To evaluate the safety of using OROS-MPH for treating ADHD in smokers and the safety of combining OROS-MPH with the nicotine patch in this population.
5. To evaluate the efficacy of OROS-MPH and standard smoking treatment, relative to placebo and standard smoking treatment, in reducing tobacco withdrawal symptoms.
6. To evaluate the relationship between ADHD symptoms during the active study phase and success with initiating and maintaining abstinence.
7. To gather information upon which to base a full-scale clinical trial of OROS-MPH (e.g., retention rates, effect size, etc.)

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a randomized, parallel, two-group design comparing the efficacy of OROS-MPH and placebo in the treatment of smokers meeting DSM-IV criteria for ADHD. The study consists of two primary phases: the OROS-MPH/Placebo Stabilization phase, and the OROS-MPH/Placebo and Standard Smoking Treatment (O-MPH/P-Stnd Smoking Tx) phase. The primary outcome measure for the O-MPH/P-Stnd Smoking Tx phase will be prolonged abstinence rate. Secondary outcomes will include point-prevalence abstinence, ADHD symptom severity, tobacco withdrawal symptoms, and cpd. Safety measures will include vital signs, adverse events (AEs), and mood measures.

6.2 Number of Sites and Participants

Approximately 252 participants will be randomized into this pilot study. Approximately six sites will participate, with each site enrolling between approximately 15 and 100 participants, with a target of 42. An attempt will be made to randomize approximately 50% female participants. In addition, efforts will be made to recruit a sample of study participants that reflects the proportion of minorities in the community where the site is located. Such efforts could include recruiting study participants from African American and other ethnic churches and establishing recruitment relationships/linkages with local churches and primary care providers that specifically serve minority populations. The primary source will be participants recruited from the community by advertising in the local media. Recruitment advertisements will be approved by the site's Institutional Review Board (IRB). Participants will be recruited from a variety of other sources as well.

6.3 Study Implementation

6.3.1 Staged Implementation

This pilot 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. For example, we are assuming that with advertising, the randomization rate per site will be approximately 2.5 participants per month. If the experience with the initial three sites indicates that this assumption is incorrect, then the protocol will need to be adjusted (e.g., increasing the number of sites or extending the recruitment period). Any study amendments or procedural changes deemed necessary based on the experiences with the first three sites will be completed prior to stage two of implementation. It is estimated that the first stage will entail approximately six months of randomization at the sites initiated in stage one. In stage two, the remaining study sites will be initiated.

6.3.2 Study Duration

Once all sites are initiated, enrollment is expected to take place over a period of approximately 14 months. If enrollment is significantly slower than expected, a site, or the entire trial, may be discontinued early.

6.4 Site and Participant Selection

6.4.1 Site Selection

6.4.1.1 Site Characteristics

Participating sites should:

1. have access to a medical clinician (e.g., R.N., P.A., M.D., etc.; the degree and licensing requirements depend on the regulations of the state in which the site is located), to 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
2. have access to, or the ability to contract with, a pharmacy/pharmacist (or other appropriate licensed entity) to store/dispense study medications
3. be able to provide after-hours clinical back-up for study-related emergencies

6.4.1.2 Rationale for Site Selection

The site eligibility criteria outlined in section 6.4.1.1 consist of the minimal staffing that is required in order to safely and effectively conduct a medication trial.

6.4.2 Participant Selection

6.4.2.1 Inclusion Criteria

Potential participants must:

1. be an adult 18-55 years of age
2. be able to understand the study, and having understood, provide written informed consent in English
3. have a DSM-IV diagnosis of ADHD as determined by the Adult Clinician Diagnostic Scale (ACDS) v. 1.2
4. have a DSM-IV ADHD Symptom Score >22 as measured by the DSM-IV checklist
5. have smoked cigarettes for at least 3 months, currently smoking ≥ 10 cigarettes/day, and have a measured exhaled CO level ≥ 8 ppm
6. have an interest in quitting smoking and a willingness to comply with all study procedures and medication instructions
7. if female and of child bearing potential, agree to use one of the following methods of birth control:

- oral contraceptives
 - contraceptive patch
 - barrier (diaphragm or condom)
 - intrauterine contraceptive system
 - levonorgestrel implant
 - medroxyprogesterone acetate contraceptive injection
 - complete abstinence from sexual intercourse
 - hormonal vaginal contraceptive ring
8. have a negative urine screen for cocaine, methamphetamine, opiates, benzodiazepines, and marijuana

6.4.2.2 Exclusion Criteria

Potential participants must not:

1. meet DSM-IV criteria for current abuse or dependence for any psychoactive substance other than nicotine
2. have a life-time diagnosis of psychosis or bipolar disorder
3. meet DSM-IV criteria for current major depression or any anxiety disorder except specific phobias
4. currently have or have had a medical or psychiatric condition which, in the judgment of the study medical clinician (MC), would make study participation unsafe (e.g., a history of myocardial infarction, stroke, cerebrovascular disease, serious arrhythmias or heart blocks, cancer or HIV requiring treatment, active peptic ulcer disease, uncontrolled hypertension), or which would make treatment compliance difficult, or put the study staff at undo risk. Participants may be asked about chest pains, heart disease, stomach ulcers, thyroid disease, diabetes, skipped or irregular heart beats, allergies to tape, bandages or medicines, skin rashes or skin diseases, high blood pressure, kidney disease, and liver disease and other medical symptoms.
5. have been treated for ADHD in the last 30 days with psychomotor stimulants
6. use other smoking cessation counseling programs or medication treatments currently, or within the last 30 days
7. have a history of narrow angle glaucoma
8. have a history of a seizure disorder
9. have tics or Tourette's syndrome, or a family history of Tourette's syndrome
10. be known to be allergic to OROS-MPH
11. be pregnant or breastfeeding

12. have an ECG with significant arrhythmias or abnormal conduction, which in the opinion of a study cardiologist preclude participating in the study
13. be taking a Monoamine Oxidase (MAO) Inhibitor, or have taken one within two weeks of randomization
14. be taking any medication used for treating either ADHD or smoking
15. be taking any medications which, in the judgment of the study medical clinician (MC), 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. Some of the possible interactions are discussed in section 8.12.
16. be anyone who, in the judgment of the investigator, would not be expected to complete the study protocol (e.g., due to relocation from the clinic area, work-related difficulties, etc.)
17. have used tobacco products other than cigarettes in the past week
18. if 40 to 55 years of age, have blood pressure readings greater than 130/80 and/or a heart rate more than 88 beats per minute on two clinic visits; if less than 40 years old have blood pressure readings greater than 135/85 and/or heart rate more than 90 beats per minute on two clinic visits
19. meet DSM-IV criteria for Antisocial Personality Disorder
20. have previously received reasonable treatment with methylphenidate (as judged by medical clinician (MC)) and failed to evidence a reduction in ADHD symptoms in response to this treatment
21. is a significant suicidal/homicidal risk

6.4.2.3 Rationale for Eligibility Criteria

The rationale for each inclusion and exclusion criterion is provided in Table 1.

Table 1: Rationale for Study Eligibility Criteria

Criterion#	Criterion Description	Criterion Rationale
I1	18-55 years of age	NRT not recommended for <18; participants >55 might have poorer recall of childhood ADHD symptoms. The onset of some significant ADHD symptoms prior to the age of 7 years old is a cornerstone of making the clinical diagnosis of ADHD as per DSM-IV. By allowing inclusion of patients up to the age of 55 years we will be including a sufficient cohort of older subjects and allow generalizability of the findings to this age group, but not compromise the study by possibly including patients who do not have ADHD based upon inadequate or confounded retrospective recall of symptoms. Furthermore, extending the age

Criterion#	Criterion Description	Criterion Rationale
		limit beyond 55 would include a patient population of adult ADHD that has not been previously well studied, as most treatment studies of adult ADHD have not included patients 55-65 (Spencer, 2004).
I2	Understand study and give consent	GCP Requirement
I3	DSM-IV Diagnosis of ADHD	Definition of Study Sample (ADHD)
I4	ADHD DSM-IV checklist score >22	Need to have a least this level of severity to benefit significantly from OROS-MPH
I5	Smoking requirements	Definition of Study Sample (Smoker)
I6	Wants to quit smoking, willingness to comply with study procedures	To help ensure that the participant will provide useful data
I7	Agree to birth-control	Pregnancy counter indication for both OROS-MPH and nicotine patch
I8	Negative for illicit drugs	Illicit drugs may alter ADHD symptoms
E1	Meet DSM-IV criteria for current substance abuse	Substance abuse may alter ADHD symptoms
E2	Life-time diagnosis of psychosis or bipolar disorder	These conditions can be exacerbated by OROS-MPH
E3	Meet DSM-IV criteria for current major depression or anxiety	OROS-MPH may intensify anxiety; smoking cessation may intensify depression
E4	Medical clinician determines medical condition makes study participation unsafe	Safety
E5	Treated for ADHD in last 30 days with medications	Participants may still have these medications, or a prescription for them
E6	Use of other smoking-cessation tx	Would interfere with primary objective of study
E7	History of narrow-angle glaucoma	This condition can be exacerbated by OROS-MPH
E8	History of a seizure disorder	This condition can be exacerbated by OROS-MPH
E9	Tics or Tourette's syndrome	This condition can be exacerbated by OROS-MPH
E10	Be allergic to OROS-MPH	Safety
E11	Pregnancy or lactation	Counter indication for both OROS-MPH and nicotine patch
E12	ECG with significant arrhythmia	Safety
E13	Be taking a Monoamine Oxidase (MAO) Inhibitor	Contraindication
E14	Be taking medication used for treating either ADHD or smoking	Will interfere with the primary objective of the study.
E15	Taking medications with possible dangerous interactions with OROS-MPH or nicotine patch	Safety
E16	Unlikely to complete the study	To help ensure that the participant will provide useful data

Criterion#	Criterion Description	Criterion Rationale
E17	Use tobacco products other than cigarettes	Would interfere with primary objective of study
E18	Blood pressure and heart rate criteria	Safety
E19	Meet criteria for Antisocial Personality Disorder	Potential Study Confound
E20	Non-response to methylphenidate	Could reduce effect size
E21	Significant Suicide/Homicide risk	Safety

6.5 Outcome Measures

6.5.1 Primary Outcome Measure – Prolonged Abstinence

The Society for Research on Nicotine and Tobacco (SRNT) has recommended that prolonged abstinence be used as the primary outcome measure in smoking cessation clinical trials [Hughes et al., 2003]. Prolonged abstinence refers to a sustained period of abstinence following a quit date with some grace period following the quit date in which the smoker can smoke without being counted as a failure [Hughes et al., 2003]. The SRNT recommended a two-week grace period as a standard when using prolonged abstinence as a measure [Hughes et al., 2003] and, thus, this study will utilize a two-week grace period. The present study will also utilize the SRNT-recommended definition of a treatment failure: self-report of smoking each day for seven consecutive days or self report of having smoked at least one day of each week in two consecutive weeks [Hughes et al., 2003].

In the present study, the smoking quit date will occur during study week 4. The smoking quit date will be considered the first day of the O-MPH/P-Std Smoking Tx phase, which will last for 6 weeks or more precisely 42 days (i.e., approximately weeks 5-10). The grace period will be the first two weeks (i.e., days 1-14) with the remaining four weeks (days 15-42) comprising the period in which the participant must not meet criteria for treatment failure (see above) in order to be scored as obtaining prolonged abstinence. The selection of a 4-week period is consistent with FDA standards for approving smoking cessation medications [Hughes et al., 2003]. Self-report of cigarette use will be assessed using a time-line follow-back (TLFB) assessment. If the participant terminates early from the study, then s/he will be scored as a treatment failure.

It is important to note that the assessment of the participant's self-reported smoking status for a given week occurs during the research visit in the following week. For example, assessment of the participant's smoking status during week 9 will occur at the week 10 research visit. This delay is necessary in order to obtain the participant's smoking status throughout the entire week.

6.5.2 Secondary Outcome Measures

6.5.2.1 ADHD CGI -Severity

The severity portion of the National Institute of Mental Health Clinical Global Impression (CGI) scale [Guy et al., 1970] will be used to rate the severity of the participant's ADHD symptoms. A single severity score ranging from 1 to 7 is yielded by the CGI severity scale. This instrument will be administered by a study staff member with at least a Bachelor's degree who has received training on the administration of the ADHD CGI-Severity instrument.

6.5.2.2 Carbon Monoxide (CO) level

CO in each participant's breath will be tested using a standard calibrated CO gas-monitoring device connected to a disposable mouthpiece. CO will ideally be assessed twice during each study visit. Ideally study staff should attempt to collect samples at a uniform time (preferably after 12 noon). Expired CO will be assessed according to the schedule outlined in Table 2 (labeled "Tobacco Use Assessment").

Because of the importance of regular CO level measurements to the outcome measures, special attention will be given to avoiding missing measurements during the four-week post-grace-period interval. Study staff will attempt to communicate with any study participant who is in danger of missing a visit and will, if necessary, arrange to meet him or her at home or other location to obtain the CO level.

6.5.2.3 Cotinine Level

Cotinine is the primary metabolite of nicotine and can be measured in saliva and urine. Cotinine has excellent specificity for tobacco in individuals who are not on nicotine replacement treatment [SRNT, 2002]. Urine to assess cotinine level will be collected as outlined in Table 2. The cotinine levels obtained will allow an analysis of the effect that OROS-MPH, compared to placebo, has on smoking behavior prior to the initiation of the standard smoking treatment phase.

6.5.2.4 DSM-IV ADHD Symptom Score

The DSM-IV ADHD Symptom Score will be obtained from the interviewer-administered DSM-IV checklist [DuPaul et al., 1998], with prompts for the interviewer [Adler et al., 2004]. This instrument will be administered by a study staff member with at least a Bachelor's degree who has received training on the administration of the DSM-IV checklist.

6.5.2.5 Initial Quit

Achieving an initial quit is defined as a self-report of no smoking for 24 hours or more [Hughes et al., 2003]. In the present protocol, if the participant meets this criterion at any time during the first two weeks following the smoking quit date (as determined by TLFB) then s/he will be scored as having achieved an initial quit.

6.5.2.6 Point-Prevalence Abstinence

Point-prevalence abstinence is defined as not smoking in the previous seven days based on self-report and confirmed with a Carbon Monoxide (CO) level <8 ppm (Hurt et al., 2003). Self-report of cigarette use (measured by TLFB) and expired CO will be obtained as outlined in Table 2.

6.5.2.7 Withdrawal Scale for Tobacco (WST)

The WST is a modified version of the Minnesota Withdrawal Scale [Hughes et al, 1991; Hatsukami et al, 1997; Hughes and Hatsukami, 1986]. The WST is a self-report questionnaire which asks participants to rate 9 items of withdrawal on a scale from 0=None to 4=Severe. A total score is then computed from the responses to these 9 items. In addition, the 9 items are also examined separately.

6.5.2.8 Cigarettes per Day

A TLFB assessment will be used to evaluate the number of cpd that the participant reports using throughout the study as outlined in Table 2 (labeled “Tobacco Use Assessment”).

6.5.2.9 Non-cigarette Tobacco Use

Participant use of non-cigarette tobacco products will be assessed throughout the study as outlined in Table 2 (labeled “Tobacco Use Assessment”).

6.5.2.10 Complete Abstinence

A combination of daily self-reported smoking data and weekly measured CO levels will be used to determine complete abstinence during post-quit days 15-42. Complete abstinence will be defined as no self-reported smoking on any of the days during this four-week period AND no positive or missing CO level measurements that indicate smoking during the same period. Because a positive CO level almost always indicates smoking on either the day of the measurement or the previous day, smoking during the post-grace period will be indicated by a positive CO level measured on any of the post-quit days 16-42. (A positive value on day 15 might be due to smoking on day 14, which is within the grace period.) In order to have no missing CO measurements, the following conditions must be met: at least four measurements must be obtained during this period; the first one may be no later than post-quit day 23, and no subsequent measurement may fall more than 13 days after the previous measurement.

6.5.2.11 Self-reported Smoking Days corrected by CO levels

Since the present study includes frequent contact with participants, it is appropriate to use CO levels to correct self-reported smoking days [J. Hughes, personal communication, January 13, 2005]. Thus, we will assess the number of “Smoking Days” for each participant. “Smoking days” are determined by starting with self-reported smoking and non-smoking days and using CO levels measured at weekly visits to modify the self-reports as follows:

- A self-reported smoking day is defined as a smoking day.
- A positive CO level (≥ 8 ppm) causes the day of the CO measurement to be converted into a smoking day unless either that day or the previous day is a self-reported smoking day.
- If at least 14 days elapse between one CO measurement and the next, each missed measurement is counted as a positive measurement occurring on the regularly scheduled day and treated as described in the previous bullet item.

At each study visit, the participant’s self-reported smoking status for each day since the previous visit will be assessed. This assessment will not include the smoking status for the day of the current visit, which will be assessed at the following week’s visit.

6.5.3 Safety Measures

6.5.3.1 Adverse Events (AEs)

AEs will be assessed by study staff at each visit. If an AE requires medical attention, it should be reported to a study medical clinician immediately.

6.5.3.2 Beck Anxiety Inventory

The Beck Anxiety Inventory [Beck et al, 1988; Somoza et al., 1994] is a 21-item self-report questionnaire designed to discriminate between symptoms of anxiety and depression.

6.5.3.3 Beck Depression Inventory-II

The BDI-II [Beck, 1996] is a participant-administered questionnaire designed to assess the intensity of depression in a participant over the past two weeks. The BDI-II yields one total score. Participants who score in the moderate or high range for depression (total score of 20 or higher) should be assessed by the medical clinician. Participants rating suicidal ideation greater than zero must also consult with the medical clinician. The medical clinician may refer the participant to a CTP/other mental health professional if the participant is in need of immediate treatment.

6.5.3.4 Pregnancy Test

A urine pregnancy test designed to measure human chorionic gonadotropin hormone will be used. All female participants will be tested except for women who have a documented hysterectomy.

6.5.3.5 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 medications taken by the participant while on study and during follow-up must be pre-approved by the medical clinician whenever possible to avoid interactions with the study drug. Medications taken will be recorded on a Prior/ Concomitant Medications CRF. The reported medications will be reviewed and approved by the site principal investigator/ medical clinician.

6.5.3.7 Vital Signs and Weight

Vital signs, including blood pressure and heart rate, will be assessed at each visit. In addition, the participant's weight will be recorded during screening/baseline, and at the week-6 and week-11 study visits. Vital signs will be evaluated by a trained staff member, either manually or by using a digital blood pressure monitor calibrated within the past twelve months and approved by the Lead Investigator. If the blood pressure is abnormally high or low, it will be repeated one more time approximately 5 minutes later using the same technique. These readings will then be averaged. The RA will seek consultation with a medical clinician for any out-of-range values when participants are not scheduled to see a medical clinician.

6.5.4 Other Measures

6.5.4.1 Adult Self-Report Scale V1.1 Screener

The Adult Self-Report Scale – V1.1 (ASRS-V1.1) Screener [Copyright © 2003 World Health Organization; Kessler et al., in press] is a 6-item questionnaire that has strong concurrent validity with DSM-IV criteria for ADHD.

6.5.4.2 Adult Clinician Diagnostic Scale (ACDS) v. 1.2

The ACDS v. 1.2 [Kessler et al., in press] is an interviewer-administered diagnostic scale that will be utilized to evaluate whether each potential participant meets DSM-IV diagnosis for ADHD. This scale will be used with prompts for the interviewer [Adler et al., 2004] and will be administered by a staff member with at least a Master's degree who has received training on the administration of this instrument.

6.5.4.3 CIDI

The Composite International Diagnostic Interview (<http://www.crufad.unsw.edu.au/cidi/cidi.htm>) (CIDI) will be administered during screening/baseline, with the results being used to evaluate the participant on study exclusion criteria 1, 2, and 3. The CIDI will be administered by a RA who has been trained in the proper administration of this instrument. In addition, each interviewer will undergo a certification check, in which the administration of the instrument is rated by a CIDI trainer. In addition, at least once during the active trial a re-certification check will be completed; interviewers found to be performing below CTN criteria will be provided with additional training as needed.

6.5.4.4 Demographics

This assessment will include questions about the participant's ethnicity, age, employment status, education, and substance use.

6.5.4.5 Information for Designing a Full-Scale Study

Information that will greatly facilitate the design of a full-scale trial will be obtained in the present pilot study. This information includes effect size, randomization rate, completion rates, proportion of participants who achieve prolonged abstinence, and medication and counseling compliance. This information will be obtained through two mechanisms. The first mechanism is the typical trial performance monitoring that is completed for a clinical trial. The information that will be assessed through this mechanism includes randomization rate per site and across sites, the participant completion rates for the OROS-MPH/Placebo Stabilization and O-MPH/P-Std Smoking Tx phases, and the types of recruitment efforts that produce randomized participants per site and across sites. The second mechanism through which data will be obtained consists of an analysis of the outcome measures. For example, the effect size of OROS-MPH for obtaining prolonged abstinence will be obtained from the analysis comparing the prolonged abstinence rates for the OROS-MPH, with standard smoking treatment, to placebo with standard smoking treatment.

6.5.4.6 Medical History and Addendum

A medical history will be performed by a medical clinician certified to perform this. In addition, the medical clinician will complete a Medical History Addendum form that includes questions specific to assessing participant eligibility/safety for the present protocol. For example, this form will include questions for assessing the participant's risk of sudden cardiac death and family history of tics or Tourette's Syndrome. Any history relevant to cardiac functioning will be provided to the cardiologist responsible for reviewing the participant's ECG (see section 6.5.4.16).

6.5.4.7 Physical Exam

Performance of a brief physical exam during screening/baseline will be done at each site; a more thorough physical exam will be completed at the discretion of each participating site.

6.5.4.8 Smoking History Survey

The Smoking History Survey is a modified version of the Mayo Nicotine Dependence Center Patient Questionnaire [1991] and is administered by the RA. It asks participants how many cpd they smoke, at what age they started smoking, number of years smoking, how many times they have attempted to quit (including methods), when the last quit attempt occurred, their longest period of cigarette abstinence, and if there are other smokers in their household. Information on other non-cigarette tobacco products will also be noted.

6.5.4.9 Urine Toxicology Screen

A rapid urine screen system that screens for opiates, cocaine, methamphetamine, benzodiazepines, and marijuana will be used to analyze the urine sample collected during screening/baseline. Urine samples will be collected using temperature monitoring to help ensure the validity of all samples.

6.5.4.10 Drug Rating Questionnaire

Participant liking of OROS-MPH/placebo will be assessed with the Drug Rating Questionnaire. This questionnaire is a derivative of the ARCI Bensedrine scales [Martin et al., 1971] to evaluate likeability and potential abuse based on the subjective response of the participant with ADHD. The Drug Rating Questionnaire is a visual analog scale that includes additional questions that assist in disentangling the therapeutic effects of the medication from the euphoria scales - an important confound as recently articulated by Kollins [2003] in children with ADHD. There are no currently psychometrically validated scales available for such purposes in ADHD adults. The Drug Rating Questionnaire has been used successfully in clinical trials of adults with ADHD.

6.5.4.11 Medication Compliance

Medication Compliance will be assessed through pill and patch counts according to the schedule provided in Table 2.

6.5.4.12 Counseling Compliance

Counseling Compliance will be assessed through the number of counseling sessions that the participant attends and completion of homework assignments/session participation.

6.5.4.13 Check on Blind

A check on the medication blind will be completed for both the participant and an RA who completes assessments for the participant. In this assessment the respondent (i.e., the participant, RA) is asked which medication the participant was taking (OROS-MPH or placebo). This assessment is scheduled to be completed during study week 11.

6.5.4.14 Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND) is a brief self-administered assessment of cigarette use patterns [Heatherton et al., 1991]. The FTND yields a single overall dependence score.

6.5.4.15 Suicide and Homicide Screening Form

The Suicide and Homicide Screening Form is a structured, reliable interview modified from the Psychiatric Research Interview for Substance and Mental Disorders- PRISM [Hasin, et al. 1996]. This form will be completed by the RA during screening/baseline and study week 11.

6.5.4.16 DSM-IV Screen for Antisocial Personality Disorder

This screen has been used in a number of NIDA-sponsored clinical trials. This instrument begins with an assessment of whether the participant evidenced symptoms of Conduct Disorder prior to the age of 15 (which is required to meet DSM-IV criteria for Antisocial Personality Disorder). If the participant does evidence a history of Conduct Disorder, then the interview continues with an assessment of the DSM-IV criteria for Antisocial Personality Disorder. This screen will be completed by the RA during screening/baseline.

6.5.4.17 ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. Ventricular rate (bpm), PR (ms), QRS (ms) and QTc (ms) will be reported on the ECG readouts. The results will be reviewed by a board-certified cardiologist for interpretation and for a clinical judgment about whether the participant is eligible for the study based on the ECG results.

6.5.4.18 Thoughts about Abstinence

Participants' commitment to stopping smoking will be assessed with the Thoughts about Abstinence assessment (Hall et al., 1991), modified to assess the participants' thoughts related to cigarettes. This measure assesses the participant's desire to quit, expected success in quitting and estimated difficulty in avoiding relapse. The participant will complete this measure during the screening/baseline period.

6.6 Randomization Plan

The randomization process will be performed by computer at a centralized location. Randomization will be stratified by site. The block size chosen will be adequate to ensure approximate treatment balance. The number in each treatment group will never differ by more than a factor of $b/2$ where b is the block size.

7.0 STUDY PROCEDURES

7.1 Study Overview

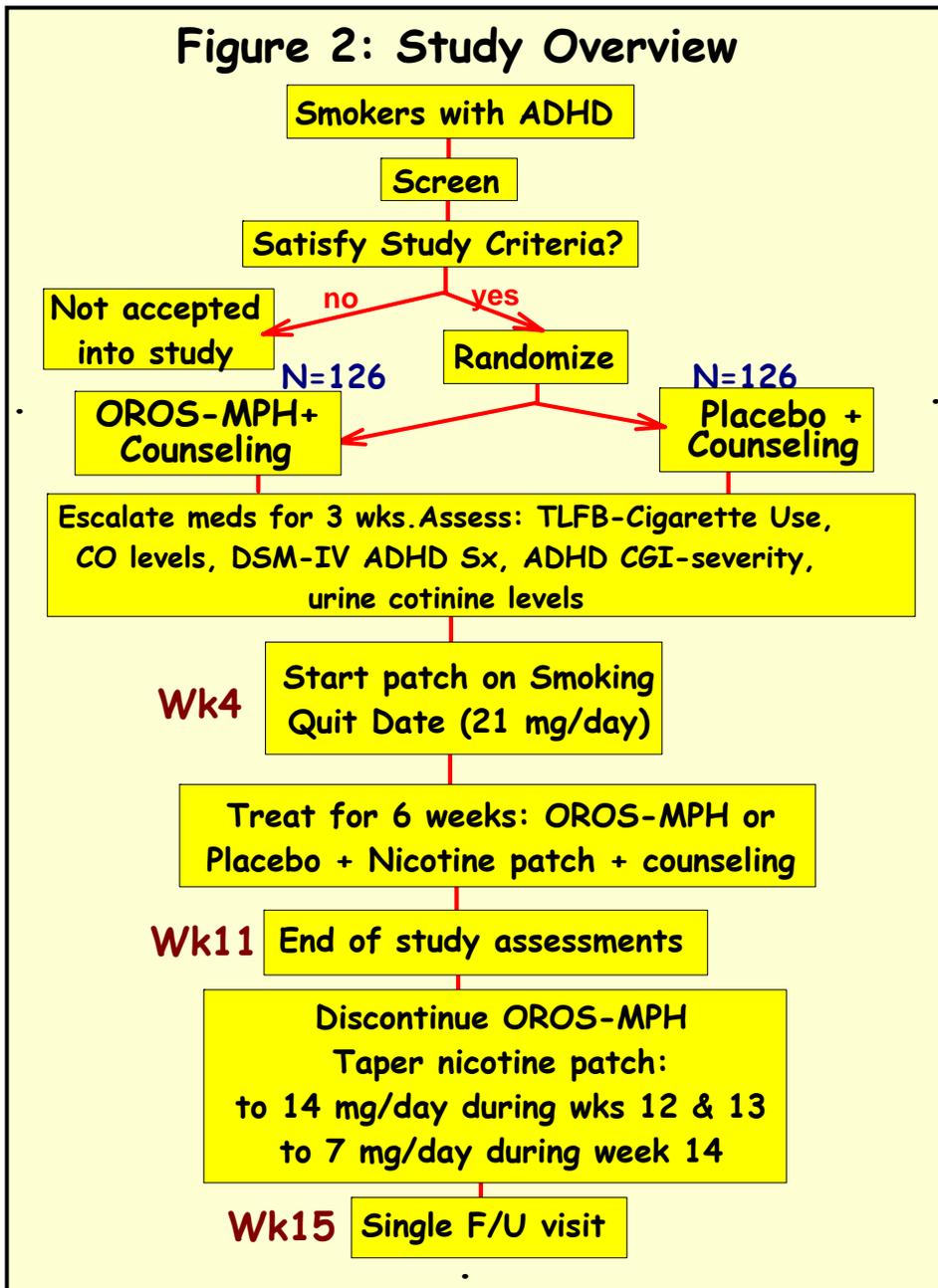


Figure 2 provides an overview of the participant procedures and assessments.

7.2 Overview of study assessments

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

Assessment/ Procedure	Time Est. (Min)	Screen /Base	O-MPH/Placebo Stabilization				O-MPH/Placebo & Standard Smoking Treatment							FU	
			1	2	3	4	5	6	7	8	9	10	11		15
Treatment															
Efficacy Assessments															
Tobacco Use Assessment	10	X*	X	X	X	X	X	X	X	X	X	X	X	X	X
DSM-IV ADHD Sx	15	X*	X	X	X	X			X		X		X		
ADHD CGI-Severity	1	X*	X	X	X	X			X		X		X		
Urine for Cotinine Level	3	X*	X	X	X	X									
Withdrawal Scale Tobacco	2	X*					X	X	X	X	X	X	X	X	X
Other Assessments															
Fagerström (FTND)	2	X*													
Locator Information	10	X*												X	
Study Questionnaire	5									X					
Drug Rating Questionnaire	5					X								X	
Compliance – Medication	5			X	X	X	X	X	X	X	X	X	X	X	X
Compliance - Counseling	0			X	X	X	X	X	X	X	X	X	X	X	
Check on Blind - Participant	5													X	
Approximate Length (minutes)		330	59	64	64	61	47	55	65	44	63	37	110	32	

Notes: “X*” = once during phase; “X” represents a procedure or assessment performed once per Visit.

⁺ At the week 11 visit the participant will be reminded that there is no longer any need to take the OROS-MPD/Placebo and will be encouraged to return the remaining unused pills from week-11 along with those of week 10. Note that the week 11 visit should ideally not be delayed beyond the end of week 11.

⁺⁺ Patches for three weeks of taper will be dispensed at this visit.

7.3 Participant Recruitment and Consent

Interested candidates who have been determined by telephone or face-to-face interview to smoke 10 or more cpd and who are likely to meet the diagnostic criteria for ADHD are invited to receive an explanation of the study purpose and requirements. If still interested after receiving a face-to-face explanation of the study, the candidate is given an opportunity to review, inquire about, and sign the informed consent form.

Any participant who has difficulty understanding the information contained in the consent form is asked to review the misunderstood portion(s) of the consent and discuss them with a research staff member until he or she shows complete understanding of the information and may thus give full consent. Research staff members work closely with the study candidates in an effort to help them understand the requirements of their participation. Persons with literacy problems are assisted to the extent possible. Any participant who is unable to demonstrate understanding of the information contained in the informed consent is excluded from study participation and assisted in finding other sources of treatment. Persons who are excluded, or who decline participation, are given referrals to other resources in the area.

7.4 Screening/Baseline

After signing the informed consent form, the study participant proceeds through the screening/baseline phase. Ideally, the screening/baseline procedures will be completed in three visits, but they can be completed in fewer visits or more visits if necessary. Ideally, the screening/baseline procedures will be completed within a one-week time-frame but the allowable time for completion is within 30 days of signing consent. Under certain circumstances a participant will be allowed to re-consent and repeat the screening/baseline procedures if he or she was unable to complete the screening/baseline procedures within the 30-day time-frame.

Participants who meet study eligibility and complete screening/baseline as outlined above will be randomly assigned to receive OROS-MPH or matching placebo.

7.5 OROS-MPH/Placebo Stabilization phase

Study participants will be randomly assigned to receive either OROS-MPH or matching placebo. The dose escalation schedule is provided in section 8.13. During this phase, participants will be encouraged to decrease their smoking (cpd) to a level at which they are still comfortable. As described in section 9.2, participants will initiate individual smoking cessation treatment during the OROS-MPH/Placebo Stabilization phase.

7.6 OROS-MPH/Placebo and Standard Smoking Treatment Phase

The O-MPH/P-Stnd Smoking Tx phase will begin near the end of week 4. The week-4 data, which are obtained prior to the smoking quit date, will be included in the analysis of the efficacy of OROS-MPH in treating ADHD and in reducing cpd and cotinine levels in smokers with ADHD in the absence of the nicotine patch. The timing of the quit date, ideally two days before the week-5 visit, is designed to allow an assessment of withdrawal symptoms, which typically peak around 2 days after quitting, and to provide smoking cessation counseling when individuals are particularly susceptible to relapse (usually in the first 3-4 days following quitting).

The smoking quit date will be considered the first day of the O-MPH/P-Stnd Smoking Tx phase, which will last for 6 weeks. The grace period will be the first two weeks, with the remaining four weeks comprising the period in which the participant must not meet criteria for treatment failure (see section 6.5.1) in order to be scored as meeting prolonged abstinence. The selection of a 4-week period is consistent with FDA standards for approving smoking cessation medications [Hughes et al., 2003]. In addition, in this pilot study we wished to keep the study length to a minimum while still being able to obtain an initial sense of the safety and efficacy of OROS-MPH. Tying the smoking assessments to the quit date, as opposed to the randomization date, is consistent with the recommendations of the SNRT [Hughes et al., 2003].

During the O-MPH/P-Stnd Smoking Tx phase each participant will continue taking the highest OROS-MPH/placebo dose tolerated and also continue individual smoking cessation counseling.

The participant will be discontinued from OROS-MPH/placebo following completion of the final O-MPH/P-Stnd Smoking Tx assessment, which will occur approximately at the beginning of study week 11. Tapering of the nicotine patch (see section 8.13) will begin approximately at the start of week 12.

7.7 Follow-up

The follow-up visit will be conducted at approximately study week 15. 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 smoking status.

7.8 Maintaining and Breaking Study Blind

The decision to break the study blind for an individual participant should be made by the site investigator or by the medical monitor after consultation with the Lead Investigator if possible, but should be resorted to only in cases of life-threatening emergency when knowledge of the treatment group investigational agent will influence clinical management.

7.9 Medication and Trial Discontinuation

7.9.1 Medication Discontinuation

An investigator may discontinue a participant's medication (without breaking the blind unless the conditions stated in section 7.8 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 not in the participant's best interest
3. inability or unwillingness of the participant to comply with the study protocol
4. serious intercurrent illness

A participant may discontinue medication anytime s/he wishes. Although the participant may withdraw entirely from the study whenever s/he wishes, participants will be strongly encouraged to continue attending visits at which safety measures are scheduled to be assessed. Participants who wish to discontinue from study

medications early or to withdraw from the study will have their OROS-MPH/Placebo discontinued and will be offered a taper for the nicotine patch following the taper schedule outlined in section 8.13.

Any participant who discontinues prematurely, regardless of the reason, will be requested to return for a final visit during week 11 to perform the necessary procedures listed in Table-2 and to obtain data for end of study/early termination. 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.

Study participants withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Participants will be asked to sign a general consent for the release of information to the referred health care provider. Study staff may request transportation for emergency treatment of a participant if medically appropriate (e.g., for acutely psychotic or suicidal participants).

7.9.2 Stopping Guidelines

Participants who develop elevations of blood pressure $>140/90$ or heart rate >100 on two consecutive clinic visits during the study, without elevation of OROS-MPH dose during the consecutive clinic visits, will be considered as developing clinically significant elevations of blood pressure provided no other contributing causes can be identified other than the study medication. Participants who fail to re-establish normotensive blood pressure readings or normal heart rates, will have their dose of OROS-MPH adjusted downward if necessary to re-establish normotensive blood pressure readings/ normal heart rate or will be withdrawn from the study medication at the investigator's discretion. Initiation of antihypertensive medication during the study, or an increase in the prescribed dose of an antihypertensive medication, will be taken to signify the development of clinically significant elevations of blood pressure and will trigger the investigator to consider reduction of the study medication dose or withdrawal of a participant from the study medication.

7.9.3 Trial Discontinuation

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

7.10 Participant Reimbursement

Participants will be reimbursed for their transportation, inconvenience, and time. It is recommended that participants receive a total of \$100 for completing screening/baseline. For the study visits it is recommended that the participants receive \$50 for the week-11 visit, which is significantly longer than the other visits, and \$25 for each of the other research visits. However, participant reimbursement might vary across study sites to take into account local IRB guidelines, as well as special circumstances and geographic differences across sites. The Lead Node should be informed of any changes in level of participant reimbursement.

8.0 INVESTIGATIONAL AGENTS

8.1 OROS-MPH

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 $C_{14}H_{19}NO_2 \cdot HCl$. 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.

OROS-MPH is manufactured by Alza Corporation and marketed by McNeil Consumer and Specialty Pharmaceuticals. The active medication will be obtained from the manufacturer.

8.2 Placebo

Placebo will be supplied by the manufacturer (Alza Corporation) and will be an exact match of OROS-MPH tablets minus the active ingredient, methylphenidate HCl.

8.3 Nicotine Transdermal Patch

Transdermal nicotine patches will be utilized. Nicotine patches will be provided in three strengths during the study: 1) 21 mg/24 hours during the O-MPH/P-Stnd Smoking Tx phase, 2) 14 mg/24 hours during the first two weeks of taper (approximately study weeks 12 and 13), and 3) 7 mg/24 hours during the third week of taper (approximately study week 14). If a participant is unable to tolerate the scheduled patch strength then a reduced strength will be provided.

8.4 Dispensing Investigational Agents

8.4.1 OROS-MPH/Placebo

In study week 1, 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 study week 2, and each successive week through week 10, 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.

8.4.2 Nicotine Transdermal Patch

In study weeks 4, 5, 7, and 9 a two-week supply of nicotine patches will be dispensed to the participant for self-administration. Patches for the three week taper will be dispensed at week 11. This procedure will provide the participant with enough extra patches at all times to account for holidays or missed visits, while keeping waste and confusion to a minimum.

8.5 Packaging and Labeling

8.5.1 OROS-MPH/Placebo

The investigational agents will be packaged in unit-of-use bottles, containing 1 week's tablets, that are child-resistant. The product will be labeled with the protocol number, treatment/randomization number, the study week, number of doses in the bottle, and the directions for use. The following statement will also be printed on the bottles—"Caution: Federal law PROHIBITS the transfer of this drug to any person other than the patient for whom it was prescribed".

8.5.2 Nicotine Transdermal Patch

Nicotine patches will be supplied in manufacturer's packaging that includes all required labeling. Study sites may supply additional prescription labels indicating patient name, date of dispensing, directions for use, quantity dispensed, prescribing clinician, and prescription number if required.

8.6 Storage

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

8.7 Record of Administration

Comprehensive drug-accountability records including perpetual inventory, will be maintained at all times, using study-specific forms provided to the study staff. These will include a record of the number of tablets and patches transferred between areas of the study site (from pharmacy to clinic and back, for example), and those dispensed to and returned by an individual participant.

Accurate recording of all investigational agent dispensed/administered will be made in the appropriate sections of the CRF.

8.8 Used/Unused Supplies

Empty, partially used, and unused bottles of investigational agent will be returned to the pharmacy (or other appropriately licensed entity) and logged into a perpetual inventory of study drug returned. The study staff will accurately maintain study drug accountability.

8.9 Side Effects of OROS-MPH

OROS-MPH should be used with caution in individuals with bipolar disorder, diabetes mellitus, cardiovascular disease, seizure disorders, insomnia, psychosis, small bowel disease, peritonitis, cystic fibrosis, or chronic intestinal pseudo-obstruction.

Most frequent adverse effects of methylphenidate appear to be dose related and include nervousness, edginess, and insomnia. Other adverse effects include anorexia, nausea, abdominal pain, dryness of the throat and mouth, dizziness, tachycardia, headache, nervousness, tics or spasms, drowsiness, vomiting, sadness, fever, cough, sore throat, and upper respiratory infection. Chest discomfort, abnormal heart rhythm, and changes in blood pressure or pulse may also occur.

Hypersensitivity reactions include 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.

Other rare adverse events include hepatotoxicity, thrombocytopenia, epistaxis, gingival bleeding, leukopenia, anemia, eosinophilia, transiently depressed mood, and hair loss.

8.10 SIDE EFFECTS OF NICOTINE PATCH

The main side-effect of using nicotine patches is the possibility of a skin rash developing at the location of the patch. Applying the new patch to a different part of the body each day may help, as may simple antihistamine creams. Other possible side-effects include sleep disturbances or insomnia (removing the patch after 8 PM each evening may help here), vivid dreams, and nausea. Nicotine may also increase blood pressure and heart rate and thus may exacerbate cardiovascular disorders. It may also exacerbate depression, anxiety, hyperthyroidism, pheochromocytoma, and peptic ulcers. It should be used cautiously in individuals with diabetes or with severe kidney or liver problems. It should not be used by pregnant or breastfeeding women or by persons under the age of 18 (since it has not been formally tested on this population).

Symptoms of overdose include: nausea, vomiting, watering mouth, diarrhea, abdominal pain, cold sweat, headache, dizziness, disturbed hearing and vision, confusion, weakness, weak, irregular heartbeats, chest pain, and seizures.

8.11 Safety of OROS-MPH in the Presence of Nicotine

The direct drug-drug interaction of nicotine and methylphenidate has not been studied. One study evaluating the use of nicotine for treatment of ADHD found that individuals treated with a combination of nicotine and methylphenidate reported less depression than other groups [Levin et al., 2001].

Nicotine can act as a stimulant, and therefore there may be an additive or synergistic effect on blood pressure and heart rate when it is used in combination with methylphenidate. These effects will be carefully evaluated in the present study.

8.12 Concomitant Medications

Any medication (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the investigator. The following medications should be used only after careful consideration by the medical clinician.

1. Anticonvulsants, tricyclic and SSRI antidepressants, and coumadin (OROS-MPH may increase their plasma levels).
2. Sympathomimetics (because of possible synergistic increases in blood pressure with OROS-MPH)
3. Centrally acting antihypertensive agents such as clonidine and alpha-methyldopa (their effects may be diminished by OROS-MPH)
4. Substrates of CYP2D6 (their plasma levels may decrease on smoking cessation)
 - amiodarone (Cordarone)
 - chlorpheniramine Maleate (Chlor-Trimeton)
 - cimetidine (Tagamet)
 - clomipramine (Anafranil)
 - fluoxetine (Prozac)
 - haloperidol (Haldol)

- methadone
- paroxetine (Paxil)
- quinidine
- ritanovir (Norvir)

8.13 Treatment Plan

Table 3: OROS-MPH/Placebo Dose Escalation

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

Study participants will be randomly assigned to receive either OROS-MPH or matching placebo. The dose escalation schedule is given in Table 3. By the end of this three-week dose-escalation phase study participants should be stabilized at the highest tolerated dose not exceeding 72 mg.

OROS-MPH 18 mg tablets or matching placebo will be dispensed at each weekly visit as described in section 8.4.1. This procedure will provide enough extra medication that the participants will not run out of medication if they should miss a visit.

Participants will be instructed on how to take the investigational agent during each week, and they will be instructed to return empty bottles or any unused medication during each study week’s visit. Note that the maximum dose to be used for this study has recently been approved by the FDA for adults with ADHD.

Nicotine patches will be dispensed during clinic visits as described in section 8.4.2. The dosing schedule for these patches is outlined in Table 4.

Table 4: Nicotine Patch Dosing Schedule

Patch Strength	Study Weeks (approximate)
21 mg/24 hours	4-11
14 mg/24 hours	12-13
7 mg/24 hours	14

9.0 SMOKING CESSATION COUNSELING

9.1 Introduction

The U.S. Public Health Service (USPHS) Clinical Practice Guideline recommends that smoking cessation interventions should include counseling and behavioral therapy as this specifically results in higher tobacco abstinence rates. Consistent with the guideline, participants enrolled in the present study will receive brief, individualized counseling with the aim of providing them with problem-solving skills, training, and social support as part of treatment. The “Smoke Free and Living It” manual© has been developed and used extensively in research by the Mayo Clinic Nicotine Research Center (Nicotine Research Program Staff. Smoke-Free and Living It. Mayo Foundation for Medical Education and Research - Nicotine Dependence Center - Research Program. 2005).

The “Smoke Free and Living It” manual© has been used in large scale, multi-center, multi-country trials as an adjunct to medication in helping smokers abstain from smoking. Since 1998, this manual has been used in clinical trials involving over 7,500 smokers. It serves both as a self-help manual and the basis for brief counseling, based on the USPHS guideline. An interventionist guide accompanies the patient manual that will assist the interventionist in the delivery of each counseling topic. This will assure that all intervention topics are covered in a consistent manner. Key points are listed for each topic and discussion points are available as time allows. The topics included in the patient manual and in the guide are based on smokers’ experiences when trying to stop smoking through the Mayo Clinic Nicotine Dependence Center (Treatment and Research Programs). We chose to use the brief office intervention because of its past success in helping smokers through their nicotine dependence treatment. It is also currently being used as a smoking cessation treatment within various clinical settings. We feel that providing “Smoke Free and Living It”© will encourage study enrollment by offering all participants a recognizable and meaningful level of intervention.

9.2 Overview of “Smoke Free and Living It”©

The “Smoke Free and Living It” © counseling will consist of an approximately 10-minute session administered by a trained interventionist during each research visit during study weeks 1-10. Although this therapy is in the form of a manual, the intention is to cover the material in a sequence that best meets the need of a given participant. Table 5 lists the modules from “Smoke-free and Living It” along with the study week during which they typically will be implemented.

Table 5: Typical Time-line for Administering Psychosocial Treatment Modules

Study Week	Treatment Module	Administered by
1	Nicotine Addiction/Congratulations	Medical Clinician
2	Benefits of quitting smoking	Interventionist
3	Rewarding yourself for not smoking	Interventionist
4	Day Before Quit Day/Making not smoking easier	Interventionist
5-9	Triggers/Withdrawal	Interventionist
	Managing Stress	Interventionist
	Weight/Exercise	Interventionist
	Self Image	Interventionist
	Time Management	Interventionist
10	Maintenance	Interventionist
11	Stopping Study Medication/Focus on the Future	Interventionist

*The Treatment Modules can be completed in the order listed or rearranged to best meet the needs of a given participant

9.3 Interventionist Selection

Interventionist Selection Criteria:

- A minimum of a bachelor's degree, preferably in a behavioral science (e.g., psychology, sociology, etc.)
- willing to learn and implement the “Smoke Free and Living It” © counseling program
- willing to have counseling sessions videotaped and then reviewed by a Site Trainer and/or a Mayo Clinic staff member

9.4 Interventionist training and supervision

9.4.1 Training Model

The present study will utilize a “training of trainers” (TOT) model for training the interventionists.

9.4.2 Interventionist Training

TOT Training – Site Trainers will attend a training provided by staff from the Mayo Clinic Nicotine Research Program. This approximately four-hour training will be focused on learning about the “Smoke Free and Living It” © manuals to be used in the present study. Training will include a lecture format, review of video examples of counseling sessions, and role playing exercises.

Interventionist Training – Once certified (see below), Site Trainers will provide training to the Interventionists. These training sessions will ideally be completed over a period of a week, taking at least 4 hours to work with the staff initially and then allowing for time over two to three days for the staff to practice sessions with each other or the trainer. The last step will involve the trainer observing staff administering mock counseling sessions for certification (see below). Training will include a lecture format, review of video examples of counseling sessions, and role playing exercises.

9.4.3 Site Trainer and Interventionist Certification

Site Trainers – The Site Trainer will complete a mock counseling session, which will be rated by a qualified staff member from the Mayo Clinic Nicotine Research Program. To be certified, the Site Trainer will be scored on the following criteria:

- Familiarity with each of the intervention topics
- Ability to effectively guide study participant through key points in the 10 minute time allowed
- Ability to make and maintain eye contact
- Ability to listen
- Ability to identify individual needs and provide the appropriate intervention
- Ability to remain non-judgmental and encouraging
- Ability to recognize the opportunity for teaching vs the need to allow for more interaction and discussion remaining within the 10 minute time allowed

The rater will use a three (3) point scale (1-Meets expectations, 2-Needs improvement, 3-Expectations not met and additional training required) that will determine if the staff member meets each criterion.

If a Site Trainer does not meet 6 out of 7 of the established criteria, more time must be allowed for additional training. This would include watching recorded sessions and doing practice sessions with other staff. Another mock counseling session would need to be completed by the Site Trainer for certification.

In addition, the Site Trainer must demonstrate reasonable inter-rater agreement with Mayo staff and thus, will rate two sessions that have been rated by Mayo staff, with the second rated session serving as the certification session. To be certified, the Site Trainer's ratings must be in perfect agreement with those of the Mayo staff for at least six of the seven items rated. Site Trainers who fail to be certified on the first certification session will receive additional training and will complete an additional certification session(s); a Site Trainer who is unable to meet the inter-rater agreement criterion will not be allowed to supervise the Interventionist(s).

Interventionist – The Interventionist will complete a mock counseling session, which will be rated by the Site Trainer. To be certified, the Interventionist will be scored on the following criteria:

- Familiarity with each of the intervention topics
- Ability to effectively guide study participant through key points in the 10 minute time allowed
- Ability to make and maintain eye contact
- Ability to listen
- Ability to identify individual needs and provide the appropriate intervention
- Ability to remain non-judgmental and encouraging
- Ability to recognize the opportunity for teaching vs the need to allow for more interaction and discussion remaining within the 10 minute time allowed

The rater will use a three (3) point scale (1-Meets expectations, 2-Needs improvement, 3-Expectations not met and additional training required) that will determine if the staff member meets each criterion.

If an Interventionist does not meet 6 out of 7 of the established criteria, more time must be allowed for additional training. This would include watching recorded sessions and doing practice sessions with other staff. Another mock counseling session would need to be completed by the Interventionist for certification.

9.4.4 Ongoing Interventionist Supervision and Training

A certified Site Trainer will have primary responsibility for supervising the interventionists' "Smoke Free and Living It" © counseling. It is expected that the Site Trainer will rate one videotape per interventionist, on an approximately per month basis, contingent upon the interventionist having active cases to review. The Site Trainer will then provide feedback, and if needed, additional training, to each interventionist.

9.4.5 Quality Control of Counseling Administered

Quality control checks will include the rating of a randomly selected videotaped session by a certified Site Trainer on an approximately monthly basis, contingent upon the Interventionist having active cases. If an interventionist falls below criterion for certification (see section 9.4.3) additional supervision will be provided. If an interventionist falls below criterion on three consecutive sessions then the interventionist will

need to repeat the certification process (see section 9.4.3) prior to being assigned any additional study participants.

In addition, videotapes will be independently rated by Mayo Clinic staff to determine inter-rater agreement. For Site Trainers who originally met the inter-rater agreement certification criterion on their first certification tape (see section 9.4.3), the independent rating by Mayo Clinic staff will occur approximately 6 months after the Site Trainer's original certification. For Site Trainers who originally failed to meet the inter-rater agreement certification criterion on their first certification tape (see section 9.4.3), the independent rating by Mayo Clinic staff will occur approximately 3 months after the Site Trainer's original certification. For the independent rating assessments, if the Site Trainer's ratings are in perfect agreement with those of the Mayo staff for at least six of the seven items rated, then the next independent rating by Mayo staff will occur approximately 6 months later. Otherwise, the Site Trainer will: 1. receive additional training, 2. have another tape independently rated by the Mayo staff, and 3. have an independent rating by Mayo staff approximately 3 months later.

10.0 ANALYTICAL PLAN

10.1 Statistical Hypotheses

10.1.1 Primary Hypothesis

The primary hypothesis is that the rate of prolonged abstinence (0-1 variable) will be greater for the OROS-MPH group than for the placebo group.

10.1.2 Secondary Hypotheses

It is also hypothesized that:

1. OROS-MPH, relative to placebo, will be more effective in reducing ADHD symptoms in smokers with ADHD.
2. OROS-MPH with individual smoking-cessation counseling, relative to placebo with individual smoking-cessation counseling, will reduce cotinine levels in smokers with ADHD.
3. OROS-MPH with individual smoking-cessation counseling, relative to placebo with individual smoking-cessation counseling, will reduce cpd in smokers with ADHD.
4. OROS-MPH and standard smoking treatment (i.e., counseling and the nicotine patch), relative to placebo and standard smoking treatment, will be more effective in achieving an initial quit, point-prevalence abstinence, complete abstinence, and in reducing the number of smoking days in smokers with ADHD.
5. OROS-MPH will be safe for treating ADHD in smokers, and the combination of OROS-MPH and nicotine patch will be safe and well tolerated.
6. OROS-MPH and standard smoking treatment, relative to placebo and standard smoking treatment, will be more effective in reducing tobacco withdrawal symptoms.

7. ADHD symptom severity as assessed during study week 4 will be associated with the ability to obtain an initial quit and to achieve prolonged abstinence.

10.2 Intent-to-Treat and Evaluable Participant Populations

The intent-to-treat population is defined as the participants who are randomized to treatment. The evaluable population is defined as the participants who are randomized and who complete at least two visits during the first four weeks following randomization, who reach the full dose of OROS-MPH /placebo, who have a OROS-MPH /placebo medication compliance rate of at least 75% each week for study weeks 4 through 10, and who attend at least one meeting after initiating the nicotine patch.

10.3 Analysis Plan

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat (ITT) and for the evaluable population. Major differences in the results for the ITT and evaluable populations, if any, will be further explored. While there is every intention to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency, and some adjustments may be required to meet constraints posed by the structure of the data.

For this pilot study, all statistical test tests will be conducted at the 5% Type I error rate (two-sided). The statistical tests are exploratory and any significant results will need to be confirmed in prospective studies. When multiple tests are conducted, the chance of finding a significant difference in one of the tests, when in fact no difference exists, is greater than the stated Type I error rate. The investigators are aware of the multiple testing issues and will interpret results with caution and use confidence intervals where possible.

10.3.1 Primary Outcome

The primary hypothesis will be tested by comparing the OROS-MPH and placebo groups on prolonged abstinence rate (see section 6.5.1). Missing self-report smoking data will be treated as positive for smoking. A logistic regression will be used to model the response variable as a function of treatment group.

10.3.2 Secondary Outcome

Several secondary analyses that will further elucidate the efficacy and safety of OROS-MPH, compared to placebo, for treating smokers with ADHD have been included in this study. For all Generalized Estimating Equations (GEE) analyses, the response variable will be modeled as a function of treatment group, time (treated as a continuous variable), and their interaction.

1. GEE will be used to compare the treatment groups on ADHD symptoms (defined by the DSM-IV checklist and the CGI severity score) as measured at screening/baseline and study weeks 1-4. This analysis will provide information about the efficacy of OROS-MPH, in the absence of nicotine patch, in treating ADHD in smokers.
2. GEE will be used to compare the treatment groups on cotinine levels as measured at screening/baseline and study weeks 1-4. This analysis will provide information about the efficacy of OROS-MPH with individual smoking-cessation counseling, vs. placebo with individual smoking-cessation counseling, in reducing cotinine levels in smokers with ADHD.

3. GEE will be used to compare the treatment groups on cpd as measured at screening/baseline and study weeks 1-4. This analysis will provide information about the efficacy of OROS-MPH with individual smoking-cessation counseling, vs. placebo with individual smoking-cessation counseling, in reducing cpd in smokers with ADHD.
4. A logistic regression including site and treatment group will be used to model rates of achieving an initial quit. This analysis will provide information about the efficacy of OROS-MPH in the presence of standard smoking treatment, vs. placebo in the presence of standard smoking treatment, in helping smokers with ADHD to initially quit smoking.
5. A logistic regression including site and treatment group will be used to model rates of achieving point-prevalence abstinence as assessed at the final visit of the O-MPH/P-Stnd Smoking Tx phase. This analysis will provide information about the efficacy of OROS-MPH in the presence of standard smoking treatment, vs. placebo in the presence of standard smoking treatment, in helping smokers with ADHD to achieve abstinence.
6. GEE will be used to compare the treatment groups on ADHD symptoms (defined by the DSM-IV checklist and the CGI severity score) as measured at screening/baseline and after the smoking Quit date, through week 11. This analysis will provide information about the efficacy of OROS-MPH vs. placebo, in the presence of standard smoking treatment, in treating ADHD in smokers attempting to stop smoking.
7. GEE will be used to compare the treatment groups on Tobacco Withdrawal symptoms (defined by the Withdrawal scale for Tobacco) measured during study weeks 5 through 11. This analysis will provide information about the efficacy of OROS-MPH vs. placebo, in the presence of standard smoking treatment, in reducing withdrawal symptoms.
8. GEE will be used to compare the treatment groups on cpd as measured at screening/baseline through study week 11.
9. 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. GEE will be used to compare the treatment groups on the BDI-II and Beck Anxiety Inventory from screening/baseline through study week 11.
11. A logistic regression including ADHD symptom level at study week 4 will be used to model rates of achieving an initial quit. This analysis will provide information about the relationship between ADHD symptom severity just prior to a quit attempt and the ability to initially quit smoking.

12. A logistic regression including ADHD symptom level at study week 4 will be used to model rates of achieving prolonged abstinence. This analysis will provide information about the relationship between ADHD symptom severity just prior to a quit attempt and the ability to initially achieve prolonged abstinence.
13. A logistic regression including site and treatment group will be used to model rates of achieving complete abstinence. This analysis will provide information about the efficacy of OROS-MPH in the presence of standard smoking treatment, vs. placebo in the presence of standard smoking treatment, in helping smokers with ADHD to quit smoking.
14. GEE will be used to compare the treatment groups on number of smoking days as measured for screening/baseline through study week 10.
15. A logistic regression will be used to model prolonged abstinence rates (see section 6.5.1) as a function of treatment group, site, gender, ADHD Symptom Score (23-30 vs. >30), cpd (10-24 vs. >24), site-by-treatment-group interaction, gender-by-treatment-group interaction, ADHD Symptom Score-by-treatment-group interaction, and cpd -by-treatment-group interaction.

10.3.3 Missing Data

Logistic regression analyses will be conducted to identify patterns of attrition and to determine if there is differential attrition by treatment condition. A binary indicator variable for missing data will be regressed on treatment assignment and other covariates. Variables that are associated with attrition at or below the $\alpha=0.10$ level of significance will be included in subsequent analyses where the assumption of data missing at random (conditional on covariates) is required.

For the primary outcome measure, prolonged abstinence, missing smoking self-report data will be treated as positive for smoking. The same strategy will be used for the secondary outcome measures of achieving initial abstinence and achieving point-prevalence abstinence: participants with missing data for these measures will be scored as having smoked. For the secondary outcome measures of complete abstinence and number of smoking days, missing smoking self-report data and CO will be treated as positive for smoking.

For all other outcome measures, and as a supplementary sensitivity analysis for the outcome measures above, a model to predict the existence of missing data based on the baseline covariates will be examined. Any baseline covariate that is related to the occurrence of missing data will be added to the list of control covariates for the hypothesis test. To minimize any impact of attrition on the test of hypotheses, intent-to-treat analyses will be conducted for all hypotheses. Missing outcome measures (e.g. caused by missing an assessment) will not be imputed. Rather, the hypotheses will be modeled in an intent-to-treat fashion, including cases with missing data with the assumption that these data are missing at random, conditional on the observed covariates. Thus, for estimation to be robust to data which are missing at random, any observed covariates that predict the occurrence of missing data must be included as covariates in the model.

10.4 Sample Size Estimate

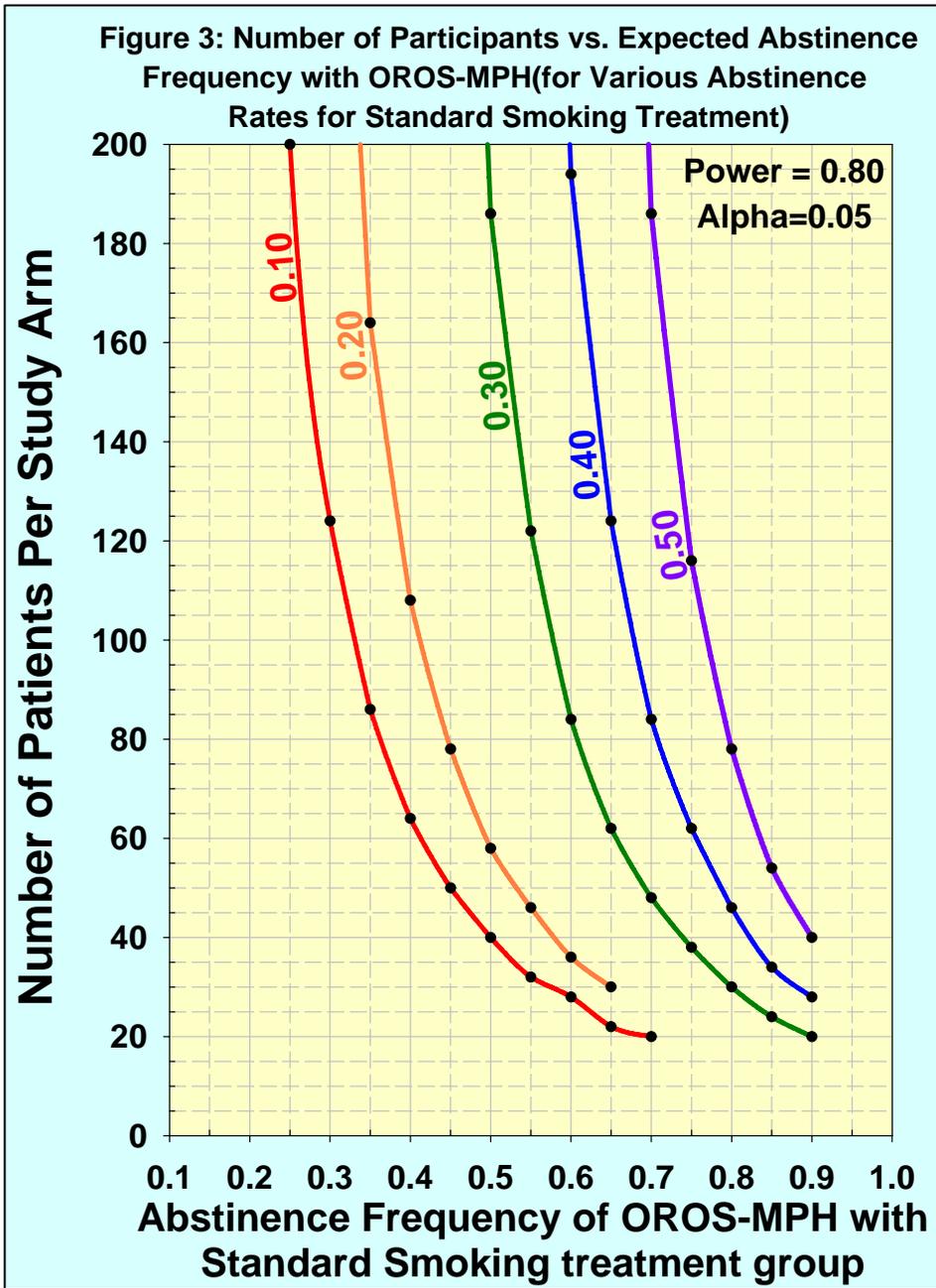
The present study is a pilot study; thus, it is desirable to limit the overall sample size and, hence, the cost of the study. The difficulty associated with a limited sample size lies in having adequate statistical power to answer a number of possible questions. This study has been powered to detect differences between the

treatment groups when the data are pooled across sites. Thus, this study is not powered to detect potential site or site-by-treatment interaction effects; consequently, the detection of these effects will be sacrificed for this pilot study. Should this initial trial suggest that OROS-MPH is a promising intervention for smokers with ADHD, a larger-scale follow-up study can be conducted. The information gathered from the present trial will also provide preliminary data on variability across sites to aid in the planning of a larger follow-up study.

The logistic regression module in PASS 2002 (NCSS Statistical Software, Kaysville, Utah) was used to conduct a power analysis for the primary outcome measures. Figure 3 shows the number of participants needed per arm, assuming a level of significance equal to .05 (two-sided) and 80% power, as a function of the prolonged abstinence rate for standard smoking treatment (nicotine patch and psychosocial treatment) and the prolonged abstinence rate expected when OROS-MPH is added.

In our sample size estimate, we are assuming that 30% of the Placebo + Standard Smoking Treatment group will meet criteria for prolonged abstinence. This rate is consistent with the abstinence rate that has been found for nicotine patch treatment with a self-help manual in a sample not selected based on ADHD (Hurt et al., 2003). To our knowledge, there have been no studies of the effectiveness of the nicotine patch in initiating abstinence in smokers with ADHD.

For the prolonged abstinence rate in the OROS-MPH + Standard Smoking Treatment group we estimate that the rate might be close to double that of the Placebo + Standard Smoking Treatment group. This estimate is based on the general trend seen when comparing the abstinence rates found with brief advice alone (10%) or nicotine replacement therapy (NRT) alone (10%) compared to the rates found when both NRT and brief advice are provided (20%). The premise behind the present study is that smokers with ADHD have more difficulty quitting due to their ADHD symptoms and that effective treatment of ADHD will significantly increase the ability of these smokers to quit. While nicotine also reduces ADHD symptoms, it is not as effective as OROS-MPH. Thus, we are expecting that the effect of adding OROS-MPH to the Standard Smoking Treatment, which is expected to be minimally effective for smokers with ADHD, will be similar in strength to the combination of two treatments (NRT+brief advice) compared to a single treatment (e.g., NRT alone or brief advice alone). We thus are assuming a prolonged abstinence rate of approximately 55% in the OROS-MPH + Standard Smoking Treatment group. Thus, we will need to include approximately 126 participants per arm.



10.5 Descriptive Statistics

Summaries of the characteristics of the participant population in both treatment arms at screening/baseline will be prepared for both the intent-to-treat and evaluable participants. 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 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, smoking cessation, will

be indirectly impacted by the experimental treatment (i.e., OROS-MPH will treat ADHD, and the relief of ADHD symptoms should make obtaining prolonged abstinence easier). Thus while we expect to find a statistically and clinically significant treatment effect at the end of the study, we do not expect to find a large enough treatment effect to warrant an interim efficacy analysis.

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

Each study site must have the study informed consent approved by their local IRB(s). A copy of the IRB-approved consent, along with the IRB study approval, must be sent to NIDA and the LN by fax prior to the site initiation visit. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent 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 form.

Prior to signing the informed consent form, research staff who are knowledgeable about the study will explain the study to the potential participant and provide the participant with a copy of the consent to read. If the participant is interested in participating in the study, a researcher who is authorized to obtain informed consent by the PI and if applicable by the IRB, will review each section of the informed consent form in detail, answer any of the participant's questions, and determine if the participant comprehends the information provided by administering the comprehension tool. 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 must be properly executed and complete to be valid. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Persons delegated by the PI to obtain informed consent 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 PIs 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 monitors

Monitoring 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 QA plan for this protocol and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Monitors will verify that study procedures are properly followed and that submitted data are complete, accurate, and in agreement with source documentation. 100 % of the data will be reviewed for some participants as specified in the QA plan, and for all participants, monitors will verify that consent for study participation has been properly obtained and documented, that research participants enrolled in the study meet inclusion and exclusion criteria, and that serious adverse events have been properly documented and reported. Monitors will also ensure that all essential documentation required by Good Clinical Practice guidelines is present and appropriately filed. If the monitor's review of study documentation indicates that additional training of study personnel is needed, node monitors will undertake or arrange for that training. A report on each monitoring visit will be written and distributed in a timely manner according to the CTN standards for QA reporting currently in effect.

11.3.3 NIDA contract monitors

Investigators will host periodic visits by NIDA contract monitors to audit 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 CTN trials. 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.

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

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. 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

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 will elicit AEs/SAEs at each visit (starting with the screening/baseline) 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 or other medical clinician 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.

NIDA contracted monitors and local node quality assurance (QA) monitors will monitor the study sites and study data on a regular basis and will promptly report any previously unreported safety issues. Local QA monitors will monitor 100% of all SAEs and related documentation and ensure that the SAE is followed appropriately by the research staff. The local QA monitor will ensure that any unreported or unidentified SAEs discovered during monitoring visits are promptly reported by the site to NIDA, the LN, Node or Protocol PI or designee, and the IRB per local IRB requirements and will be reported on the monitoring report. 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 or other medical clinician will review each AE for seriousness, relatedness, and severity. An experienced medical clinician and/or protocol PI will review all AEs and SAEs for severity and relatedness during each clinician visit with the participant, and will consult with the study 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 participants 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 and Management Procedures

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

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

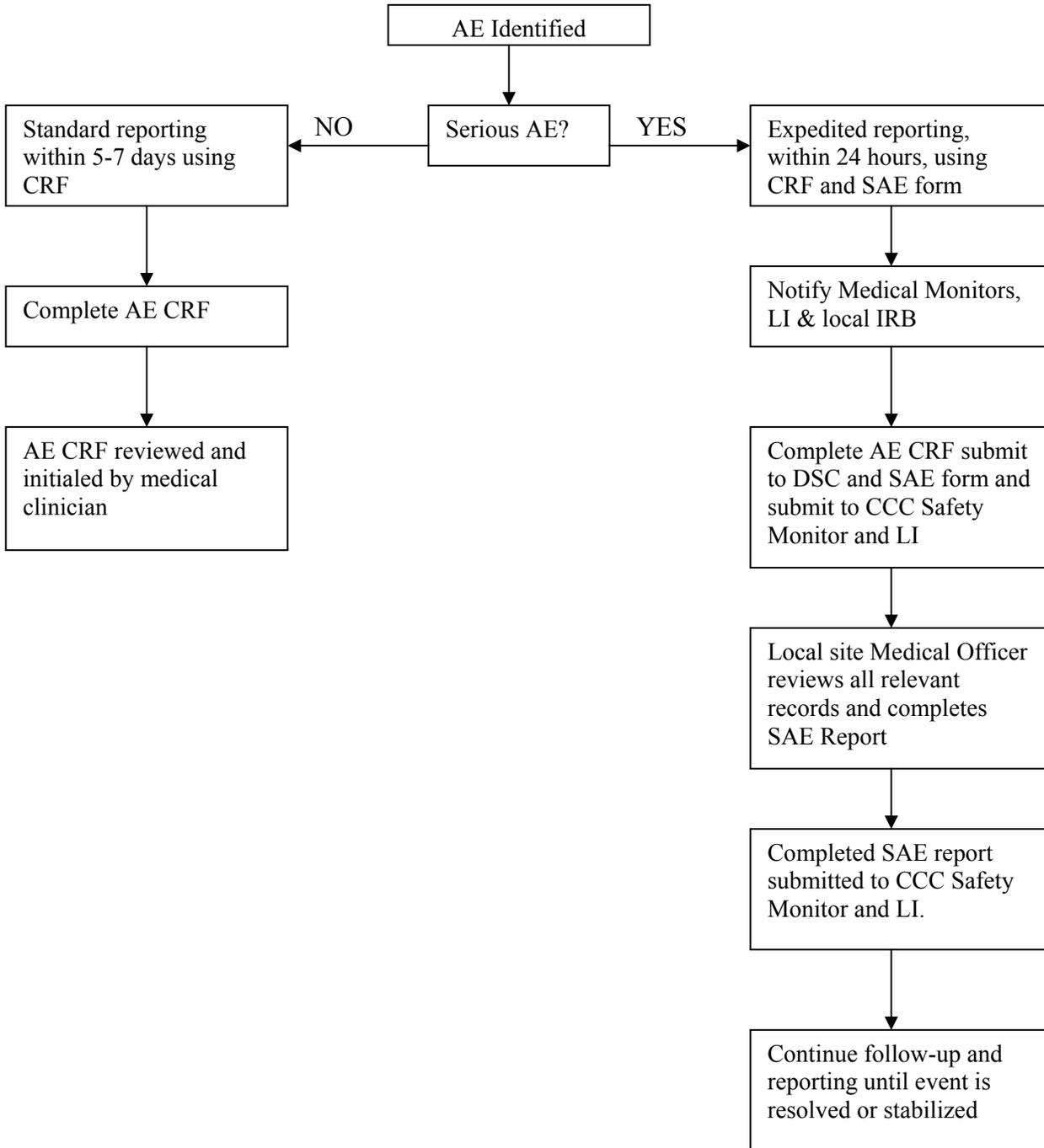
Additional information may need to be gathered to evaluate the SAE and to complete the AE and SAE forms. This process may include obtaining hospital discharge reports, physician records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the 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 LN and NIDA appointed Medical Monitor. 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.

A Medical Monitor associated with the Clinical Coordinating Center (CCC) is responsible for reviewing all serious adverse event reports. The monitor will also make recommendations to the CCC 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 at least annually.

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 LN or NIDA may also request additional and updated information. Details regarding remarkable adverse events, their treatment and resolution, should be summarized by the Investigator in writing upon request for review by the Medical Monitor, local ethics Committee/IRBs or regulatory authorities.

Figure 4



12.0 DATA MANAGEMENT AND PROCEDURES

12.1 Design and Development

This protocol will utilize a centralized data management center (CDMC). The CDMC 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 by the CDMC.

12.1.2 Data Center Responsibilities

The CDMC 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

Completed forms and electronic data will be entered into the data management system in accordance with the SOPs established by the CDMC. Only authorized individuals shall have access to electronic CRFs.

12.3 Data Editing

Corrections to electronic CRFs must be tracked electronically (audited) with time, date, individual making the change, both the old data value and new data value, and the reason for the correction. The CDMC will implement comprehensive error checking and data management procedures.

12.4 Data Transfer

Data will be transmitted by the CDMC to the NIDA central data repository as requested by NIDA. The CDMC 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, and computerized systems.

12.6 Data QA

To address the issue of data quality, the CDMC will follow a standard data monitoring plan detailed in the study Operations Manual. An acceptable data quality level prior to any database lock will be given as part of the data management plan. Data quality summaries will be made available during the course of the study.

13.0 QUALITY ASSURANCE MONITORING

13.1 The Goals of QA Monitoring

The primary goals of quality assurance (QA) monitoring are to protect the rights and safety of participants and to ensure that the study is conducted in compliance with the protocol and applicable regulations and results are credible. Specific guidelines are detailed in the associated, endorsed QA plan for this protocol. All aspects of the study will be carefully monitored with respect to current good clinical practices.

The NIDA-CTN Data and Safety Monitoring Board (DSMB), the lead investigator (LI)-appointed medical monitor, NIDA-CTN contracted clinical monitors, representatives from the lead investigator's node, and local QA monitors from the participating node will be given access to facilities and records to review data pertinent to the study and to verify the conduct of study procedures at the site. These individuals will have access to all records and study documentation as necessary to ensure integrity of the data and periodically will review progress of the study with the principal investigator and research staff. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and inform the sponsor of potential problems at the study sites.

13.2 Node QA Monitors and NIDA-Contracted QA Monitors

Local QA monitors will conduct a Site Pre-Initiation visit prior to the start of the study at a given site to ensure that proper study-related documentation exists, all relevant training has been completed, and the appropriate infrastructure and facilities are in place. Following the local QA visit, NIDA-CTN contracted monitors may conduct a Site Initiation visit, as directed by NIDA.

The minimum requirements for interim monitoring visits by local QA monitors are specified in the QA plan. The following will be monitored during the course of the study, as applicable: Informed consent forms (and HIPAA authorizations, if applicable); inclusion/exclusion criteria; primary outcome measures; safety assessments; all related documents and reporting for protocol violations; randomization process; medications; and related documentation and reporting for expedited reportable adverse events/serious adverse events (SAEs). Monitors will also review all study materials for a select number or percentage of study participants, as specified in the protocol's QA plan. Each CRF selected will be 100% source document verified for accuracy of data recording. Quality assurance monitoring instructions/checklists will be provided by the lead node as an attachment to the QA plan.

Routine monitoring visits by the local QA monitors will be scheduled at appropriate intervals, usually more frequently at the beginning of the study. The minimum frequency of site monitoring visits is specified in the QA plan for this protocol, but visits should occur as often as needed to help prevent, detect, and correct problems at the study sites. Utilizing checklists and other QA tools provided by the lead node or from other sources, monitors will verify that procedures are being conducted according to the protocol and GCP guidelines. Participating site's regulatory files will be monitored comprehensively at the beginning and end

of the study, when significant events occur, and as specified in the QA plan. All node-level QA reports will be disseminated as specified in the protocol QA plan.

NIDA-contracted monitors will also schedule monitoring visits during the course of the study, at a frequency determined by their arrangements with NIDA. These monitoring visits allow for an independent evaluation of study progress and potential problems at the study sites. These monitors may review regulatory documents, verify participants' consents, confirm that participants meet inclusion and exclusion criteria and are randomized as specified in the protocol, ensure that adverse and serious adverse events are properly documented and reported, verify that study treatments are properly provided, ensure that submitted data are complete, accurate, and in agreement with source documentation, check that study medications are properly dispensed, recorded, and accounted for, and check that study procedures are followed as per protocol.

Local QA monitors will conduct closeout visits per CTN requirements upon completion of all data collection at their participating sites. NIDA-CTN contracted monitors may conduct site closeout visits upon completion of all data collection, as directed by NIDA. During closeout monitoring visits monitors will verify that regulatory files, including IRB and safety reporting, are complete and up to date, all study procedures are completed and documented and all data has been reported as required, study medication and supplies have been inventoried and returned or disposed of properly and documented in accordance with the guidelines that govern the conduct of the study, and staff are aware of record retention and study closeout procedures.

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.

16.0 REFERENCES

- Adler L and Cohen J. (2004) Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. *Psychiatr Clin N Am* 27: 187-201.
- Adler LA and Chua H. (2002) Management of ADHD in Adults. *J Clin Psychiatry* 63 (suppl): 29-35.
- Beck AT, Epstein N, Brown G, et al. (1988) An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*;56:893-897.
- Beck AT, Steer RA, Brown GK. Beck Depression Inventory-II. (1996) The Psychological Corporation, Harcourt Brace & Company, San Antonio.
- Biederman J (2002), Practical considerations in stimulant drug selection for the attention-deficit/hyperactivity disorder patient- efficacy, potency and titration. *Today's Therapeutic Trends* 20: 311-328
- Biederman J and Faraone SV. (2004) Marked Functional Impairments Associated with ADHD: A controlled Study of 500 Adults in the Community. Presented at the 157th Annual Meeting of the American Psychiatric Association, New York, N.Y.
- Biederman J, Quinn D, Weiss M, Markabi S, Weidenman M, Edson K, Karlsson G, Pohlmann H, Wigal S (2003), Efficacy and safety of Ritalin LA, a new, once daily, extended-release dosage form of methylphenidate, in children with attention deficit hyperactivity disorder. *Paediatric Drugs* 5: 833-841
- Biederman J, Wilens T, Mick E, et al. (1995) Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): effects of ADHD and psychiatric co-morbidity. *Am J Psychiatry*; 152: 1652-1658.
- Brandon TH, Meade CD, Herzog TA, Chirikos TN, Webb MS, Cantor AB (2004). Efficacy and cost-effectiveness of a minimal intervention to prevent smoking relapse: dismantling the effects of amount of content versus contact. *J Consult Clin Psychol* 72:797-808.
- Cacciola JS, Alterman AI, O'Brien CP, McLellan AT (1997). The Addiction Severity Index in clinical efficacy trials of medications for cocaine dependence. In *NIDA Research Monograph Series No. 175* (pp. 182-191). Rockville, MD: NIDA.
- Center for Disease Control. (2002) Annual Smoking Attributable Mortality, Years of Potential Life Lost, and Economic Costs – United States, 1995-1999. *MMWR*, 51: 300-303.
- Chang WH, Chuang-Stein C. (2004). Type I error and power in trials with one interim futility analysis. *Pharmaceutical Statistics* 3: 51-59.
- Cox D, Merkel R, Penberthy J, Kovatchev B, Hankin C (2004), Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: A pilot study. *Journal of the American Academy of Child & Adolescent Psychiatry* 43: 269-275

- Darke S, Hall W, Heather N, Ward J, Wodak A (1991). The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS* 5(2):181-5.
- DuPaul GJ, Power TJ, Anastopoulos AD, et al. (1998). *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. New York: Guilford Press.
- First MB, Spitzer RL, Gibbon M, Williams JBW (1996). *Structured Clinical Interview of Axis I DSM-IV Disorders - Patient Edition (With Psychotic Screen) (SCID-I/P w/ Psychotic Screen, Version 2.0)*, Biometrics Research Department, New York State Psychiatric Institute, New York.
- Fischman MW and Foltin RW (1991). Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *Br J Addict.* Dec;86(12):1563-70.
- Greenhill L, Abikoff H, Arnold L, Cantwell D, Conners C, Elliott G, Hechtman L, Hinshaw S, Hoza B, Jensen P, March J, Newcorn J, Pelham W, Severe J, Swanson J, Vitiello B, Wells K (1996), Medication treatment strategies in the MTA Study: Relevance to clinicians and researchers. *Journal of the American Academy of Child & Adolescent Psychiatry* 35: 1304-1313
- Greenhill L, Halperin J, Abikoff H (1999), Stimulant medications. *Journal of the American Academy of Child & Adolescent Psychiatry* 38: 503-512
- Guy W, Bonato RR, eds. (1970) *Manual for the ECDEU Assessment Battery.2*. Rev ed. Chevy Chase, Md: National Institute of Mental Health; 12-1-12-6.
- Halperin M, Lan KKG, Ware JH, Johnson NJ and DeMets DL. (1982). An aid to data monitoring in long-term clinical trials. *Controlled Clinical Trials* 3: 311-323.
- Hall, S., Havassy, B., Wasserman, D. (1991). Effects of commitment to abstinence, positive moods, stress, and coping on relapse to cocaine use. *Journal of Consulting and Clinical Psychology*, 59, 526-532.
- Hasin DS, Trautman KD, Miele GM, Samet S, Smith M, Endicott J. (1996). Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry*. 153(9):1195-201.
- Hatsukami DK, Grillo M, Pentel PR, Oncken C and Bliss R (1997) Safety of cotinine in humans: Physiologic, subjective, and cognitive effects. *Pharmacol Biochem Behav* 57(4): 643-650.
- Heatherton T, Kozlowski L, Freckler R, Fagerstrom K (1991) The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *Brit. J. Addiction* 86, 1119-1127.
- Hughes JR, Gust SW, Skoog K, Keenan RM and Fenwick JW (1991) Symptoms of tobacco withdrawal: A replication and extension. *Arch Gen Psychiatry* 48:52-59.
- Hughes J R and Hatsukami D (1986) Signs and symptoms of tobacco withdrawal. *Arch. Gen. Psychiatry* 43: 289-294.
- Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE (2003). Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tob Res.* 5:603

Hurt RD, Krook JE, Croghan IT, Loprinzi CL, Sloan JA, Novotny PJ, Kardinal CG, Knost JA, Tirona MT, Addo F, Morton RF, Michalak JC, Schaefer PL, Porter PA, Stella PJ. (2003). Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. *J Clin Oncol.* 1;21(5):914-20.

Kessler RC, Adler L, Ames M et al. (in press) The World Health Organization Adult ADHD Self-Report Scale (ASRS). *Psychol Med.*

Kessler RC et al. Prevalence of Adult ADHD in the United States: Results from the National Comorbidity Survey Replication (NCS-R) Presented at the 157th Annual Meeting of the American Psychiatric Association, New York, N.Y., May 2004.

Kollins S (2003), Comparing the abuse potential of methylphenidate versus other stimulants: A review of available evidence and relevance to the ADHD patient. *Journal of Clinical Psychiatry* 64 (Suppl 11): 14-18

Krause K-H, Dresel SH, Krause J, la Fougere C, Ackenheil M. (2003) The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. *Neurobiorev* ; 27: 605-613

Lerman C, Wileyto EP, Patterson F, Rukstalis M, Audrain-McGovern J, Restine S, Shields PG, Kaufmann V, Redden D, Benowitz N, Berrettini WH (2004) The functional mu opioid receptor (OPRM1) Asn40Asp variant predicts short-term response to nicotine replacement therapy in a clinical trial. *Pharmacogenomics J* 4: 184-192.

Levin E, Conners K, Sparrow E et al. (1996) Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychopharmacology* ; 123: 55-63

Liang K-Y, Zeger SL (1986). Longitudinal data analysis using generalized linear models. *Biometrics* 73:13-22.

Lopez F, Silva R, Pestreich L, Muniz R (2003), Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. *Paediatric Drugs* 5: 545-555

Martin, W.R., Sloan, J.W., Sapira, J.D., Jasinski, D.R. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man, *Clinical Pharmacology and Therapeutics*, 12, 245-258.

McGahan PL, Griffith JA, Parante R, McLellan AT (1982). Composite scores from the Addiction Severity Index. Washington, DC: National Institute on Drug Abuse Project DA02554 and the Veterans Administration.

Mereu G, Yoon K, Gessa G, Naes L. (1987) Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. *Eur J Pharmacol* ; 141: 395-399

Mezinskis J, Dyrenforth S, Goldsmith J, Cohen M, and Somoza E (1998). Craving and withdrawal symptoms for various drugs of abuse. *Psychiatric Annals* 28:577-583.

Milberger S, Biederman J, Faraone SV et al. (1997). ADHD is associated with early initiation of cigarette smoking in children and adolescents. *J Am Acad Child Adolesc Psychiatry*; 36: 37-43

- Pelham W, Gnagy E, Burrows-Maclean L, Williams A, Fabiano G, Morrisey S, Chronis A, Forehand G, Nguyen C, Hoffman M, Lock T, Fielbelkorn K, Coles E, Panahon C, Steiner R, Meichenbaum D, Onyango A, Morse G (2001), Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics* 107: E105
- Pepe MS, Anderson GL. (1992). Two-stage experimental designs: early stopping with a negative result. *Applied Statistics* 41:181-190.
- Pomerleau O, Downey K, Stelson F, Pomerleau C. (1996). Cigarette smoking in adult patients diagnosed with ADHD. *J Subst Abuse*; 7: 373-378
- Potter AS and Newhouse PA. (2004). Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology*; 176: 182-194.
- Schachter H, Pham B, King J, Langford S, Moher D (2001), How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *Canadian Medical Association Journal* 165: 1475-1488
- Sobell LC, Sobell MB (1992). Timeline follow back: A technique for assessing self-reported ethanol consumption. In J. Allen & R. Lit-ten (Eds.), *Techniques to Assess Alcohol Consumption*. Pp 19-28. New Jersey: Humana Press, Inc.
- Spencer TJ. (2004). Adult attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am.* 27(2):XI-XII.
- Spitzer RL, Williams JB, Gibbon M, First MB (1995). *The Structured Clinical Interview for the DSM-IV (SCID)*. Washington, D.C.: American Psychiatric Press.
- SRNT Subcommittee on Biochemical Verification. (2002) Biochemical verification of tobacco use and cessation. *Nicotine Tob Res.* May;4(2):149-59.
- Stout, R. L., Wirtz, P., Carbonari, J. P., & Del Boca, F. (1994). Ensuring balanced distribution of prognostic factors in treatment outcome research. *Journal of Studies on Alcohol*, Supplement No. 12, 70-75.
- Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, Lindemulder E, Wigal S (2003), Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: Proof-of-concept and proof-of-product studies. *Archives of General Psychiatry* 60: 204-211
- Swanson J, Wigal S, Wigal T, Sonuga-Barke E, Greenhill L, Biederman J, Kollins S, Nguyen A, DeCory H, Hirshe Dirksen S, Hatch S, Group CS (2004), A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics* 113: e206-16
- Westfall T, Grant H, Perry H. (1983). Release of dopamine and 5-hydroxytryptamine from rat striatal slices following activation of nicotinic cholinergic receptors. *Gen Pharmacol*; 14: 321-325

- Wilens TE, Biederman J, Spencer TJ et al. (1999) A Pilot Controlled Trial of ABT-418, a Cholinergic Agonist in the Treatment of Adults With Attention Deficit Hyperactivity Disorder. *Am J Psychiatry*; 156: 1931-1937
- Wilens, TD, Faraone SV, Biederman J. (2004). Attention-Deficit/Hyperactivity Disorder in Adults. *JAMA* 292: 619-623.
- Wolraich M, Doffing M (2004), Pharmacokinetic considerations in the treatment of attention-deficit hyperactivity disorder with methylphenidate. *CNS Drugs* 18: 243-250
- Wolraich M, Greenhill L, Pelham W, Swanson J, Wilens T, Palumbo D, Atkins M, McBurnett K, Bukstein O, August G (2001), Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 108: 883-892