

NIDA CTN Protocol 0037

Stimulant Reduction Intervention using Dosed Exercise (STRIDE)

Lead Investigator: Madhukar H. Trivedi, M.D.
Professor of Psychiatry
Betty Jo Hay Distinguished Chair In Mental Health

June 8, 2011

Version 6.0

**NATIONAL INSTITUTE ON DRUG ABUSE
CLINICAL TRIALS NETWORK
NIDA-CTN-0037**

**Version 6.0
June 8, 2011**

Lead Investigator (LI):

Madhukar H. Trivedi, MD

Project Director:

Tracy L. Greer, PhD

National Intervention Director:

Chad Rethorst, PhD

Exercise Protocol Specialist:

Mark Stoutenberg, PhD

Scientific Collaborators:

Steven Blair, PED

Timothy Church, MD, MPH, PhD

Bess Marcus, PhD

Edward Nunes, MD

John Rotrosen, MD

Eugene Somoza, MD, PhD

James Sorensen, PhD

Diane Warden, PhD

CTP Collaborators:

Becca Crowell, MEd, EdS, LPC, LCDC

Tiffany Linkovich Kyle, PhD

Biostatistician:

Neal Oden, PhD

Regulatory Specialist:

Kathy Shores-Wilson, PhD

Training Directors:

Robrina Walker, PhD

David Morris, PhD

Project Coordinator:

Kolette Ring, BA

NIDA Liaisons:

David Liu, MD

Michele Straus, RPh, MS

Clinical Coordinating Center Liaison:

Jack Chally, MBA

Data Management Center Liaison:

Ashley Vena

TABLE OF CONTENTS

1.0	LIST OF ABBREVIATIONS	1
2.0	STUDY SCHEMA.....	3
3.0	STUDY SYNOPSIS	4
4.0	BACKGROUND	6
4.1	Current Treatments for Cocaine and Other Stimulant Abuse and Dependence	6
4.2	Exercise as a Treatment for Substance Abuse	6
4.2.1	Exercise and Substance Use	6
4.2.2	Exercise and Smoking Cessation.....	7
4.2.3	Exercise and Alcohol Use	8
4.2.4	Exercise and Drug Withdrawal	8
4.3	Exercise as a Treatment for Other Clinical Disorders	8
4.3.1	Efficacy of Exercise in Major Depressive Disorder	8
4.3.2	Postmenopausal and Mobility Impaired Individuals	9
4.4	Possible Mechanisms of Action of Exercise.....	10
4.5	Additional Beneficial Effects of Exercise	11
4.6	Significance to the Field	11
5.0	STUDY OBJECTIVES.....	12
5.1	Primary Objectives	12
5.2	Secondary Objectives.....	12
6.0	STUDY DESIGN.....	13
6.1	Overview of Study Design	13
6.2	Duration of Study and Study Timeline	13
6.3	Rationale for Study Design Choices	14
6.3.1	Choice of Primary Outcome	14
6.3.2	Study Population.....	14
6.3.3	Inclusion of Women and Minorities.....	14
6.3.4	Selection of Exercise Type, Dose and Intensity.....	14
6.3.5	Rationale for Choice of Control Group	15
6.3.6	Beginning the Study While in a Residential Setting	16
6.3.7	Characteristics of the Treatment Facilities with a Residential Component.....	16
7.0	STUDY POPULATION.....	17
7.1	Inclusion Criteria.....	17
7.2	Exclusion Criteria	17
7.3	Participant Recruitment and Retention	18
8.0	NUMBER OF CTP SITES AND SITE CHARACTERISTICS	19

9.0	STUDY PROCEDURES	20
9.1	Informed Consent	20
9.2	Screening	20
9.3	Baseline	20
9.4	Randomization	20
9.5	Treatment and Study Interventions	21
9.6	Continuation Phase	21
9.7	Participant Discontinuation	21
9.8	Participant Remuneration	21
9.9	Waves of Enrollment	22
10.0	STUDY ASSESSMENTS	23
10.1	Time and Event Table (Summary of Assessments)	23
10.2	Types of Assessments	27
10.2.1	Diagnostic and Screening Measures	27
10.2.2	Substance Use and Treatment Assessments	29
10.2.3	Measures of Mood, Sleep and Anhedonia	30
10.2.4	Psychosocial Assessments	31
10.2.5	Cognitive Function Assessments	31
10.2.6	Physiological Measures	32
10.2.7	Retention	32
10.2.8	Safety Assessments	32
10.3	Administration Time	32
11.0	STUDY TREATMENTS	33
11.1	Usual Care (Treatment as Usual, or TAU)	33
11.2	Study Interventions	33
11.2.1	Exercise	33
11.2.2	Health Education	34
11.2.3	Heart Rate Monitors and Pedometers	35
11.2.4	Adherence	35
11.3	Staff Training	36
11.4	Safety Considerations	36
11.4.1	Maximal Exercise Testing	36
11.4.2	Exercise Intervention	36
12.0	CONCOMITANT THERAPY	37
13.0	STATISTICAL ANALYSES	38
13.1	Primary Outcome	38
13.2	Statistical Methods for Primary Analysis	38
13.3	Rationale for Sample Size and Statistical Power	38
13.4	Interim Analyses	40
13.5	Secondary Endpoints and Analyses	40
13.6	Exploratory Aims and Analyses	42

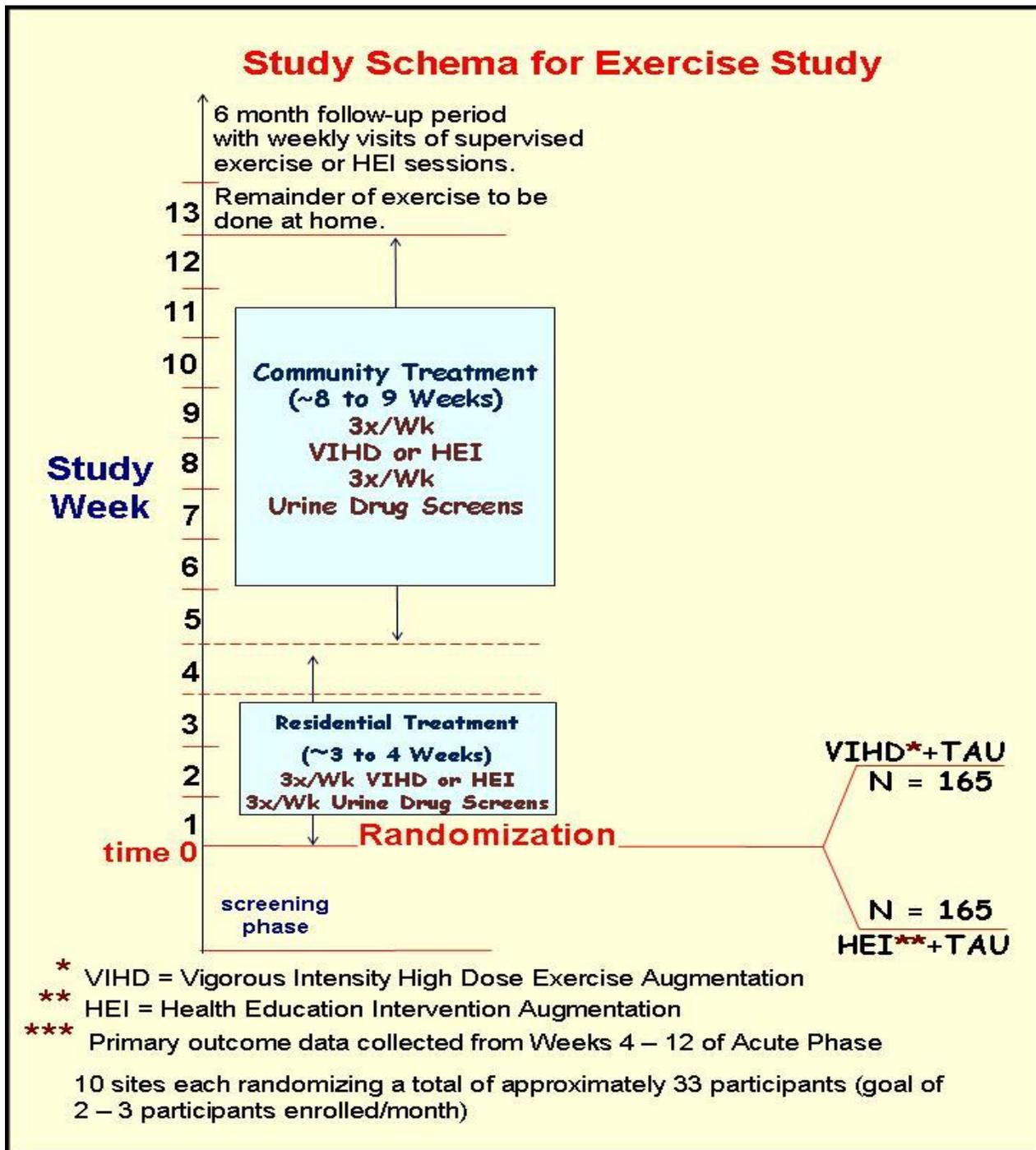
13.7	Factors for Stratification.....	42
13.8	Significance Testing	42
13.9	Missing Data and Dropouts	43
13.10	Poolability of Data.....	43
13.11	Demographic and Baseline Characteristics	43
13.12	Safety Analysis	43
14.0	REPORTING AND MONITORING	44
14.1	Statement of Compliance	44
14.2	Regulatory Files	44
14.3	Informed Consent.....	44
14.4	Health Insurance Portability and Accountability Act (HIPAA)	45
14.5	Release of Information	45
14.6	Investigator Assurances	45
14.7	Financial Disclosure	45
14.8	Clinical Monitoring	45
14.9	Study Documentation	46
14.10	Records Retention and Requirements	46
14.11	Audits	46
14.12	Reporting to Sponsor.....	46
14.13	Safety Monitoring.....	46
14.13.1	Data and Safety Monitoring Board (DSMB)	46
14.13.2	Protocol Violations Reporting and Management.....	47
14.13.3	Subject Confidentiality/Privacy	47
14.13.4	Adverse Events (AEs) and Serious Adverse Events (SAEs)	48
14.13.5	Definitions of Adverse Event and Serious Adverse Event	48
14.13.6	Non-Reportable Adverse Event and Serious Adverse Events	48
15.0	DATA MANAGEMENT AND PROCEDURES.....	49
15.1	Design and Development	49
15.2	Data Collection Forms	49
15.3	Data Acquisition and Entry	49
15.3.1	Site Responsibilities	49
15.3.2	Data Center Responsibilities	49
15.4	Data Editing.....	49
15.5	Data Transfer	49
15.6	Data QA	50
16.0	HUMAN SUBJECTS PROTECTION.....	51
17.0	SIGNATURES	52
18.0	REFERENCES	53

1.0 LIST OF ABBREVIATIONS

ACSM	American College of Sports Medicine
AE	Adverse Events
ASI-Lite	Addiction Severity Index - Lite
BMI	Body Mass Index
CAST-SR	Concise Associated Symptoms Tracking- Self Report
CCC	CTN Clinical Coordinating Center
CHRT-SR	Concise Health Risk Tracking- Self Report
CIDI	Composite International Diagnostic Interview
CoC	Certificate of Confidentiality
CPFQ	Cognitive and Physical Functioning Questionnaire
CRF	Case Report Form
CTP	Community Treatment Program
DSC	CTN Data and Statistics Center
DSMB	Data Safety and Monitoring Board
DSM-IV TR	Diagnostic and Statistical Manual - IV – Text Revision
EDC	Electronic Data Capture
FTND	Fagerstrom Test for Nicotine Dependence
GCP	Good Clinical Practice
HEI	Health Education Intervention
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
ICC	Intraclass Correlation
IRB	Institutional Review Board
kcal	Kilocalorie
KKW	Kilocalorie per Kilogram per Week
MAR	Missing at Random
MDD	Major Depressive Disorder
METS	Metabolic Equivalent
MINI	Mini International Neuropsychiatric Interview
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PAR-Q	Physical Activity Readiness Questionnaire
P-FIBS	Pain Frequency, Intensity and Burden Scale
QIDS-C	Quick Inventory of Depressive Symptomatology - Clinician Rated version
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire Short Form
RPE	Rating of Perceived Exertion

RTP	Residential Treatment Program
SAE	Serious Adverse Event
SCQ	Self-Administered Comorbidity Questionnaire
SF-36	Short-Form Health Survey
SHAPS	Snaith-Hamilton Pleasure Scale
SSSA	Stimulant Selective Severity Assessment
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STCQ-Brief	Stimulant Craving Questionnaire - Brief
Stroop	Stroop Color and Word Test
SUD	Substance Use Diary
TAU	Treatment as Usual/ Usual Care
TLFB	Timeline Follow Back
TPQ	Treatment Participation Questionnaire
TREAD	Treatment with Exercise Augmentation for Depression
UDS	Urine Drug Screen
VIHD	Vigorous Intensity High Dose
VO2 max	Maximal Oxygen Consumption
WTAR	Wechsler Test of Adult Reading

2.0 STUDY SCHEMA



3.0 STUDY SYNOPSIS

There is a need for novel treatment approaches in substance use disorders that increase the likelihood of abstinence and sustain this abstinence in the long term. Clinical data examining the use of exercise as a treatment for the abuse of nicotine, alcohol, and other substances suggest that exercise may be a beneficial treatment for substance use disorders, with direct effects on decreased use and craving. In addition, exercise has the potential to improve other health domains that may be adversely affected by substance use or its treatment, such as sleep disturbance, cognitive function, mood, weight, quality of life, and anhedonia, since it has been shown to improve many of these domains in a number of other clinical disorders.

This study is designed as a two-group, randomized controlled trial to test the effectiveness of the addition of exercise to treatment as usual in improving drug treatment outcomes. The study will include individuals diagnosed with stimulant abuse or dependence (cocaine, methamphetamine, amphetamine or other stimulant, except caffeine or nicotine) who begin substance use treatment in a residential setting. Three hundred and thirty eligible and interested participants who provide informed consent will be randomized to one of two treatment arms:

VIHD (Vigorous Intensity High Dose Exercise Augmentation): Usual Care Augmented with Vigorous Intensity High Dose Exercise

HEI (Health Education Intervention Augmentation): Usual Care Augmented with Health Education.

Participants will receive 3 months of acute phase intervention followed by an additional 6 months of intervention with less frequent supervision. Both groups will receive drug abuse treatment as usual (TAU; i.e., usual care), which will begin while the participant is in a residential setting (with a length of stay generally between 21-30 days where feasible), typically followed by community treatment. Treatment programs with residential stays of more than 21 days may be included if these programs have limited supervision after 30 days and participants will have good access to the community and therefore the opportunity to use substances. The two treatment conditions are structured such that they are similar with respect to number of visits to allow for equivalent contact between groups. Participants randomized to the exercise condition will begin with supervised exercise sessions 3 times per week during the 12-week acute phase of the study. Supervised sessions will be conducted as one-on-one (i.e., individual) sessions, although other participants may be exercising at the same time. Supervised sessions will be monitored closely through the use of heart rate monitors. Additional exercise sessions may be completed for those needing more than three sessions a week to achieve the target dose. Vigorous intensity high dose exercise will be prescribed at a dose of 12 kcal/kg/week (KKW), with intensity ranging from 70-85% maximal heart rate. This exercise dose has been used in several studies of physical activity and also in efficacy studies with smokers (Marcus et al., 1997, 1999). This dose is also equivalent to ≥ 150 min of moderate exercise per week (i.e., approximately 30-50 min, 3-5 days per week). Participants randomized to the health education condition will also begin with visits 3 times per week during the 12-week acute phase. The health education sessions will be conducted as one-on-one (i.e., individual) sessions, although other participants may be receiving health education at the same time. Health education sessions will consist of information on health-related topics distributed via methods such as didactics, websites, audio and video materials, and written materials. During the 6-month continuation phase, the frequency of supervised intervention visits for both the exercise and health education groups will reduce to one time per week.

This study aims to answer the following question: "Can exercise be used to improve the effectiveness of substance use treatment?" If exercise is found to improve outcomes for substance use disorders, the public health significance would be great. A novel component of

treatment would be available for substance users that may not only aid in acute treatment, but may also aid in the long-term prevention of subsequent relapse. Furthermore, additional health benefits for substance users could be realized, including improved cardiovascular status, decreased risk of diabetes, cardiovascular disease, metabolic syndrome and certain cancers, and increased longevity.

4.0 BACKGROUND

Outcomes in the treatment of substance use disorders suggest a need for innovative treatments (Carroll et al., 2004). There have been a limited number of studies of the effectiveness of exercise in improving outcomes with alcohol, other substance abuse or tobacco, with the impact of exercise on smoking cessation receiving the most attention. There are few well-designed randomized controlled trials, but as a whole this small literature suggests that exercise may have good potential to impact outcomes with substance use disorders and merits a large randomized controlled trial that is sufficiently powered to identify the effect of an exercise intervention. There are also a number of studies of the impact of exercise on improving depressive symptom severity which add to the promise of this intervention and provide strong encouragement for the feasibility of the use of exercise as an augmentation to usual care in randomized controlled trials for substance use disorders.

If exercise were to have an impact on acute and longer-term outcomes when added to usual substance abuse treatment, this would be of substantial public health importance. Exercise has limited side effects compared with medications, is not likely to interact with concurrent pharmacotherapy (Trivedi et al, 2006a), is lower in cost (Broocks et al, 1998), can be performed at home, can be continued indefinitely if effective in diverting relapse, and may be useful with vulnerable populations such as pregnant women. Exercise may also improve overall health and functional status (Trivedi et al, 2006a) and reduce the cost burden associated with substance use disorders.

4.1 Current Treatments for Cocaine and Other Stimulant Abuse and Dependence

In control conditions (Treatment as Usual) for substance use disorders, typically only about 13% of participants achieve abstinence (Dutra et al, 2008). Various definitions have been used for abstinence, including mean weeks (or days) of abstinence, mean percent of weeks (or days) abstinent, percent of sample abstinent for a particular duration of time, percent of sample achieving post treatment abstinence, and post treatment scores on the Addiction Severity Index drug scale (Dutra et al, 2008). Similarly, studies vary with respect to the use of self-report or objective measure of drug use. Therefore, abstinence rates for treatments designed to augment TAU vary widely – ranging from 14%-60% (Ball et al, 2007; Carroll et al, 2006; Rawson et al, 2006; Wetzel et al, 2004) – depending on the outcome variable and primary endpoint selected. Currently, the best treatments for cocaine and other stimulant abuse are behavioral treatments that combine cognitive behavioral therapy (CBT) with contingency management. However, it is clear that new treatments are still needed for stimulant abuse and dependence.

4.2 Exercise as a Treatment for Substance Abuse

4.2.1 Exercise and Substance Use

With substances other than tobacco or alcohol, randomized controlled trials with adults are not available, although there are some studies suggesting some benefit of exercise. Exercise resulted in higher abstinence at follow-up in inpatients receiving substance abuse treatment (Sinyor et al, 1982). In a post hoc analysis of data from 187 participants in two randomized trials evaluating contingency management in the treatment of substance abuse disorders (Petry et al., 2004, 2005), participants that reported exercise-related activities had an increased length of abstinence (Weinstock et al, 2008). In two trials with adolescent substance abusers (Collingswood et al, 1991, 1994) exercise increased abstinence and less substance use was reported.

4.2.2 Exercise and Smoking Cessation

Several controlled trials found vigorous high intensity exercise to improve outcomes in smoking cessation (Marcus et al, 1991, 1995, 1999), although others did not find this effective (Hill 1985; Russell et al, 1988; Taylor et al, 1988). These older studies, however, had small samples and other methodological limitations.

Several studies were more adequately powered to examine this question (Marcus et al, 1999; Martin et al, 1997; Marcus et al, 2005). In one randomized controlled trial, Marcus et al, (1999) evaluated a 12 week vigorous intensity high dose supervised exercise intervention (target of 60-85% of heart rate reserve, three supervised sessions per week at 30-40 minutes per session) added to a 12 week group cognitive behavioral smoking cessation program as compared with cognitive behavioral intervention plus attentional control (health and lifestyle sessions) in 281 women. Participants who exercised were significantly more likely than participants in the health education control group to achieve continuous abstinence at three time points: 1) after 12 weeks of treatment (19.4% vs 10.2%, $p = 0.03$), 2) three months following treatment (16.4% vs 8.2%, $p = 0.03$), and 3) one year following treatment (11.9% vs 5.4%, $p = 0.05$), and were less likely to have relapsed at these time points. This study illustrates two important points relevant to this protocol; namely: 1) vigorous exercise added to traditional care can effectively reduce nicotine use, and therefore it may also be effective in reducing use of other substances, and 2) a health intervention control can be effectively used in trials assessing exercise as an intervention.

In a similar study of smoking cessation in 205 recovering alcoholics, moderate intensity exercise and behavioral counseling was superior to behavioral counseling and nicotine gum or usual treatment one week post treatment quit point, but there were no differences at 6 or 12 month follow up (Martin et al, 1997). Interventions in this study were of differing lengths of time, however.

Marcus et al, (2005) completed a randomized controlled trial assessing an 8-week moderate intensity exercise program (target of 59-69% of maximum heart rate, one supervised session and 4 additional weekly sessions of at least 30 minute duration) added to an 8-week group cognitive behavioral smoking cessation program as compared to a cognitive behavioral program plus equal staff time, in 217 women. There were no differences in 7-day point prevalence abstinence between the groups at 8 weeks. The exercise group had better abstinence at 3-month follow-up, but not at 12-month follow-up with no differences at any time point between the groups in continuous abstinence. In a post hoc analysis, among those with a higher level of exercise participation, however, the likelihood of smoking cessation was greater. Of interest, however, is that adherence, or attendance at exercise sessions, did not appear to differ meaningfully in the two studies of vigorous and moderate intensity exercise by Marcus and colleagues with an attendance at exercise sessions of 67.3% for vigorous intensity exercise (three sessions per week) (Marcus et al, 1999) and 70.5% for moderate intensity exercise (one supervised session per week). Attendance was similar in the vigorous intensity trial even though the weekly attendance requirement was three times as high.

Ussher et al, (2003) evaluated nicotine replacement therapy in combination with either exercise counseling or health education over 7 weeks and found no differences in abstinence, although it is not clear whether the required dose of exercise was received. One small study with subjects over 50 years old compared four groups: 1) behavioral treatment, 2) behavioral treatment and nicotine gum, 3) moderate intensity exercise and behavioral treatment, 4) moderate intensity exercise. No differences were found across groups in smoking cessation at treatment end, and the behavioral treatment outcomes were better than the exercise alone intervention at 12 months (Hill et al, 1993).

Other studies have suggested positive effects of exercise such as reductions in stress, anxiety, irritability and restlessness at several points during the first few weeks of abstinence during exercise based smoking cessation intervention (Ussher et al, 2003).

Moderate intensity exercise has been reported to reduce cigarette craving in abstinent smokers (Ussher et al, 2001) and it has been suggested that adherence might be greater than with vigorous intensity exercise (Blair and Connelly, 1996).

4.2.3 Exercise and Alcohol Use

In two small controlled trials evaluating the efficacy of exercise with alcohol use, exercise improved outcomes. In one study with 58 inpatients in alcohol rehabilitation, abstinence was better post treatment and at 3 and 18-month follow-ups (Sinyor et al, 1982), although subjects were not randomized to intervention and control groups, and control group sizes were very small. In a sample of college students who were drinking heavily, an exercise program reduced alcohol use compared with a control group, although sample sizes again were small (Murphy et al, 1986).

4.2.4 Exercise and Drug Withdrawal

In a review of 12 studies evaluating the effect of one session of exercise versus a passive condition on smoking cravings, withdrawal symptoms, or smoking, nine out of ten studies evaluating cravings showed reduction in cravings during and after exercise. Eight out of nine reported decreased withdrawal symptoms such as stress, anxiety, tension, poor concentration, irritability and restlessness during and following exercise, although exercise interventions were of variable intensity (Taylor et al, 2007). These studies, however, measured abstinence within periods of only minutes or hours following exercise. For example, brief moderate intensity exercise in abstinent smokers reduced withdrawal from tobacco, mood disturbance, and urges to smoke (Ussher et al, 2001; Daniel et al, 2004, 2006, 2007).

Ussher et al, (2004) evaluated the impact of brief moderate vs. light intensity exercise on alcohol urges and mood but found effects on urges only during the intervention itself with no improvements post intervention, although the exercise intervention was only 10 minutes in length. It may also be that exercise has a different effect on withdrawal from central nervous system (CNS) stimulants such as tobacco as compared with CNS sedatives such as alcohol.

4.3 Exercise as a Treatment for Other Clinical Disorders

4.3.1 Efficacy of Exercise in Major Depressive Disorder

Observational studies and clinical trials suggest beneficial effects of exercise on depression and anxiety (Dunn et al, 2001). The results of several randomized controlled trials evaluating the use of exercise as a monotherapy or augmentation in the treatment of depression suggest that exercise is efficacious in improving the symptoms of depression and provide additional support for the feasibility of exercise trials for stimulant users.

The Depression Outcomes Study of Exercise (DOSE) (Dunn et al, 2002, 2005) evaluated exercise as a monotherapy in four groups with energy expenditures of either 7 or 17.5 kcal/kg/week and frequencies of exercise of either 3 or 5 times a week, and a control group receiving flexibility exercise, in subjects with mild to moderate major depressive disorder. Exercise was supervised for 12 weeks followed by unsupervised exercise for 12 weeks. The high dose groups had more improvement than the low dose or control groups and frequency of sessions per week was not a factor in outcome. Adherence rates were 71% for the public health dose of 17.5 KKW and 72% for the 7 KKW dose.

Another study tested group exercise, medication, or a combination of the two in older adults with mild to moderate MDD and found all three to be efficacious (Blumenthal et al, 1999), although it

is unclear what additional psychosocial support was contributed by the group nature of the intervention. At 10-month follow-up, the exercise alone group had better recovery outcomes than the medication group and less incidence of relapse than the other two groups (Babyak et al, 2000), although many participants began other treatments including exercise in this naturalistic phase of the study. In another study, 202 subjects with MDD received either supervised group exercise, home based exercise, sertraline, or placebo with no significant difference in outcomes (Blumenthal et al, 2007).

In a pair of studies totaling 124 subjects, three supervised exercise sessions per week were added to usual care for 12 weeks with improvement in depressive symptoms in the exercise group; however, the control group subjects had variable treatment including psychotherapy and/or medications, exercise was performed in a group context, there were group differences at baseline in depression symptom severity and there was variable adherence to the exercise intervention (Veale et al, 1992).

In a study augmenting antidepressants with exercise in partial responders, 86 older adults with 6 weeks of antidepressant use with no sustained response received group exercise or health education classes twice a week for 10 weeks. More of the exercise group improved at least 30% in depressive symptoms (Mather et al, 2002).

As a precursor to a randomized controlled trial entitled, Treatment with Exercise Augmentation for Depression (TREAD), Trivedi et al. (2006a) conducted an open label pilot study in 17 subjects with MDD who received a therapeutic dose of antidepressant medication for at least 6 weeks, and had some benefit, but residual symptoms remained (Hamilton Rating Scale for Depression [HRSD] score of greater than or equal to 14). Participants received 12 weeks of 16 KKW of aerobic exercise in supervised and home based sessions. There was a nearly 6-point reduction on the HRSD in the intent to treat group and more than a 10-point improvement in the 8 completers despite a mean of about 4 months of antidepressant treatment prior to study entry. Improvements in quality of life were also observed. This pilot study also assisted with developing a home-based exercise program, and suggested that beginning with supervised exercise but tapering to home-based exercise is generalizable to routine clinical care and essential for participants to be likely to incorporate exercise into their ongoing routines.

The TREAD study evaluated improvement in depressive symptoms as well as functioning and quality of life in 126 subjects with MDD who had received 2-6 months of selective serotonin reuptake inhibitor (SSRI) treatment, at least 6 weeks at an adequate dose, but still had residual symptoms as reflected by an HRSD score of greater than or equal to 14. Subjects received 24 weeks of either a high, public health dose (16 KKW) or low dose (4 KKW) of exercise, avoiding the pitfalls of the other trials such as group exercise, un-blinded outcome evaluation and lack of rigorous standardized diagnosis of MDD (Trivedi et al., 2006b). The first 12 weeks included individualized aerobic exercise prescription, self monitoring tools and an interactive website to maximize adherence, and a combination of supervised and home based sessions – 3 supervised sessions in week 1, two in week 2 and one per week in weeks 3-12 to maximize scheduling flexibility and minimize burden. The second 12 weeks included home-based exercise only. Pedometers and heart rate monitors were used to monitor activity. Results from this trial are in preparation at the time of this protocol version.

4.3.2 Postmenopausal and Mobility Impaired Individuals

Studies of exercise interventions in other populations also provide support for the feasibility of the use of exercise for stimulant users. The DREW study with postmenopausal women (Morss et al, 2004; Church et al, 2007) had adherence rates of 94.6% for the exercise dose of 4 KKW, 89% for the dose of 8 KKW, and 93% for the dose of 12 KKW. LIFE, which was a 12 month study in mobility impaired participants 70-89 years of age, achieved a retention rate of 94% at

12 months; and the exercise group had adherence rates of 71% and 61% at 6 and 12 months respectively (LIFE Study Investigators, 2006). These studies illustrate that exercise can be successfully implemented in a variety of populations.

4.4 Possible Mechanisms of Action of Exercise

The mechanisms by which exercise may exert an effect on use of alcohol or substances are unknown. Possible mechanisms are described by Read et al. (2003), Brown et al. (2009), Ussher et al, (2004) and Meeusen (2005).

It has been suggested that exercise may be a distraction (Breus and O'Connor, 1998), allowing attention to be diverted from urges to drink (Ussher et al, 2004) or a lifestyle change that can substitute for use of substances such as alcohol (Marlatt and Gordon 1985, Smith and Meyers, 1995).

In summarizing studies of the effect of exercise on neurotransmitters, Meeusen (2005) concludes that exercise influences central dopaminergic, noradrenergic and serotonergic systems. Evidence supports changes in the synthesis and metabolism of monoamines. For example, activation of the serotonergic system from cardiovascular exercise may be a mechanism by which exercise impacts alcohol urges (Chaouloff, 1997; Weicker and Struder, 2001) since reduced serotonin levels are found with alcohol dependence (Heinz et al, 2001). Exercise may also achieve effects via the endogenous opioid system and dopaminergic reinforcement mechanisms (Carlson, 1991; Cronon and Howley, 1974; Thoren et al, 1990) similar to the effects induced by alcohol and drug use (Froelich 1997, O'Malley et al, 1996). Unlike alcohol and drug use, however, physical activity is associated with increases in dopamine receptor densities in the reward pathways of the animal brain that persist for days after physical activity ends (Hattori, Naoi, & Nishino, 1994; Meeusen et al, 1997; Wilson & Marsden, 1995), which may be particularly salient for stimulant abuse.

Another possible advantage of exercise as an intervention for stimulant abuse is the evidence of improved hippocampal function seen with exercise. There is clear evidence in animal studies that exercise increases brain derived neurotrophic factor (BDNF) levels and has been shown to induce molecular changes in the hippocampus. The most recent evidence suggests that molecular changes in the hippocampus may directly impact upon several factors associated with contextual learning. Specifically Greenwood et al (2008) have demonstrated improvements in hippocampal-dependent contextual learning and memory in rats. Similar results have been found for exercise-induced hippocampal neurogenesis and improvement in spatial memory in rats and mice (Clark et al, 2008; Wojtowicz et al, 2008; Gomez-Pinilla et al, 2008). Therefore, an exercise augmentation may provide specific benefits for participants with a history of substance abuse since this disorder has been associated with memory impairments that would be influenced by hippocampal function (Bolla et al, 1999).

Reduction in sugar cravings and increased blood glucose levels also could assist with alcohol urges (Anderson and Woodend, 2003). Additionally, exercise may decrease reactivity to stress (Crews and Landers, 1987) and decrease the use of alcohol (or substances) as a way of coping with stress (Rejeski et al, 1991). Improving self-efficacy (McAuley et al, 1991; Williams and Cash, 1999) may be another mechanism for improving outcomes.

Finally, there is evidence that exercise improves anxiety, depression and self-concept in those also abusing alcohol (DiLorenzo et al, 1999; Hughes, 1984; Martin and Dubbert, 1982; Taylor et al, 1985), which may then mediate improved outcomes. Exercise has been shown to reduce depression and anxiety during alcohol treatment (Frankel and Murphy, 1974; Palmer et al, 1988, 1995) and with smoking cessation (Bock et al, 1999; Kawatchi et al, 1996). Reduction in depression symptoms in alcohol dependent participants receiving cognitive behavioral therapy

mediated improved outcomes in drinking, suggesting that exercise may improve drinking outcomes via reductions in depression and anxiety (Brown et al, 1997).

4.5 Additional Beneficial Effects of Exercise

Exercise has been related to better cognitive functioning (Blomquist and Danner, 1987; Radak et al, 2001; Cotman and Berchtold, 2002, Vaynman and Gomez-Pinilla, 2006; Weuve et al, 2004), as well as improved quality of life in those with depression and other chronic medical illnesses (Trivedi 2006a; Stewart et al, 1994; USDHHS, 1996; Galper et al, 2006; Singh et al, 1997) although it only improved quality of life in the physical domain in one small study (Carta et al, 2008). It has also been related to improved sleep in many (King et al, 1997; Sugaya et al, 2007; Singh et al, 1997) although not all studies (Elavsky and McAuley, 2007), as well as reduced weight (Sugaya et al, 2007).

4.6 Significance to the Field

It is clear that additional treatments for stimulant use disorders are needed, as no one treatment is successful for all individuals. If efficacious, exercise may provide a novel treatment strategy for stimulant use disorders. Furthermore, exercise is associated with additional health benefits, such as reduced likelihood for heart disease or diabetes and increased longevity that may further improve participants' health and quality of life.

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

Primary Aim. To compare percent days of abstinence between the VIHD and HEI groups based on stimulant (i.e., cocaine, methamphetamine, amphetamine, or other stimulant, excluding caffeine and nicotine) use during the 12-week acute phase. Days of abstinence will be measured during days 22-84, since it is anticipated that most individuals will be in a highly structured environment during the first 21 days of the study, and therefore would have little opportunity to use substances (i.e., the groups are not likely to differ during this time period). *Hypothesis 1.* VIHD will be associated with significantly greater ($p<0.05$) percent days of abstinence as measured by the Timeline Follow Back (TLFB) than HEI. Note that a urine drug screen is collected three times per week to improve the accuracy of and correct the self-report data on the TLFB. Urine drug screen data will be analyzed as a secondary outcome as described below. Also note that a Substance Use Diary will be given to participants to aid in the completion of the TLFB at the assessment visit, again to enhance assay sensitivity of TLFB.

5.2 Secondary Objectives

Secondary objectives include both secondary and exploratory aims.

Secondary Aim 1. To compare time to relapse (defined as second positive urine test [for stimulants] and use of drugs established by TLFB) between the VIHD and HEI groups. *Hypothesis 2.* VIHD will be associated with a significantly longer ($p<0.05$) time to relapse than HEI over the course of the 12-week acute phase.

Secondary Aim 2. To evaluate withdrawal symptoms between the VIHD and HEI groups. *Hypothesis 3.* VIHD will be associated with significantly reduced ($p<0.05$) withdrawal symptoms as measured by the Stimulant Selective Severity Assessment (SSSA) than HEI over the course of the 12-week acute phase. *Hypothesis 4.* VIHD will be associated with significantly reduced ($p<0.05$) craving as measured by the Stimulant Craving Questionnaire-Brief (STCQ-Brief) than HEI over the course of the 12-week acute phase.

Secondary Aim 3. To evaluate drug use and related outcomes for all substances (categorized as alcohol, cannabinoids, nicotine, opioids, or sedative/hypnotic/anxiolytics). *Hypothesis 5.* VIHD will be associated with significantly higher percent days abstinence from all substances and a significantly lower relapse for all substances ($p<0.05$) than HEI over the course of the 12-week acute phase.

Secondary Aim 4. To compare time to dropout from substance abuse treatment between the VIHD and HEI groups. *Hypothesis 6.* VIHD will be associated with significantly longer ($p<0.05$) time in treatment than HEI.

Secondary Aim 5. To evaluate drug use and related outcomes during the entire course of the study (i.e., randomization to 9 months). *Hypothesis 7.* VIHD will be associated with significantly higher percent days of abstinence, significantly longer time in treatment, a significantly lower rate of relapse, significantly lower quantity of use, and significantly reduced withdrawal symptoms ($p<0.05$) than HEI over the 9-month study period.

Exploratory Aims. To determine if there are additional health benefits to using exercise augmentation in the treatment of substance use disorders. Specifically, VIHD will be associated with significantly greater improvement ($p<0.05$) in sleep, cognitive function, mood, quality of life and anhedonia, and weight gain compared to HEI over the course of the 12-week acute phase, and over the 9-month study period.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This study will evaluate individuals diagnosed with stimulant abuse or dependence receiving treatment at study inception while in a residential setting. Eligible and interested participants who provide informed consent will be randomized to one of two treatment arms: Vigorous Intensity High Dose Exercise Augmentation (VIHD) or Health Education Intervention Augmentation (HEI). Both groups will receive treatment as usual (TAU; i.e., usual care). Treatment will begin in a treatment program with a residential component. The treatment arms are structured such that the quantity of visits is similar to allow for equivalent contact between groups. Participants randomized to the exercise condition will begin with supervised exercise sessions 3 times per week during the 12-week acute phase of the study. Supervised sessions will be conducted as one-on-one (i.e., individual) sessions, although other participants may be exercising at the same time. Participants will be monitored closely through the use of heart rate monitors and step counters. Vigorous intensity high dose exercise will be prescribed at a dose of 12 kcal/kg/week (KKW), with intensity ranging from 70-85% maximal heart rate. Both dose and intensity will be achieved gradually (i.e., with a ramp-up protocol). The 12 KKW dose has been used in several studies of physical activity and also in efficacy studies with smokers (Marcus et al, 1997, 1999). This dose translates to roughly ≥ 150 min of moderate intensity exercise per week (i.e., approximately 30-50 min, 3-5 days per week). In order to ensure the prescribed vigorous intensity (70-85% maximal heart rate), we will ask participants to complete this dose in a 3-day-per-week schedule. However, additional exercise sessions can be completed for those needing more than three sessions per week to achieve the target dose. Participants randomized to the health education condition will also begin with visits 3 times per week during the 12-week acute phase. The health education sessions will be conducted as one-on-one (i.e., individual) sessions, although other participants may be receiving health education at the same time. Health education sessions will consist of information on health-related topics distributed via methods such as didactics, websites, audio and video materials, and written materials. A session-to-session curriculum will be provided and will include ongoing attention to barriers to retention. A six-month continuation phase will also be included, during which time participants will attend weekly supervised exercise or HEI sessions with the remainder of the exercise dose to be completed on their own at home or in a non-supervised exercise environment. A six-month duration for the continuation phase was selected because we would like to see if there is a sustained response to the exercise intervention. In most chronic diseases, longer-term outcomes are best seen in the six months following acute phase intervention.

6.2 Duration of Study and Study Timeline

Activities for the study are projected as follows (subject to modification):

Finalize study forms, site visits for site selection	1 month
DSC start-up period, hire and certify CTP staff and get equipment for Wave 1, site visits for site selection, IRB submissions, training meeting Wave 1	6 months
Begin Wave 1 enrollment (18 months)*, hire and certify CTP staff and get equipment for Wave 2, any final site visits for site selection for Wave 2, hold Wave 2 training meeting	7 months
Begin and complete Wave 2 enrollment	15 months

Complete data collection	9 months
Data cleaning, locking, and analysis	6 months
Total:	44 months

Sites are expected to complete approximately 15-18 months of enrollment.

6.3 Rationale for Study Design Choices

6.3.1 Choice of Primary Outcome

Percent days of abstinence was chosen as our primary outcome because it is: 1) a standard outcome measure in the field, both in general and within CTN studies (e.g., Carroll et al, 2002; Carroll et al, 2006), and 2) an outcome measure that is clinically meaningful in evaluating stimulant abuse and dependence. Time to dropout from treatment and time to relapse will be evaluated as secondary outcomes.

6.3.2 Study Population

For this study, we chose to evaluate those with stimulant (i.e., cocaine, methamphetamine, amphetamine, or other stimulant, excluding caffeine and nicotine) abuse or dependence. This decision was made in order to reduce heterogeneity of the sample, since this is an early efficacy trial with a new intervention in the substance use population.

6.3.3 Inclusion of Women and Minorities

Individual CTPs will make significant efforts to recruit minority participants from the community. The goal will be to recruit a sample of study participants that reflect the proportion of minorities in the community where the CTP is located. All attempts will be made to include female and male participants with a range of age, race, ethnicity, and socio-economic status.

6.3.4 Selection of Exercise Type, Dose and Intensity

One of the major hurdles in successfully conducting exercise trials has been the inconsistency of type, dose and intensity of exercise achieved. We have elected to define exercise type, dose and intensity in this study to minimize variability and achieve target goals for both dose and intensity.

Type. We have selected to use aerobic exercise in this trial. While there is some evidence that other types of exercise (e.g., weight training) may be beneficial to individuals with other disorders, such as depression, the preponderance of evidence is for aerobic exercise. Furthermore, the support for the use of exercise in substance use disorders has been with aerobic exercise.

Dose. A 12 KKW dose of exercise was selected for this study for the following reasons: 1) it is consistent with public health guidelines; 2) it has been used in previous studies of physical activity (Morss et al, 2004) and also in efficacy studies with smokers (Marcus et al, 1997, 1999) and is similar to doses used in the treatment of other disorders such as depression (Trivedi et al, 2006a, 2006b).

The recommended public health dose is a range. The Centers for Disease Control and American College of Sports Medicine recommend at least 30 minutes of moderate physical activity most days of the week (Pate et al, 1995; Haskell et al, 2007a, 2007b; Nelson et al, 2007a, 2007b), consistent with recommendations of the NIH Consensus panel (NIH Consensus 1996), the American Heart Association (Fletcher et al, 1995; Smith et al, 1995; Haskell et al, 2007a, 2007b; Nelson et al, 2007a, 2007b) and the US Surgeon General (US Department of Health and Human Services, 1996).

Intensity. Intensity of exercise refers to the relative effort expended, and we selected the range of 70-85% of a person's maximal heart rate. This intensity also is within the current guidelines, but is well above the minimal intensity of 50% described in the guidelines. Although it is not clear if higher exercise intensities will produce greater changes in outcomes when the total dose is constant, it is possible that this will occur. As indicated earlier, in this efficacy trial we want to be certain that we are well above minimal exercise guidelines for both dose and intensity. The range of intensity still allows some flexibility, for comfort and to increase adherence, but ensures that everyone will be above the minimal intensity, which will decrease the likelihood that someone might exercise below an intensity threshold that would be required for possible beneficial effects. The reason for allowing some persons to attend more than three exercise sessions/week is based on variation in baseline fitness levels. Individuals who are quite unfit will have a relatively low caloric expenditure/kg body weight when exercising within the intensity range. This will require unfit individuals to exercise more minutes to achieve the 12 KKW dose than individuals who have a higher baseline fitness. For example, one person exercising at 70% of their maximal heart rate might require 150 min/week (50 min/session for 3 sessions/week) to achieve the 12 KKW dose; and a less fit person might require 240 min/week to achieve the 12 KKW dose. This latter person would need to exercise 80 min/session for 3 sessions/week, which might prove too challenging. In our experience many individuals would prefer to exercise four or even five days/week to achieve their dose than to exercise three/days week of very long sessions.

Alternatively, we could have let participants decide their own intensity, based on rating of perceived exertion, so long as they achieved the target dose (i.e., self-selected intensity). While this approach may allow significant flexibility for participants in achieving their dose, it also may result in some participants exercising at a much slower pace than others, and it can significantly increase the amount of time needed to complete the exercise dose. Another alternative would be to have a fixed exercise intensity (i.e., 80% maximal heart rate) to require that participants exercise at a high intensity based on heart rate in order to maximize the effectiveness of the exercise intervention. However, a fixed intensity allows no flexibility for participants to find a comfortable exercise level, and may therefore result in poor adherence and increased drop-outs.

6.3.5 Rationale for Choice of Control Group

An active health education intervention control group was selected so that any effect of the exercise intervention could not be attributed to the additional contact associated with the exercise intervention. Our rationale for the choice of HEI as our control group is as follows: HEI has been established as an ineffective, yet attentionally equivalent control condition in studies of exercise and has been used successfully (e.g, Marcus et al, 1999; Smolander et al, 2000; Rejeski et al, 2005; LIFE Study Investigators, 2006) and with good adherence. Members of our Protocol Development Team (Drs. Marcus, Nunes and Blair) have experience in using HEI as a control condition and the knowledge gained from their experience will ensure that participants randomized to this arm of the study find this intervention acceptable. Participants will be recruited to a "health intervention study", one arm of which is exercise, and another health education. While it is true that participants will know their group assignment, this has not been problematic in other studies using HEI controls. Participants in the HEI group will be able to participate in selecting the topics that are discussed in order to help maintain interest. Furthermore, they will be monitored similarly to participants who exercise, and they will receive behavioral adherence strategies that exercise participants receive in order to maximize adherence. All attempts will be made to address barriers to retention in the control condition, as in the exercise intervention. HEI, as opposed to TAU alone, is also intended to ensure continued participant engagement in the study and thus minimize dropouts that might occur if attention in the two groups were not equivalent. Other possible active control conditions (e.g., resistance

training, relaxation, yoga, or meditation) have the potential for efficacy, and in fact some have shown efficacy both in substance use and in other disorders (e.g., depression (Pilkington et al, 2005)). Thus, the use of an active comparator would make it difficult to see a treatment effect, so these alternative active control conditions are not ideal comparators for an efficacy study of exercise.

6.3.6 Beginning the Study While in a Residential Setting

We chose this design approach to maximize the availability of participants to be present for the initial evaluation and training of the exercise intervention. As mentioned above, one of the major hurdles in successfully conducting exercise trials has been the inconsistency of dose and intensity of exercise achieved. Given the dose and intensity of exercise selected for this study, it is critical that participants be consistent in attending supervised sessions, particularly as they are first learning how to implement the exercise protocol, how to use all related equipment, and how to collect and record all exercise-related data. A transition to outpatient care is a typical occurrence in the treatment of substance use disorders. This study is designed to continue to evaluate participants as they transition to the next phase of care. While this could result in somewhat less generalizability of findings, since this is an early efficacy study on the use of exercise as an augmentation to TAU in the treatment of substance use disorders, we determined that it was more important to ensure that our study population was present to receive sufficient training and supervision in the exercise intervention and to maximize adherence during this time.

6.3.7 Characteristics of the Treatment Facilities with a Residential Component

Site variability will occur in this protocol, but its impact will be minimized in three ways. First, participants will be randomized into each treatment arm at each site. Second, the effects of site will be assessed to determine if there are site differences that differentially impact treatment outcomes. Third, we have attempted to minimize variability in certain aspects of treatment in order to provide as much consistency across sites as is possible:

Duration of treatment in a residential setting. We are targeting a range of 21-30 days of treatment in a residential setting in order to have participants more likely to be present for at least the first 3-4 weeks of the study, for the reasons described above regarding exercise dose. We will select treatment providers with residential stays that come as close to 21-30 days as possible to minimize this variability across sites. However, we recognize that variability in specific participants' lengths of stay will occur.

Access to the community. We will select treatment providers where discharge or good access to the community can generally occur between 21 and 30 days. Every attempt will be made during the site selection process to select sites with similar access to the community, but we believe variability is representative of true community care. Alternative approaches to these criteria could include: 1) Selecting only RTPs with a 3 month or greater duration of stay so that all exercise sessions are conducted during the RTP program. Pros of this choice would be the uniformity of treatment type during the entire acute phase of the study, whereas cons may include the potential for a much more severe population and the fact that results may not be very generalizable. 2) Switching only to community care settings, so that supervised sessions are not conducted in RTP. However, our ability to conduct supervised exercise sessions, particularly in the first weeks of study participation, is very likely to be hampered by this choice. Additionally, there is likely to still be substantial variability even in these outpatient programs, so this approach would likely not fully resolve this issue.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

- Male or female age 18-65.
- Admitted to residential setting and receiving substance use treatment.
- Ability to understand and willingness to provide written informed consent.
- Agree to remain in facility for authorized treatment.
- Willing to provide contact information.
- Self-reported use of stimulant drug (cocaine, methamphetamine, amphetamine, or other stimulant, excluding caffeine and nicotine) within the 30 days prior to admission for treatment.
- Meets DSM-IV criteria for substance abuse or dependence for stimulants (cocaine, methamphetamine, amphetamine, or other stimulant, excluding caffeine and nicotine) within the last 12 months.
- Medical clearance with protocol-defined stress testing (in accordance with American College of Sports Medicine (ACSM) guidelines) from protocol approved medical personnel. Details of guidelines and related testing protocol are provided in the study Manual of Procedures.
- Body mass index (BMI) $\leq 40 \text{ kg/m}^2$ or BMI $> 40 \text{ kg/m}^2$ and cleared by medical personnel to exercise.
- Able to comprehend and communicate in English.

7.2 Exclusion Criteria

- Evidence of general medical condition or other abnormality that contraindicates use of exercise, based on the Medical Screening Visit.
- Current opiate dependence (i.e., within the last 12 months).
- Currently considered a high suicide risk and/or high risk for being unable to complete the study due to the need for psychiatric hospitalization, suicide attempts or suicidality, significant self-mutilation, or other self-injurious or destructive behavior based on the judgment of the site PI, medical personnel, or designee.
- Pregnancy.
- Significant physical activity, defined as aerobic exercise more than 3 times per week for 20 minutes or more, completed consistently for the three months prior to study enrollment.
- Current psychotic disorder. Other comorbid psychiatric diagnosis that, in the investigator's judgment, will pose a safety issue or make it difficult for the participant to understand or complete the intervention.
- Concomitant treatments: beta blockers; methadone, buprenorphine or any other opioid replacement therapies.
- Anticipated circumstances over the 9-month course of the trial that would render the participant unlikely to complete the study in the judgment of the site PI or designee.

- Anticipated living arrangements after the first month of the study that are likely to restrict exposure to substance use in the judgment of the site PI or designee.
- Any reason not listed herein yet, determined by the site PI, medical personnel, or designee that constitutes good clinical practice and that would in the opinion of the site PI, medical personnel, or designee make participation in the study hazardous.

7.3 Participant Recruitment and Retention

Participants will be recruited from selected CTP sites. Interested persons identified by the program or study personnel during the intake at the treatment facility, or thereafter, as potential participants will begin the pre-screening process followed by the informed consent and screening process to determine eligibility. It is recommended that CTP personnel responsible for intake be trained in the study aims, general procedures and recruitment process so that they have a thorough understanding of the study and study procedures. Study personnel, however will be responsible for recruitment and explaining procedures to interested participants. Because we are recruiting from CTPs, we will be allowing participation of anyone who presents at a participating CTP and is interested and eligible for the protocol. However, during site selection we will attend to a general balance of gender in site selection. For example, we will attempt to balance the number of programs enrolling only women or only men. We expect to be very successful with minority recruitment by selecting sites with strong minority representation, which is the very best way, we believe, to ensure excellent minority study enrollment. This is the strategy that was used for STAR*D which resulted in our enrolling Hispanic participants in the same proportion as in the national census and 18% African American participants, somewhat higher than the national census.

A behavioral adherence plan has been developed (Trivedi et al, 2006) to help retain participants in the interventions and optimize participant adherence. This multi-component behavioral adherence plan incorporates empirically-validated behavioral strategies to reinforce participation in the interventions and reduce salient participant- and disease-related barriers to intervention adoption and maintenance. These strategies include: 1) multidisciplinary psychoeducation about adherence and the use of behavioral reinforcers for attendance/adherence to the intervention (e.g., water bottles, pen and notepad, gift cards); 2) written reference materials; 3) skills training (e.g., instruction in appropriate exercise form, intensity); 4) weekly exercise prescription (for participants randomized to exercise); 5) self-monitoring of adherence and performance (e.g., heart rate, RPE, tracking of HEI topics); 6) adherence feedback from study website and intervention facilitators; and 7) weekly intervention planning (individually-tailored plan).

8.0 NUMBER OF CTP SITES AND SITE CHARACTERISTICS

Site characteristics were developed based on the original exercise concept proposal, as well as the results of our initial residential treatment program survey, which yielded over 65 responses. The primary issues considered were feasibility of conducting the current study design. An estimated ten sites will be selected based on the following characteristics:

1. Treatment program with a residential component. Length of stays will generally be between 21 and 30 days where feasible.
2. No formal or current exercise program, unless the duration of exercise in the program is 1 hour or less per week or the program is able to exclude participants from exercising in the residential setting's exercise program.
3. Continuation of community treatment within the same or another organization in close geographic proximity to the residential facility or in a location that makes it feasible that participants can return to the study site to complete study activities during the 9 months of the study.
4. Clients are allowed in community in 30 days or less and have a good opportunity to use substances.
5. Program serves a sufficient number of clients that would be potentially eligible to participate in the study.
6. Program has adequate space to accommodate study staff and activities.

Based on participation of 10 sites, an expected sample size of 330 (as described in section 13.3) and an enrollment period of 15-18 months, we expect each site to enroll approximately 33 participants. This will result in a randomization rate of 2-3 participants per month.

9.0 STUDY PROCEDURES

9.1 Informed Consent

Interested persons identified during the treatment facility's intake process, or thereafter, as potential participants will be given an explanation of the study and will undergo a brief pre-screening with trained study personnel. The study will be described as a study of a health intervention to aid in the treatment of stimulant abuse or dependence, one arm of which is health education and another exercise. Interested and preliminarily eligible participants will begin the informed consent process. Study personnel will explain the details of the study to the potential participant and then give him or her time to read through the informed consent document. Study personnel will then go through the document with the potential participant and answer any questions he or she may have. The potential participant will then complete a consent quiz to ensure (s)he understands the study and study procedures. Potential participants who choose to provide informed consent and sign the informed consent form will then proceed to the screening assessment.

9.2 Screening

Potential participants will be screened for eligibility based on all inclusion and exclusion criteria, detailed in sections 7.1 and 7.2. The Demographics Form will be completed by all participants who are screened. The Composite International Diagnostic Interview (CIDI) will be used to diagnose substance use disorders, and the Mini International Neuropsychiatric Interview (MINI) will be used to rule out excluded comorbid psychiatric disorders. The Timeline Follow Back will be used to verify stimulant use within the prior 30 days prior to admission to residential treatment. Laboratory tests will be obtained and maximal exercise testing will be conducted, as described in section 10.21, to ensure the safety of participants.

Participants will meet with a trained study physician (or other trained medical personnel) for a physical evaluation. The medical staff member will review all laboratory/exam results and the maximal exercise testing report and will use this information to provide medical clearance to exercise. This evaluation may take place in a facility that complies with ACSM testing guidelines (approved by the study lead team) when the required personnel and equipment are not available at the treatment facility.

9.3 Baseline

The Timeline Follow Back will be completed to assess substance use since the screening visit. A urine drug screen will be obtained and the ASI-Lite, Fagerstrom Test of Nicotine Dependence, Stimulant Craving Questionnaire - Brief and Stimulant Selective Severity Assessment will be administered. Baseline evaluation of other outcomes such as mood, sleep, and anhedonia (QIDS-C₁₆, CHRT, CAST and SHAPS), psychosocial function (P-FIBS, SF-36 and Q-LES-Q-SF), and cognitive function (WTAR, CPFQ and Stroop) will be obtained. Height and baseline weight, waist circumference, and body mass index (BMI) will be obtained.

9.4 Randomization

Participants will be randomized to one of the two treatment arms. The randomization is used to provide balance with respect to measured and not measured participant characteristics across the randomized treatment arms. Randomization will be stratified by site and within site, by presence of depressive symptoms (QIDS-C₁₆ score of ≤ 10 or ≥ 11) and by severity of stimulant use (≤ 18 days or > 18 days of use in the 30 days prior to admission to residential treatment). The randomization procedure will be conducted via a centralized process through the CTN Data and Statistics Center (DSC). The DSC statistician will generate the randomization scheme for the study. The randomization schedules will consist of balanced blocks within strata to ensure relative equality of assignment across treatment groups. The block sizes will be varied and

randomly permuted to further prevent the potential for guessing the next assignment, which is heightened when a fixed block-size is used. The block size will not be revealed to participating investigators and will be randomly selected from a small number of different block sizes to help reduce the likelihood of an investigator predicting the next treatment assignment. This scheme will provide chronological balance during participant enrollment with respect to the number of participants allocated to each treatment arm, and will thus balance the treatment groups with respect to possible changes in the mix of participants over time. The DSC statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. The randomization slot will not be re-allocated to a new participant due to the intent-to-treat nature of the study. Assessment administrators and participants will be aware of treatment assignment throughout the study.

9.5 Treatment and Study Interventions

All participants will receive treatment as usual during the study from their residential and outpatient/community treatment providers. Participants will receive study interventions as described in sections 11.2.1 and 11.2.3. Assessments will be conducted based on the schedule outlined in section 10.1. Qualified, trained, and certified personnel will conduct clinician-rated assessments (all assessments which are not self-report), as indicated in the Time and Event Table (Summary of Assessments) in section 10.1. During the acute phase of the trial (12 weeks), the primary outcome measure (Timeline Follow Back) will be obtained three times per week, along with relevant items used to help complete or correct the TLFB (Substance Use Diary and urine drug screen). Secondary measures such as withdrawal symptoms, craving, and mood will be assessed weekly. Additional secondary outcomes (e.g., quality of life and anhedonia) will be assessed monthly throughout the study. If the participant is not able to come to the site and (s)he agrees, some assessments and/or visits may be conducted by phone, by mail, or at appropriate off-site locations, and/or on participants' or other off-site computers via the secure study website(s) if access to a computer with internet service is available. Detailed descriptions of the assessments are provided in section 10.2.

9.6 Continuation Phase

During the six-month continuation phase, participants will have one weekly supervised intervention session, with the remainder of their required intervention dose (for those randomized to exercise) conducted on their own. Urine drug screens and TLFB will continue to be obtained at every study visit (i.e., weekly), preferably prior to the supervised intervention session. Other outcome measures will be conducted on a weekly or monthly (or longer in the case of the ASI and cognitive function measures) basis.

9.7 Participant Discontinuation

In order to ensure safety, participants who begin an excluded medication or treatment (i.e., beta blockers, methadone, buprenorphine, or other opioid replacement therapies) during participation in the study will be required to stop the study intervention. Female participants who become pregnant during the study will be required to discontinue participation in the intervention. Participants may be asked to stop study intervention if any situation arises that, in the investigator's judgment, poses a safety risk. Participants who must stop the study intervention will still be asked to complete assessment visits as scheduled.

9.8 Participant Remuneration

Participants will receive monetary remuneration for their participation in the trial to compensate for their time, travel arrangements, and the burden of participation. Essential to the study is appropriate support for participants' time and effort contributing to the study. Recommendations are subject to change per IRB guidelines and other local considerations. Reimbursement for attending data collection visits will be made based on the following schedule:

- Acute phase (weeks 1-12): reimbursements will be made for the primary data collection visit during a week for a total of 12 payments and reimbursements will be made for the second and third data collection visits of the week for a total of 24 payments
- Continuation phase [weeks 13-37 (24 weeks)]: data collection visits are once a week for a total of 24 payments

During the 6-month continuation phase, participants will be additionally reimbursed for attending 2 or 3 out of the 4 required sessions in a given month.

Additional reimbursements will be made for participants who achieve the following study milestones: screening visit, baseline visit, transition from treatment in residential setting to community treatment (expected at Week 4), the last week of acute phase (Week 12) or second maximal exercise test (Week 13), and the last week of the study (Week 37).

In order to receive maximum compensation, all attendance requirements must be met.

Participants will be paid for each eligible visit in the form of cash or equivalent gift card, per the preference of the CTPs and IRB regulations.

9.9 Waves of Enrollment

We will begin implementation of the study at four sites during Wave 1 of the trial to aid in working out logistical issues in trial implementation. Wave 2 sites will be opened to enrollment approximately seven months after Wave 1 sites (see Section 6.2).

10.0 STUDY ASSESSMENTS

10.1 Time and Event Table (Summary of Assessments)

	Estimated Time	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33	37	
		SCR	BL	Acute Phase												Continuation Phase					ET	
Diagnostic and Screening Measures																						
Informed Consent	30	X																				
Demographics	5	X																				
CIDI (Substances)	30	X																				
MINI	30	X																				
Locator Form	10/2	X					X				X				X	X	X	X	X	X		
Prior and Concomitant Meds*	10	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCQ	5	X																				
PAR-Q	2	X																				
Medical History-Self-report Form	15	X																				
Max Ex Test Screening Questions	2	X																				
Maximal Exercise Test	30	X													X							
Physical Exam/Medical History	40	X																				
Labs (Chemistry, lipids, hematology, urinalysis, pregnancy test [if indicated])	10	X																				
Pregnancy test	N/A ⁺	X					X				X				X	X	X	X	X	X		

	Estimated Time	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33	37	
		SCR	BL	Acute Phase												Continuation Phase					ET	
Substance Use and Treatment Assessments																						
TLFB/SUD*	30/5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen*	5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SSSA*	10		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ASI-Lite/ASI-Lite F/U	45/15		X												X			X			X	X
TAU Tracking Form*	5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
STCQ-Brief*	1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FTND	2		X																			
Psychosocial and Quality of Life Measures																						
SF-36	10		X				X				X				X	X	X	X	X	X	X	X
Q-LES-Q-SF	2		X				X				X				X	X	X	X	X	X	X	X
P-FIBS	1		X				X				X				X	X	X	X	X	X	X	X
Cognitive Function																						
WTAR	15		X																			
Stroop	10		X												X						X	X
CPFQ	4		X				X				X				X	X	X	X	X	X	X	X
Mood, Sleep⁺, and Anhedonia																						
QIDS-C16*	7		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CHRT-SR*	2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CAST-SR*	2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SHAPS	5		X				X				X				X	X	X	X	X	X	X	X

	Estimated Time	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33	37		
		SCR	BL	Acute Phase												Continuation Phase					ET		
Physiological Measures																							
Physiological Measures**	5		X				X				X				X	X	X	X	X	X	X	X	
Exercise Readiness Form***	5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Retention																							
TPQ*	3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Estimated Time	≈	<u>249</u>	<u>144</u>	<u>50</u>	<u>45</u>	<u>45</u>	<u>84</u>	<u>45</u>	<u>45</u>	<u>45</u>	<u>84</u>	<u>45</u>	<u>45</u>	<u>45</u>	<u>139</u>	<u>84</u>	<u>84</u>	<u>99</u>	<u>84</u>	<u>84</u>	<u>89</u>	<u>89</u>	
Adverse Events and Safety																							
AE Form	<i>Complete as Needed</i>																						
SAE Form	<i>Complete as Needed</i>																						
Termination																							
Termination Form	<i>Complete as Needed</i>																						

Note that clinician-rated assessments (all assessments which are not self-report) will be conducted by trained evaluators; gray shading indicates clinician-rated measures.

Numbers indicate estimated time (in minutes) to complete each assessment. Week 1, 13, 25, and 37 visits are longer because of the addition of the ASI-Lite. This measure is included at these intervals to allow data from this study to be directly compared to other studies currently being conducted in the CTN.

*TLFB/SUD and urine drug screens will be obtained 3 times per week during the first 12 weeks of the study and weekly during the continuation phase. The Prior and Concomitant Medications, STCQ-Brief, SSSA, QIDS-C, CHRT, CAST, TAU Tracking Form and TPQ (until Week 36) will continue to be administered weekly (through Week 37) during the continuation phase.

**Physiological Measures include height, weight, body mass index (BMI) and waist circumference. Height will be assessed once at baseline and the others will be assessed monthly. Weight will be assessed weekly.

***Exercise Readiness Form is given at each Exercise Intervention visit. It includes measures of heart rate and blood pressure. A Maximal Exercise Test Data Form will collect heart rate and blood pressure information at the screening visit for all participants.

+ Pregnancy tests are conducted at screening and monthly thereafter. The urine collected for urinalysis at screening and for the UDS at monthly visits will be used to complete the pregnancy tests. Therefore, it is expected that these tests can be completed within the timeframe currently allotted for labs and UDS.

SCR – Screening Visit
BL – Baseline (occurs at the first visit of Week 1)
ET – Early Termination. Note that the Maximal Exercise Test will be completed at the ET visit if termination occurs prior to Week 13.
CIDI – Composite International Diagnostic Interview – CTN version (Substance Modules)
MINI – Mini International Neuropsychiatric Interview
SCQ – Self-Administered Comorbidity Questionnaire
PAR-Q – Physical Activity Readiness Questionnaire
TLFB – Timeline Follow Back
SUD – Substance Use Diary
STCQ-Brief – Stimulant Craving Questionnaire-Brief
SSSA – Stimulant Selective Severity Assessment
ASI-Lite – Addiction Severity Index – Lite
ASI-Lite F/U – Addiction Severity Index – Lite Follow-up
TAU Tracking Form – Treatment as Usual Tracking Form
FTND – Fagerstrom Test for Nicotine Dependence
SF-36 – Short-Form Health Survey
Q-LES-Q-SF – Quality of Life Enjoyment and Satisfaction Questionnaire Short Form
P-FIBS – Pain Frequency, Intensity and Burden Scale
WTAR – Wechsler Test of Adult Reading
CPFQ – Cognitive and Physical Functioning Questionnaire
Stroop – Stroop Color and Word Test
QIDS-C – Quick Inventory of Depressive Symptomatology - Clinician Rated version (16-item)
*note that sleep will be assessed via the 4 sleep items measured by the QIDS-C
CHRT-SR – Concise Health Risk Tracking- Self Report
CAST-SR – Concise Associated Symptoms Tracking- Self Report
SHAPS – Snaith-Hamilton Pleasure Scale
TPQ – Treatment Participation Questionnaire

10.2 Types of Assessments

10.2.1 Diagnostic and Screening Measures

Demographics Form. The demographics form will be administered to all participants at the screening visit. The form consists of basic demographic information (e.g., gender, race/ethnicity, etc.).

Composite International Diagnostic Interview (CIDI) (Modules A, J, and L: Demographics, Alcohol, and Illegal Substances) (CTN version). The CIDI is a structured diagnostic interview that evaluates the presence of Axis I disorders as defined in the Diagnostic and Statistical Manual - IV (DSM-IV TR) and World Health Organization (WHO) International Classification of Disease (ICD). Selected modules of the CIDI will be used to identify substances of abuse. Clinical evaluators will be trained and certified to administer this interview. Tests of the reliability of the CIDI-SAM based on DSM-IV diagnoses for cocaine dependence compared to SCID interviews done by trained clinicians, had percent agreement of 82.6%, with kappa=0.61. With specific criteria for the diagnosis, kappas ranged between 0.68 and 0.55. This instrument will be administered at the screening visit.

Mini International Neuropsychiatric Interview (MINI; Sheehan et al, 1997). The MINI is a structured diagnostic interview designed to screen for Axis I psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 4th ed) and International Classification of Diseases (ICD-10, 10th ed) (Sheehan et al, 1998). In comparison to the Structured Clinical Interview for DSM-IV Disorders (SCID-P), kappa values were good (only one diagnosis < .50), specificities and negative predictive values were .85 or higher across diagnoses, and in general, sensitivity was .70 or higher (Sheehan et al, 1998). The MINI is being used to ensure standardized psychiatric diagnoses. The MINI will be administered at the screening visit and will be used to identify Axis I psychiatric diagnoses (excluding substance use disorders).

Locator Form. The Locator Form will be used to obtain contact information for each participant. The Locator Form will be filled out at the screening visit and then routinely updated on a monthly basis thereafter (excluding the final visit). In addition, a Locator Form may be completed/updated any time the participant reports a change in contact information.

Prior and Concomitant Medications. The Prior and Concomitant Medications form assesses prescribed and certain over-the-counter medications taken by the participant. The Prior and Concomitant Medications form will be administered at the screening visit and then weekly thereafter, if the participant endorses a change in medication status.

Self-Administered Comorbidity Questionnaire (SCQ). The SCQ is a self-report which assesses the presence of medical problems, their severity, and whether or not the condition limits functioning (Sangha et al 2003). The medical conditions specified on the SCQ include: heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, arthritis, thyroid disease and back pain. Respondents have the option of adding three additional conditions. An individual can receive a maximum of 3 points for each medical condition (1 point for its presence, 1 point if they receive treatment for the condition, and 1 point if the condition limits activities). An intraclass correlation coefficient of 0.94 shows good test-retest reliability and is comparable to the Charlson Index intraclass correlation coefficient of 0.92. The SCQ will be administered at the screening visit.

Physical Activity Readiness Questionnaire-Revised (PAR-Q; Canadian Society for Exercise Physiology, 2002). The PAR-Q asks 7 health-related questions to determine whether a person

needs to consult with their physician prior to engaging in an exercise program. The PAR-Q will be administered at the screening visit.

Medical History- Self-report Form. The Medical History-Self-report Form obtains information that will facilitate the conduct of the physical exam, clinician-rated medical history and maximal exercise test. This form includes questions about history and/or treatment of medical conditions, such as heart disease, high blood pressure, diabetes, and cancer. The form also assesses allergies, past surgeries, regular current and past tobacco and alcohol use, and family history of medical conditions. Medical symptoms over the past 30 days, such as excessive fatigue, chest pain, shortness of breath, and blurred vision, are also assessed. The Medical History-Self-report Form will be administered at the screening visit.

Maximal Exercise Test Screening Questions. The Maximal Exercise Test Screening Questions will be filled out by the participant before the Maximal Exercise Test to aid the medical personnel in ensuring that it is safe for the participant to undergo the test. This form includes questions about exercise, smoking, shortness of breath and unexplained dizziness or fainting. The Maximal Exercise Test Screening Questions will be administered at the screening visit.

Maximal Exercise Testing. Maximal exercise testing will be conducted during the screening process to examine cardiorespiratory responses in order to rule out ischemic response to exercise (with its implications of cardiovascular disease), to identify participants for whom exercise might be hazardous, and to provide data for the exercise prescription. The test will be repeated at the end of the 12-week acute phase. If a participant terminates study participation in Weeks 9-13, the repeat maximal exercise testing will occur during the early termination visit. Testing may take place in a facility that complies with ACSM testing guidelines when the required personnel and equipment are not available at the treatment facility. Equipment and supplies needed include an ECG System and ECG electrodes (diaphoresis resistant), commercial grade treadmill, Borg Rating of Perceived Exertion (RPE) scale, blood pressure cuff and sphygmomanometer, and automated external defibrillator (AED). A trained technician will process the test data and a report will be generated that contains the following information: 1) participant's symptoms before, during and after testing, 2) maximal heart rate achieved and percent of predicted maximal heart rate achieved, 3) time on treadmill and estimated maximal metabolic equivalent (METs) achieved, and 4) ECG interpretation. Identification of symptoms or conditions that require the test be stopped (based on ACSM's Guidelines for Exercise Testing and Prescription) will result in discontinuation of the test, as well as ineligibility for participation in the study. In the event of equipment difficulty or failure, the failure of the participant to achieve their age-predicted maximal heart rate, or other situations determined by the testing and/or medical personnel to warrant a rescheduling of the test, the test may be rescheduled and/or repeated. Greater detail on the testing protocol and ACSM guidelines can be found in the Manual of Procedures and Study Tools Manual.

Physical Exam/ Medical History. A physical exam will be conducted for all participants to provide clearance for exercise. The medical personnel conducting the exam will also review the participant's medical history. The medical personnel will also evaluate results from the medical exam, maximal testing and lab results, and will determine whether or not the participant is medically cleared to exercise.

Laboratory Tests. Clinical laboratory tests will include hematology, lipids, blood chemistry, and urinalysis. A urine pregnancy test will be performed for any woman who is able to have children and wishes to participate in this research. Pregnancy tests will be repeated later in the study. A pregnancy test will be performed at screen and monthly thereafter. A pregnancy test may also be performed at any other time throughout the study if pregnancy is indicated or suspected.

10.2.2 Substance Use and Treatment Assessments

Timeline Follow Back (TLFB; Sobell and Sobell, 1973, 1996) and Substance Use Diary (SUD). The Timeline Follow Back was originally developed to aid in the recall of past drinking behavior (Sobell and Sobell, 1992). It has been adapted to acquire use information for a variety of other substances, including cocaine and other stimulants (Sobell and Sobell, 1996). The TLFB is a semi-structured interview which uses a calendar to prompt participants to provide retrospective estimates of their daily drug use over a specified period of time that can vary up to 12 months before the interview date. Memory aids and other mechanisms are used to enhance recall. The measure provides prompts to facilitate accurate recollection of use behavior, and in this protocol, the Substance Use Diary will be given to participants at the beginning of the study to assist with accurate recall in completing the TLFB at each study visit. Urine drug screens will also be used to corroborate information on the TLFB. The TLFB has been shown to have high test-retest reliability (ICC values ranging from 0.70 to .94, with all $p < 0.001$), good convergent and discriminate validity, and acceptable agreement between the TLFB and urine drug screens (Yule's Y of 87 or greater for amphetamines and cocaine) (Fals-Stewart et al, 2000). The TLFB will be administered at screening, three times per week in the first 12 weeks, and once a week in the subsequent 6 months.

Urine Drug Screen (UDS). Qualitative urine drug screens will be conducted at baseline, three times a week in the first 12 weeks, and once a week in the subsequent 6 months. Collection and recording procedures will be used consistent with typical CTN practice. The screen will test for the following substances: marijuana, cocaine, opiates, amphetamine, methamphetamine, benzodiazepines, barbiturates, methadone, methylenedioxymethamphetamine (MDMA, Ecstasy), and oxycodone.

Stimulant Craving Questionnaire-Brief (STCQ-Brief; adapted from Sussner et al, 2006). The STCQ-Brief is a 10-item self-report measure derived from the 10-item Cocaine Craving Questionnaire-Brief and the original 46-item Cocaine Craving Questionnaire-Now (Tiffany et al, 1998). The STCQ-Brief assesses current craving for stimulants (cocaine, methamphetamine and other stimulants) using a seven-point scale, with answers ranging from "strongly disagree" to "strongly agree". The CCQ-Brief, from which the STCQ-Brief is adapted, has high internal consistency, with Cronbach's alpha ranging from 0.87 (Paliwal et al, 2008) to 0.90 (Sussner et al, 2006). The instrument also has good construct validity and has shown to correlate well with other craving measures (Paliwal et al, 2008). The STCQ-Brief will be administered at baseline and weekly thereafter.

Stimulant Selective Severity Assessment (SSSA; adapted from Kampman et al, 1998). The SSSA is an 18-item clinician-rated instrument assessing the signs and symptoms of stimulant (cocaine, methamphetamine and other stimulants) abstinence. It is derived from the Cocaine Selective Severity Assessment, which contains items that are most frequently associated with early cocaine abstinence. The items are rated on a scale from 0-7 (with higher scores indicating greater intensity or frequency) with a maximum possible score of 112. The CSSA, from which the SSSA is adapted, has been shown to have good inter-rater reliability (correlation coefficient = 0.92, $p < 0.001$) and internal consistency (Cronbach's alpha = 0.80). In this protocol, the CSSA will be adapted for use with stimulants. The SSSA will be administered at baseline and weekly thereafter.

Addiction Severity Index-Lite (ASI-Lite). The Addiction Severity Index-Lite will be administered to assess common problems associated with drug use. It will be administered by a clinical evaluator at baseline, with follow-ups collected at weeks 13, 25, and 37. The ASI is a standardized, semi-structured interview. It examines multiple domains that commonly affect substance abusers: medical, employment/self-support, alcohol/drug use, legal status, family/social, and psychiatric status (McLellan et al, 1980). The measure gathers information

across the lifetime as well as current status (previous 30 days before the interview). Composite scores are calculated for each problem area and these scores can be used as outcome measures, including the drug/alcohol subscale. The ASI-Lite is a modified and shortened version of the ASI which includes key questions in the domains. Versions of the ASI-Lite contain about 160 questions and take about 30-45 minutes to administer at baseline and about 15 minutes at follow-up. The CTN version is similar to the ASI-Lite-Veterans Administration (ASI-L-VA) and should have similar psychometric characteristics. Specifically, intraclass correlations between the ASI fifth edition (ASI-5) and ASSI-L-VA are 0.79 for alcohol, 0.79 for drug, 0.85 for legal, 0.46 for family/social, and 0.53 for psychiatric (Cacciola et al, 2007). The ASI-Lite Follow-up will be administered at Weeks 13, 25, and 37, and will consist of a subset of questions from the full version administered at baseline.

Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al, 1999; Kozlowski et al, 1994). The FTND is a 6-item self-report measure that assesses dependence on nicotine, and includes assessment of the number of cigarettes smoked per day. The FTND has shown acceptable internal consistency (Cronbach's alpha of 0.61) and correlates significantly with other measures of smoking consumption. The FTND will be administered at the baseline visit.

Treatment as Usual (TAU) Tracking Form. The TAU Tracking Form is a 9-item measure used to assess the participant's treatment for substance abuse within the past week. It assesses whether the participant was scheduled to receive any treatment in the past week, such as residential, group counseling, individual counseling, family, and 12-step, and if so, how many sessions they did attend. The purpose of this instrument is to measure the treatment as usual across the groups during the length of the study. The TAU Tracking Form will be administered at baseline and weekly thereafter.

10.2.3 Measures of Mood, Sleep and Anhedonia

Quick Inventory of Depressive Symptomatology - Clinician Rated version (16-item) (QIDS-C₁₆; Rush et al, 2000, 2003, 2006, 2008; Trivedi et al, 2004). The QIDS is a 16-item version of the 30-item Inventory of Depressive Symptomatology (IDS) designed to assess severity of depression-specific symptoms. Scores range from 0 to 27 with higher scores representing greater severity of depressive symptoms. The QIDS has been used in a number of major trials such as STAR*D, the NIMH's large clinical trial in treatment resistant depression, that have been designed to evaluate the effectiveness of treatments for major depression. It has also been used effectively to evaluate depressive symptoms in other psychiatric disorders (Trivedi et al, 2004). The internal consistency coefficient is high (Cronbach's alpha of 0.90) (Trivedi et al, 2004). It also has good concurrent validity, with correlations between the QIDS and the 17-item Hamilton Rating Scale for Depression ranging between .86 and .93. It also has been shown to have good inter-rater reliability with a kappa of .85. The QIDS-C will be administered at baseline and weekly thereafter.

Sleep. Sleep will be assessed via the 4 sleep items measured by the QIDS-C. These items cover initial insomnia, middle insomnia, early morning awakening, and hypersomnia. A sleep score will be calculated weekly, consistent with the administration of the QIDS-C.

Concise Health Risk Tracking – Self Report (CHRT-SR; Trivedi et al, submitted). The CHRT-SR is a 14-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner et al, 2007). Items are rated on a fully anchored 5-point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree), with total scores ranging from 13 to 65. The CHRT-SR has good internal consistency (Cronbach's alpha of 0.78). The CHRT-SR will be assessed at baseline and weekly thereafter.

Concise Associated Symptoms Tracking – Self Report (CAST-SR; Trivedi et al, submitted). The CAST-SR assesses symptoms related to suicidal thoughts and behaviors. This scale consists of 17 self-report items rated on a fully anchored 5-point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree). Items assess symptoms of anxiety, tension, irritability, impulsivity, psychomotor agitation, physiologic hyperarousal, and hypomania/mania. The scale yields a total score ranging from 17 to 85. The internal consistency coefficient for the CAST-SR is good (Cronbach's alpha of 0.77). The CAST-SR will be assessed at baseline and weekly thereafter.

Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al, 1995). The SHAPS is a 14-item scale that measures anhedonia, the inability to experience pleasure. The items cover the domains of: social interaction, food and drink, sensory experience, and interest/pastimes. A score of 2 or less constitutes a "normal" score, while an "abnormal" score is defined as 3 or more. Each item has four possible responses: strongly disagree, disagree, agree, or strongly agree. Either of the "disagree" responses score one point, and either of the "agree" responses score 0 points. Thus, the final score ranges from 0 to 14. The SHAPS has adequate construct validity and satisfactory test-retest reliability (ICC=0.70) (Franken et al, 2007). High internal consistency has also been reported (Cronbach's alpha of 0.94) (Franken et al, 2007). The SHAPS will be measured at baseline and then monthly thereafter.

10.2.4 Psychosocial Assessments

Short-Form Health Survey (SF-36; Ware et al, 1993; Ware, 2003). The SF-36 will be used to assess quality of life and general health. It is a self-report inventory that assesses health-related quality of life (HRQoL) and was developed for the Medical Outcomes Study (MOS) (Ware and Sherbourne, 1992). The SF-36 contains eight scales measuring: Physical Functioning, Physical Role Functioning, Bodily Pain, General Health, Vitality, Social Functioning, Emotional Role Functioning, and Mental Health. Each scale scores ranges from 0 to 100, with higher scores indicating better perceived health and functioning. Internal consistency reliability coefficients are high (all greater than 0.80). Test-retest coefficients range from 0.43 to 0.90 for a 6-month interval and from 0.60 to 0.81 for a 2-week interval. The SF-36 has been shown to correlate moderately well with other health measures. Physical and Mental Summary Scores can also be derived. The SF-36 will be assessed at baseline and then monthly thereafter.

Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF; Endicott et al, 1993). The Q-LES-Q-SF evaluates general activities that are assessed in the longer form of the Q-LES-Q. Each item uses a 5-point scale ranging from 1 (very poor) to 5 (very good). A total score is derived from 14 items with a maximum score of 70 and with higher scores indicating greater life satisfaction and enjoyment. Participants rate their satisfaction with the following domains of activity: physical health, feelings, work, household duties, school/course work, leisure time activities, and social relations. Test-retest reliability for the Q-LES-Q-SF has been shown to be .86 (Rapaport et al, 2005) and internal consistency (Cronbach's alpha) has been shown to range from .86 to .90 (Rapaport et al, 2005; Wyrwich et al, 2009). The Q-LES-Q-SF will be assessed at baseline and then monthly thereafter.

Pain Frequency, Intensity and Burden Scale (P-FIBS). The P-FIBS is a 4-item self-report evaluating the frequency, intensity and burden of pain over the past week, as well as usage of pain medication to manage pain. The P-FIBS will be administered at baseline and then monthly thereafter.

10.2.5 Cognitive Function Assessments

Wechsler Test of Adult Reading (WTAR; Wechsler 2001). The WTAR is given to assess premorbid intelligence. The WTAR has been established to be a reliable and valid assessment of pre-morbid intelligence. It has been normed with the Wechsler Adult Intelligence Scale

(WAIS-III) and the Wechsler Memory Scale (WMS-III). During the test, participants are asked to read 50 words out loud and are scored on the accuracy of their pronunciation. The WTAR will be administered once at baseline.

MGH Cognitive and Physical Functioning Questionnaire (CPFQ; Fava et al, 2006). The CPFQ is a 7-item self-report measure that assesses physical well-being and cognitive and executive dysfunction. Answers range on a 6-point scale from “greater than normal” to “totally absent”, with higher scores indicating poorer functioning. The CPFQ has been shown to have high internal consistency with a Cronbach’s alpha of 0.90 and test-retest reliability (0.83, $p < 0.001$) (Fava et al, 2009). The CPFQ will be administered at baseline and then monthly thereafter.

Stroop Color and Word Test (Stroop; Stroop, 1935; Golden, 1978). The Stroop Color and Word Test is a measure of attention response inhibition. The test consists of three subscales: 1) word – color nouns (e.g., red, blue) printed in black ink are presented and participants must read the word; 2) color – the letter “x” is presented in colored ink and participants are asked to name the color; and 3) color-word – color nouns are presented in discrepantly colored ink and participants are asked to name the color. An Interference score is also calculated to represent a composite of the subscales. The Stroop will be administered at baseline and weeks 13 and 37.

10.2.6 Physiological Measures

Physiological Measures. Physiological measures include height, weight, body mass index (BMI) and waist circumference. Height will be obtained once at baseline and the other measures will be obtained monthly. For participants randomized to the exercise intervention, weight will be assessed weekly to assist in the generation of the exercise prescription. Also for those participants in the exercise intervention, resting heart rate and blood pressure will be obtained prior to each exercise session using the Exercise Readiness Form, in order to evaluate safety to exercise. Resting heart rate and blood pressure will be obtained for all participants during the screening process through the Maximal Exercise Test.

10.2.7 Retention

Treatment Participation Questionnaire (TPQ). The TPQ is a five item self-report that asks for the participant’s likelihood of remaining in treatment for substance abuse and continuing to attend study visits in the context of relapse, cravings or urges to use, or perception that the study is burdensome. The TPQ will be administered at baseline and then weekly thereafter (excluding the final visit).

10.2.8 Safety Assessments

Assessments involved in determining participants’ ability to safely participate in the protocol (maximal exercise testing, laboratory tests, and physical exam) are described under Diagnostic and Screening Measures. Additionally, reportable AEs and all SAEs will require completion of an AE Form (and SAE form as applicable) to document and track reportable AEs.

10.3 Administration Time

The estimated time for completion of study assessments is provided in Section 10.1: Time and Event Table.

11.0 STUDY TREATMENTS

11.1 Usual Care (Treatment as Usual, or TAU)

Treatment providers will be selected based on preferred site selection characteristics (see section 8.0). The content of treatment as usual (TAU) will be carried out in the typical manner for each site at both residential treatment and community care facilities. Each participant's TAU will be tracked using the TAU Tracking Form (see section 10.2.2).

11.2 Study Interventions

The interventions have been constructed such that there is equivalent contact time between groups. Additional details of each intervention are as follows:

11.2.1 Exercise

Intervention

During participants' stay in residential care (generally about 21-30 days) and for the remainder of the first 12 weeks of the study, they will receive at least 3 weekly, supervised exercise sessions with a trained exercise facilitator. Additional sessions (up to two) may be completed as needed to achieve the target exercise dose and to allow for participants to develop autonomy in completing sessions in order to prepare them for completion of home-based sessions during the continuation phase. In the first session, participants will be instructed on how to use the treadmill, and how to collect and record all variables of interest (e.g, speed, duration, rating of perceived exertion (RPE), post-session heart rate, and kcal). Participants will have written logs, as well as access to the study website, available for recording this information. In Weeks 3-12, participants will be trained to complete their sessions more autonomously in the exercise facility, but will have facilitators available to troubleshoot problems or issues that may arise. In months 4-9 (continuation phase), participants will complete one supervised exercise session per week at the residential treatment center site or an associated outpatient treatment program. The remainder of the weekly dose will be completed at home (i.e., unsupervised sessions conducted on their own), and participants can exercise on a treadmill, or by over ground walking. The Exercise Facilitator will work with participants during supervised sessions to achieve consistent intensity (which will be assessed by RPE and HR) so that participants target the same parameters during unsupervised sessions. Participants will wear pedometers throughout the study to monitor activity levels. The supervised sessions will allow us to monitor whether the target goal is being met each week, promote consistency of at-home sessions, and troubleshoot any barriers to exercise that emerge during participation. By using both a fixed kcal requirement and training participants to engage in exercise of a particular intensity, we will provide maximal control over the exercise intervention while at the same time providing participants with flexibility to optimize adherence.

Dose

The vigorous intensity high exercise dose that was selected (12 KKW) is consistent with public health recommendations for physical activity, and is also similar to doses used in the treatment of other disorders (e.g., depression), as well as in studies of smoking. In order to improve tolerability, the dose will be ramped so that participants achieve 6 KKW the first week, 9 KKW in the second, and 12 KKW by the third week. Exercise intensity will be fixed to a range consistent with moderately high to high effort (i.e., 70-85% maximal heart rate), but will also be ramped up gradually in order to increase tolerability for participants. Quantification of this range will be based on each participant's maximal heart rate as determined during maximal exercise testing at screening. This range will ensure that participants are exercising at a consistent intensity, but there will be some flexibility in the range to also allow participants to exercise at a level that is most comfortable for them, which will maximize adherence. Participants will exercise 3 days per

week under supervision during the acute phase (i.e., the first 12 weeks) and weekly supervised sessions will be completed during the continuation phase (i.e., months 4-9). During the continuation phase, participants will be expected to complete the remainder of their weekly exercise dose unsupervised, at home or in the community.

Preparation for Exercise and Safety Precautions

At the beginning of the first exercise session of the week, the participant will be weighed. At the beginning of each exercise session, the participant's resting heart rate and blood pressure will be measured twice. If the participant's resting heart rate is 100 or greater on either reading, it will be re-measured. If resting heart rate is still above the required range after the third reading, the participant will not be allowed to exercise that day. Similarly, if the participant's systolic blood pressure is above 160 or if the participant's diastolic blood pressure is above 100 on either reading, it will be re-measured. If blood pressure is still above 160/100 after the third reading, the participant will not be allowed to exercise that day.

If resting systolic blood pressure is greater than 140 or if resting diastolic blood pressure is greater than 90 at 3 consecutive visits, the participant will be referred to appropriate medical care to ensure adequate monitoring and follow-up care is obtained, if needed. The participant will not be allowed to exercise until receiving medical clearance to continue exercising.

Aerobic Training

Participants will exercise on a treadmill at a comfortable grade and speed. The participant will burn a specific amount of calories depending on the week of participation and the weight of the individual (target of 12 kcal/kg, i.e., exercise dose). Participant will wear a heart rate monitor during the duration of the exercise session. The participant will warm up (using an active warm-up as specified in the Manual of Procedures) for 5 minutes prior to initiation of the exercise prescription. During the exercise session, the participant's average heart rate must be within 70-85% of HR_{max} determined by the maximal exercise test. Heart rate and Rating of Perceived Exertion (RPE) will be assessed. Blood pressure will be assessed after 5 minutes of exercise. The exercise session will be halted if an extreme elevation in blood pressure is observed. The speed and/or grade can be adjusted to return the heart rate to a safe exercising level within the desired range. After completion of the exercise prescription, the participant will cool down (0 grade and 50-70% of speed) until their heart rate returns to within 15% of their resting heart rate. Following cool down, the participant will be led through 5-10 minutes of stretching.

11.2.2 Health Education

The health education intervention will be structured to provide equivalent contact to that of the exercise intervention. In the first 12 weeks, there will be supervised sessions three times per week, during which educational items such as didactical presentations, readings, websites, and audio and video materials will be viewed by participants and facilitators will instruct participants to log the materials reviewed. Visits will be weekly in months 4-9. Instructional topics include areas such as healthy eating habits, recipes for healthy eating, preventive health care and recommended health screenings (e.g., cancer prevention, cardiovascular disease prevention), accessing health care resources, and other health related topics that are relevant to adults with substance use disorders. Participants will be encouraged to suggest topics of interest to help maintain their involvement and engagement in the sessions throughout the duration of the study. Participants randomized to receive HEI will log sessions and receive the behavioral adherence program to maximize adherence, as in the exercise group. The HEI program is modeled after similar programs developed by Marcus et al (1999) and Rejeski et al (2005) that have been used successfully as control groups in clinical trials examining exercise as an intervention (Marcus et al, 1999; LIFE Study Investigators, 2006). Participants receiving HEI will also wear pedometers to monitor changes in activity during study participation.

11.2.3 Heart Rate Monitors and Pedometers

Participants randomized to the exercise group will wear heart rate monitors during supervised exercise sessions. As mentioned previously, participants randomized to exercise will use heart rate monitors to ensure that they are exercising in the appropriate intensity range. All participants will wear pedometers. Pedometers will be worn by participants in both groups to minimize drift between groups. Specifically, we will monitor weekly step counts to minimize the likelihood that participants who are randomized to exercise do not become more sedentary when engaged in everyday activities, and that participants who are randomized to health education do not increase their everyday activity level.

11.2.4 Adherence

A comprehensive behavioral intervention approach to facilitating and monitoring adherence to the study interventions has been developed by our team through our work in conducting exercise interventions in depressed populations (Trivedi, 2006b). A study website will be utilized to track intervention-related data, including kcal expended per week, post-exercise HR, exercise duration, HEI sessions, etc. Data can then be reviewed and monitored in real time in order to maximize adherence. Additionally, the website provides participants with flexibility and autonomy in planning intervention sessions and capturing essential data. This program serves to: 1) provide flexibility in the conduct of the interventions, and 2) allow for individualized monitoring to address person-specific adherence issues and barriers to the interventions. The program includes: 1) multidisciplinary psychoeducation about adherence and the use of behavioral reinforcers (e.g., water bottles, pen and notepad, gift cards) for attendance/adherence to the intervention, 2) written reference materials, 3) skills training (e.g., instruction in appropriate exercise form, intensity), 4) weekly exercise prescription (for participants randomized to exercise), 5) self-monitoring of adherence and performance (e.g., heart rate, RPE, tracking of HEI topics), 6) adherence feedback from study website and intervention facilitators, and 7) weekly intervention planning (individually-tailored plan). If participants do not have a computer available to them, written logs will be used and a research assistant will enter data into the electronic system. If participants miss an intervention session, they will be prompted by study personnel to make-up the session if possible and to attend their next scheduled session.

The behavioral adherence program begins with a behavioral contract that the facilitator will review with the participant. The participant will be asked to plan their weekly intervention sessions around their usual activities. For example, while in the residential treatment setting, participants will be asked to consider scheduling their exercise sessions around scheduled treatment sessions and other important activities. Once in community treatment, participants will be asked to consider other important activities that may preclude their ability to exercise, such as work schedules or vacations. The contracting process allows participants to begin thinking about their schedule, and also helps to firm up a commitment to the intervention sessions. Participants will then be asked to consider possible barriers to completing an intervention session. Possible barriers could include boredom, fatigue, lack of time, inclement weather (in the case of home-based [i.e., non-supervised] exercise during the continuation phase), etc. Facilitators will help participants troubleshoot these barriers and find ways to work around them. For example, if boredom is reported by a participant randomized to exercise, the facilitator may suggest that he or she listen to music or watch a favorite TV show during the exercise session. If an HEI participant reports boredom, the facilitator may engage the participant in a conversation to help identify health needs, concerns, or interests that can then be a focus of the next HEI session. This process will continue throughout all weeks of the intervention. The study website will ask participants to report any barriers that were encountered in a given week during which adherence goals were not met. Facilitators will be able to review barriers and strategies to resolve them for any participant not meeting his or her weekly intervention goals. An additional

important feature of the behavioral adherence program and study website is the easy access to materials on the importance of adherence and other items such as frequently asked questions and tips on stretching, guidance on the use of equipment such as pedometers, etc. This information helps to engage participants in their respective interventions and provides them with immediate answers to potential problems that may arise.

11.3 Staff Training

The study staff will be trained and certified as specified in the Manual of Procedures and Study Tools Manual. Training will cover standard NIDA training for all CTN trials (e.g., Good Clinical Practices), as well as protocol-specific training as needed (e.g., assessments, study interventions, fidelity to the protocol and safety procedures, data management and collection, research procedures including understanding reliability and validity, and problem solving). Support mechanisms are identified (e.g., who to contact for aid, questions, resources). All study staff will also be required to complete any local training requirements per their study sites and IRBs. Further details are presented in the study Training Plan.

11.4 Safety Considerations

A number of important procedures are included in this trial to maximize participant safety. Features specific to exercise testing and the exercise intervention are highlighted below.

11.4.1 Maximal Exercise Testing

A trained and licensed technician (e.g., exercise physiologist, nurse, physician's assistant, physical therapist) with basic life support and AED training will be present to perform each maximal exercise test. All maximal exercise tests should be supervised by a physician, nurse practitioner, physician's assistant or other qualified medical personnel. If not immediately present, qualified medical personnel should be in close proximity (within a minute) and readily available should there be an emergent need. An automatic defibrillator will be available during testing. A 12-lead ECG will be used to monitor participants prior to, during and following the test. The test will be conducted on a treadmill using a modified Cornell Protocol. Additional details regarding the testing, as well as absolute and relative contraindications to exercise testing, are provided in the Maximal Exercise Testing Procedures (see Manual of Procedures and Study Tools Manual).

11.4.2 Exercise Intervention

All exercise facilitators who conduct supervised exercise sessions will receive comprehensive training and will be CPR certified. Automatic defibrillators will be available in the exercise area or an easily accessible location. During supervised exercise, exercise facilitators will query participants about current symptoms and any changes that have occurred since their last session. Blood pressure and heart rate will be obtained prior to each supervised session. Participants will not be allowed to exercise during a scheduled session if either of the following occur: 1) the third of three blood pressure readings is greater than 160 (systolic) or greater than 100 (diastolic); 2) the third of three resting heart rate readings is greater than 100. Participants will also be asked to measure their heart rate during unsupervised exercise, and will be advised not to exercise if their resting heart rate exceeds 100. An active warm-up will be conducted at the beginning of each exercise sessions and a cool down and stretching exercises will be conducted at the end of each session to reduce the risk of injury.

12.0 CONCOMITANT THERAPY

The following treatments – beta blockers, methadone, and buprenorphine or any other opioid replacement therapies – will not be allowed for participants enrolled in this study, to ensure safety. Participants who begin one of these treatments while in the study will be asked to discontinue study interventions as described in section 9.7. Additionally, any medication or treatment judged by the study staff to be a safety concern for participants may be disallowed on an as needed basis.

13.0 STATISTICAL ANALYSES

13.1 Primary Outcome

The primary outcome Y is proportion of stimulant abstinent days during 9 weeks (63 days) of treatment, and for a single participant Y can have one of the values 0, 1/63, 2/63... 62/63, 1. The nine weeks included in the primary outcome are Weeks 4-12 (when participants are expected to have transitioned from residential to community treatment).

The daily abstinence status (yes/no) will be ascertained with assistance of the Timeline Follow Back (TLFB) tool and urine tests. It is assumed that as long as a participant returns for a visit, it will be possible to ascertain the abstinence status in prior days even if the associated visits were missed. Also, it is assumed that days following last contact with a participant will be considered as stimulant use days (i.e. no abstinence). With this assumption, there will be a value of the primary endpoint for each randomized participant.

13.2 Statistical Methods for Primary Analysis

The primary endpoint will be analyzed on an intent-to-treat basis. This means that participants will be analyzed according to the randomized treatment regardless of the subsequent sequence of events. In other words, participants will be considered to belong to the randomized group even though they may be not perfectly compliant or not follow the prescribed dose of exercise. Note that the follow-up visits will be performed irrespectively of compliance with the treatment regimen.

The primary analysis will compare the primary outcome between the two treatments taking into account possible variability in the overall level of abstinence between sites. In mathematical terms, denote Y_{ij} as the value of the primary outcome abstinence measure for the i^{th} subject and j^{th} site and consider the following linear mixed model for the primary analysis:

$$Y_{ij} = \beta_0 + \beta_1 trt_{ij} + b_j + \varepsilon_{ij}$$

with trt_{ij} indicating treatment value (1=VIHD, 0=HEI) for the i^{th} subject in the j^{th} site; fixed effects β_0, β_1 ; random effect $b_j \sim N(0, \sigma_{site}^2)$ reflecting site's overall level of abstinence; and independent of the random effect residual errors $\varepsilon_{ij} \sim N(0, \sigma^2)$. The model considers treatment effect to be the same in each site. The primary hypothesis is $H_0 : \beta_1 = 0$ and it indicates no difference in abstinence for VIHD and HEI. We hope to reject $H_0 : \beta_1 = 0$ in favor of $H_1 : \beta_1 \neq 0$, and rejection of $H_0 : \beta_1 = 0$ will provide evidence for difference in outcome values between VIHD and HEI treatments. P-value less than 0.05 will be considered statistically significant.

The model can be fit with SAS MIXED procedure:

PROC MIXED; class site; model Y = trt / solution; random intercept / subject=site; run;

13.3 Rationale for Sample Size and Statistical Power

We assume that the average value of the response variable (proportion of abstinent days) in the HEI group (μ_{HEC}) is 0.425 (42.5%) and in the VIHD group it is $\mu_{VIHD} = 0.575$ (57.5%). Hence, the assumed treatment effect $\mu_{VIHD} - \mu_{HEC}$ is 0.15. The error standard deviation σ is considered to be in the range between 0.40 and 0.45. Note that these error values correspond to correlation in abstinence status over 63 days within a participant between approximately 0.65 and 0.83 (with a compound symmetry covariance model) because

$$0.425*(1-0.425)*[1+(63-1)*0.65]/63 = 0.575*(1-0.575)*[1+(63-1)*0.65]/63 = 0.40^2 \text{ and}$$

$$0.575*(1-0.575)*[1+(63-1)*0.83]/63 = 0.575*(1-0.575)*[1+(63-1)*0.83]/63 = 0.451^2.$$

Even though the overall level of outcome may differ across sites (i.e. $\sigma_{site} > 0$), the primary analysis removes this variation by adjusting for site in the model. Hence, sample size computations are based on value of error standard deviation σ and the sample size estimates (Table 1) are based on a two sample t-test formula. Another source of variation may be a differing VIHD treatment effect across sites and simulations with primary analysis performed for each simulation are used later to confirm achievable power for a given sample size in Table 1.

Table 1 displays total number of subjects needed to achieve 90% power to reject $H_0 : \beta_1 = 0$ in favor of $H_1 : \beta_1 \neq 0$ or equivalently $H_0 : \mu_{VIHD} = \mu_{HEC}$ in favor of $H_1 : \mu_{VIHD} \neq \mu_{HEC}$ for several possible treatment effects, considering type I error $\alpha = 0.05$ (two-tailed), equal VIHD and HEI group sizes, and several choices of error standard deviation. Sample size computations were performed with the Power And Precision 2.1 package.

Table 1

Error standard deviation (σ)	Treatment effect $ \mu_{VIHD} - \mu_{HEC} $		
	$ \mu_{VIHD} - \mu_{HEC} = 0.10$	$ \mu_{VIHD} - \mu_{HEC} = 0.13$	$ \mu_{VIHD} - \mu_{HEC} = 0.15$
0.40	Total N=676	Total N=400	Total N=302
0.45	Total N=854	Total N=506	Total N=382

For example, if the interest is to detect an absolute difference of 0.15 (15%) between the two interventions, then if the distribution of the outcome in each arm has a standard deviation equal to 0.45, one needs 382 subjects (191 in each arm) to have a 90% chance to detect this effect if it indeed exists (i.e. to have 90% power). Alternatively, with the same treatment effect (0.15) but standard deviation equal to 0.45 we need 302 subjects (151 in each randomized group). We plan to utilize 10 sites with each site enrolling approximately the same number of participants. Hence each site would have approximately N/10 participants.

A differing VIHD treatment effect across sites may contribute additional variation and simulations with primary analysis performed for each simulation were used to confirm achievable power for sample size from Table 1. Each simulation was performed as follows. Ten (number of sites) realizations of $b_j \sim N(0, \sigma_{site}^2)$ were obtained. Ten realizations of treatment effect $t_j \sim N(0, \sigma_T^2)$ were obtained. Although not required, for simplicity b_j and t_j are assumed to be independent. Then, for each site, $N/10$ independent realizations of $\varepsilon_{ij} \sim N(0, \sigma^2)$ were obtained and response for this site was obtained as follows: $Y_{ij} = \beta_0 + \beta_1 trt_{ij} + b_j + t_j trt_{ij} + \varepsilon_{ij}$, with $trt_{ij} = 0$ for $i = 1, \dots, N/20$ and $trt_{ij} = 1$ for $i = N/20 + 1, \dots, N/10$. For each simulation, the generated data set was analyzed with the primary analysis linear mixed model and the p-value for testing $H_0 : \beta_1 = 0$ was recorded. The simulation based power is the percent of simulations with p-values < 0.05 .

As an example, consider situation with $\sigma = 0.45$, $\mu_{HEC} = 0.425$ and $\mu_{VIHD} = 0.575$ (treatment effect equal to 0.15), for which Table 1 indicates 380 participants (38 per site) for 90% power. Re-expressing, we have $\beta_0 = 0.425$ and $\beta_1 = 0.575 - 0.425 = 0.15$. Consider $\sigma_{site} = 0.1$ and $\sigma_T = 0.04$. This translates into 0.047 correlation between TAU participants

$[0.1^2 / (0.1^2 + 0.45^2)]$ and 0.054 correlation $[(0.1^2 + 0.04^2) / (0.1^2 + 0.04^2 + 0.45^2)]$ between VIHD participants, within a site. Alternatively, $\sigma_T = 0.04$ indicates that the assumed treatment effect can vary approximately between 0.07 and 0.23 ($0.15 \pm 1.96 * 0.04$).

The power based on 5000 simulations was 88.6%. Hence, based on this simulation, the sample sizes presented in Table 1 can be viewed as reasonable estimates of number of participants needed in this trial with primary analysis model as specified in this section. As an additional precaution, we increase sample size by 10% to attempt to take into consideration potential treatment effect variability. With 420 ($1.1 * 380$) participants, 5000 simulations indicate power 91.5% in the above situation. Table 2 presents such inflated sample sizes for the scenarios considered in Table 1.

Table 2

Error standard deviation (σ)	Treatment effect $ \mu_{VIHD} - \mu_{HEC} $		
	$ \mu_{VIHD} - \mu_{HEC} = 0.10$	$ \mu_{VIHD} - \mu_{HEC} = 0.13$	$ \mu_{VIHD} - \mu_{HEC} = 0.15$
0.40	Total N=740	Total N=440	Total N=330
0.45	Total N=940	Total N=560	Total N=420

Based on our assumed treatment effect of 0.15 and expecting a standard deviation of 0.40, we proposed the trial to enroll 330 participants. Clearly, the proposed sample size depends on accurate estimation of variability σ . We propose to reassess this variability midway through the study, i.e., after approximately 165 participants have enrolled and completed the acute phase of the trial. We will potentially readjust needed sample size, as discussed in more detail below.

13.4 Interim Analyses

A DSMB will monitor the progress of the trial. In coordination with the centralized Data and Statistics Center (DSC), an interim check of the assumed error standard deviation σ for the primary outcome measure will be conducted to assess the adequacy of the projected study sample size. The error standard deviation will be computed and if substantially different from the assumed value of 0.40, there may be a need to potentially adjust the sample size. This analysis will be conducted when approximately 165 participants have been enrolled and have completed the active treatment phase of the study.

Although at this time we do not plan a formal statistical interim analysis for efficacy or futility, such an interim analysis could be performed if requested by the DSMB or NIDA. In addition safety interim looks will be performed (without formal statistical testing) at the regular DSMB meetings or unscheduled times per the DSMB's request. If a formal interim efficacy analysis is requested, we propose to use two-sided, symmetric O'Brien-Fleming (1979) type boundaries generated using the flexible Lan-DeMets (1983) approach to group sequential testing. If requested, the monitoring guidance for early stopping for futility will be based upon an approach of conditional power (Jennison and Turnbull, 2000).

13.5 Secondary Endpoints and Analyses

Secondary Aim 1. To compare time to relapse (defined as second positive urine test [for stimulants] and use of drugs established by TLFB) between the VIHD and HEI groups.

Hypothesis 2. VIHD will be associated with a significantly longer time to relapse than HEI over the course of the 12-week acute phase.

Time of relapse or loss to follow-up will be recorded for each participant. If participant does not relapse by 12 weeks, this participant will be considered as censored at 12 weeks. Data from the VIHD and HEI groups will be displayed with Kaplan-Meier curves (estimating probability of no relapse until time t , over time) and the VIHD and HEI groups will be compared with a Log-Rank test stratified by site. P-value less than 0.05 will be considered statistically significant.

Secondary Aim 2. To evaluate withdrawal symptoms between the VIHD and HEI groups.

Hypothesis 3. VIHD will be associated with significantly reduced withdrawal symptoms as measured by the Stimulant Selective Severity Assessment (SSSA) than HEI over the course of the 12-week acute phase.

Hypothesis 4. VIHD will be associated with significantly reduced craving as measured by the Stimulant Craving Questionnaire – Brief (STCQ-Brief) than HEI over the course of the 12-week acute phase.

The SSSA will be performed once per week. Hence, each participant will have 12 weekly measures recorded (assuming no missing data). We will use a linear mixed models approach to account for correlation of the measures within a participant over time. In mathematical terms, denote Y_{ijt} as the value of SSSA for the i^{th} subject, on t^{th} time, and in j^{th} site at time t ($t=0,1,2,\dots,12$), and consider the following linear mixed model:

$$Y_{ijt} = \beta_0 + b_j + a_{ij} + \beta_1 t_{ijt} + \beta_2 trt_{ijt} t_{ijt} + \varepsilon_{ijt}$$

with trt_{ijt} indicating treatment value (1=VIHD, 0=HEI) for the i^{th} subject in the j^{th} site; fixed effects β_0, β_1 ; random effects β_0, β_1 ; random effect $b_j \sim N(0, \sigma_{site}^2)$ reflecting site's overall SSSA level, random effect $a_{ij} \sim N(0, \sigma_{patient}^2)$ reflecting participant's underlying SSSA level; and independent of the random effects independent residual errors $\varepsilon_{ijt} \sim N(0, \sigma^2)$. The primary hypothesis is $H_0 : \beta_2 = 0$ and indicates no difference in SSSA trajectories over time between VIHD and HEI. We hope to reject $H_0 : \beta_2 = 0$ in favor of $H_1 : \beta_2 \neq 0$ to provide evidence for differences in SSSA trajectories between VIHD and HEI groups. P-value less than 0.05 will be considered statistically significant. If suggested by data, we will also consider other than linear trajectory over time, e.g. a quadratic one. We expect occasional missing SSSA readings. However, the analytical approach is likelihood based and it will be still valid as long as data are missing at random (MAR).

Similarly, STCQ-Brief will be measured weekly over the 12-week acute phase. The same analysis approach as for weekly measured SSSA analysis described above will be utilized, except the outcome will be the STCQ-Brief values.

Secondary Aim 3. To evaluate drug use and related outcomes for all substances (categorized as alcohol, cannabinoids, nicotine, opioids, or sedative/hypnotic/anxiolytics).

Hypothesis 5. VIHD will be associated with significantly higher percent days of abstinence from all substances and a significantly lower relapse for all substances than HEI over the course of the 12-week acute phase.

The abstinence analysis is equivalent to the primary analysis for percent days of abstinence. The relapse analysis is equivalent to the Secondary Aim 1 for relapse. The only difference is that abstinence is defined in this secondary aim as abstinence from all substances, and time of relapse is defined as time of the first occurrence of use of any substance. P-value less than 0.05 will be considered statistically significant.

Secondary Aim 4. To compare time to dropout from substance use treatment between the VIHD and HEI groups.

Hypothesis 6. VIHD will be associated with significantly longer time in treatment than HEI.

After 12 weeks from randomization (i.e., after the end of acute phase intervention) subjects will be assessed as to whether they fully participated in their assigned substance use treatment. In case a subject did not complete 12 weeks of treatment, time of drop-out from substance abuse treatment will be recorded for each participant. If participant completes all 12 weeks of substance abuse treatment, then time to dropout for this participant will be considered as censored at 12 weeks. Data from the VIHD and HEI groups will be displayed with Kaplan-Meier curves (estimating probability of no drop-out until time t , over time) and the VIHD and HEI groups will be compared with a Log-Rank test stratified by site. P-value less than 0.05 will be considered statistically significant.

Secondary Aim 5. To evaluate drug use and related outcomes during the entire course of the study (i.e., randomization to 9 months).

Hypothesis 7. VIHD will be associated with significantly higher percent days of abstinence, significantly longer time in treatment, a significantly lower rate of relapse, significantly lower quantity of use, and significantly reduced withdrawal symptoms ($p < 0.05$) than HEI over the 9-month study period.

The analysis will consider both phases of the study: 12 week acute phase and 6 month continuation phase. This results in 9 months of participant data.

The treatment retention (or equivalently time to drop-out) analysis will be the same as in Secondary Aim 4, except censorship, if any, will occur at 9 months.

The relapse analysis will be the same as in Secondary Aim 1, except censorship, if any, will occur at 9 months.

The withdrawal symptoms analyses will be the same as in Secondary Aim 2 but with SSSA and STCQ-Brief outcomes measured over 9 months of follow-up.

The quantity of use analysis will be the same as in the Secondary Aim 2 but with quantity of use as the outcome measured over 9 months.

13.6 Exploratory Aims and Analyses

Exploratory Aims. To determine if there are additional health benefits to using exercise augmentation in the treatment of substance use disorders. Specifically, VIHD will be associated with significantly greater improvement ($p < 0.05$) in sleep, cognitive function, mood, quality of life and anhedonia, and weight gain compared to HEI over the course of the 12-week acute phase, and over the 9-month study period.

13.7 Factors for Stratification

Randomization will be stratified by site and within site, by two stratifying factors: presence of depressive symptoms (QIDS-C₁₆ score of ≤ 10 or ≥ 11) and by severity of drug use (≤ 18 days or > 18 days of stimulant use in the 30 days prior to admission to residential treatment). If related to the outcome, the stratification factors will be included in the analyses.

13.8 Significance Testing

With various analyses (primary and secondary) proposed in this protocol, there is a multiplicity of analyses to be performed, which leads to an increased probability that at least one of the comparisons could be "significant" by chance. Adjustment for multiplicity of testing (e.g., a Bonferroni approach) for all the considered analyses would require very small p-values to declare statistical significance and is thus not feasible.

Hence, our approach is that for the single pre-specified primary hypothesis we consider p-value < 0.05 as statistically significant.

For the secondary analyses we will not consider significance level adjustment. However, we will be conservative in the interpretation of these analyses, taking into account the degree of significance, and consistency across analyses. In addition, to guard against spurious significance results, we limited and pre-specified the secondary analyses.

13.9 Missing Data and Dropouts

The primary analysis assumes missing abstinence status information for a particular day as a drug use day. Hence, no missing data will be present for the primary outcome.

The secondary longitudinal analyses are likelihood based and will still be valid under the missing at random (MAR) assumption, which states that missingness is not related to the value of the variable had it been observed. However, if there is a substantial amount of missing abstinence data, we will conduct an exploratory sensitivity analysis by considering various scenarios of abstinence for missing abstinence data.

13.10 Poolability of Data

We intend to perform the primary treatment effect analysis by pooling data from all sites. It is possible that treatment effect will differ across sites and this will be investigated. We will fit a model with site by treatment interaction and if significant (at 0.05 level), we will present treatment effects by site. Although the study is not powered for detection of different treatment effects across sites, this analysis will provide insight into possible varied treatment effects across sites or reassure that data can reasonably be pooled over sites with respect to the treatment effect.

13.11 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for each arm of the study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages. Since randomization is expected to produce balance at baseline between the two arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics should be more informal. In case differences between treatments arms are suspected, statistical testing will be performed. For comparisons of treatment groups with respect to continuous baseline variables we will use the two sample Wilcoxon test. Group comparisons with respect to discrete baseline variables will use the chi-square test or Fisher's Exact Test as appropriate.

13.12 Safety Analysis

Appropriate reporting procedures will be followed for the collection, reporting, and follow-up of adverse events (AEs) and serious adverse events (SAEs). Additional details of the reporting procedures are presented in Appendix I.

14.0 REPORTING AND MONITORING

14.1 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, appropriate ICH guidelines (including current Good Clinical Practice [GCP]), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

14.2 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be reviewed at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at the study closure.

14.3 Informed Consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. Each study site must have the study informed consent approved by their IRB(s). A copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the lead node (LN) 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 must be offered a copy of the signed consent form. Participants may contact site personnel with any questions after signing Informed Consent.

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 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 authorized to obtain informed consent must be listed on the Signature Sheet and Delegation of Responsibilities Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

In order to ensure that potential study participants understand the research study, a comprehension "quiz" (referred to as a comprehension tool) will be administered to potential participants prior to the informed consent being signed. If the potential participant misses an item on the quiz, the research staff will re-review that information to ensure understanding of study procedures and may have the person re-take the consent quiz prior to signing the

informed consent document. The content of the quiz may be modified per local IRB requirements.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty.

Study participation is voluntary and there are no benefits lost if an individual declines participation. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

Participants will be offered copies of the signed informed consent form, and the originals will be stored in a secure location at each study site. Contract and local monitors will inspect the informed consent forms periodically to ensure that correct signatures and dates were obtained on valid informed consent forms prior to any study interventions.

14.4 Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

14.5 Release of Information

Study participants will be asked to sign a release of information form that will give study staff permission to seek and acquire their treatment records. This release of information is voluntary. There will be no benefits lost if study participants refuse to release information. They may continue to participate in the study.

14.6 Investigator Assurances

Each community treatment program site (CTP) must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

14.7 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to-date signed financial disclosure form on file with the sponsor.

14.8 Clinical Monitoring

Investigators will host periodic visits by NIDA contract monitors who will ensure all study procedures are conducted and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at

mutually agreed upon times, regulatory documents, case report forms (CRFs), and corresponding source documents for each participant.

Qualified node personnel (Node QA monitors) will provide site management for each site during the trial. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will verify that study procedures are properly followed and that site staffs are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

14.9 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.

14.10 Records Retention and Requirements

All research records for all subjects will be stored by the investigator in a secure location to be accessed only by authorized research personnel. Study records will be stored in accordance with local IRB, State, and Federal Regulations but, in any case, will be kept for a minimum of 3 years following study completion.

14.11 Audits

The Sponsor has the responsibility to oversee the trial in order to ensure that all study procedures are conducted in accordance with all appropriate good research practice guidelines and regulations.

The Lead Team and other authorized research staff may inspect research records for quality assurance and safety purposes. All aspects of the study will be monitored as needed by NIDA's contracted agents, monitors or auditors; and inspections of research data may be conducted by representatives of government agencies such as the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) as well as the local Institutional Review Board.

14.12 Reporting to Sponsor

The principal investigator will submit any and all required reports accurately to the sponsor in a timely manner. Reports may include any significant changes possibly affecting the safe and accurate conduct of the trial or its outcomes. The principal investigator will also submit to the sponsor a detailed final report on the study at its conclusion.

14.13 Safety Monitoring

14.13.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether

there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

14.13.2 Protocol Violations Reporting and Management

A protocol departure is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, deviation versus violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The decision about whether a departure from the protocol will be designated as a protocol deviation or a protocol violation will be made by the site PI or designee, with consultation with the protocol's Lead Investigator or designee and the CCC as needed. The consequences will be specified and participating sites should be informed.

All protocol violations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Violations CRF. Additionally, each site is responsible for tracking and reporting to their IRB as required. Protocol deviations will be noted by participating sites and reported to their IRBs as required. The CCC and the Data and Statistics Center and the Lead Investigator must be contacted immediately if an unqualified/ ineligible participant is randomized into the study.

14.13.3 Subject Confidentiality/Privacy

By signing the protocol signature page the Site PI affirms that information furnished to the Site PI 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. The Lead Investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure and separate storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

All research information obtained on participants is confidential, and disclosure to any third parties without specific authorization is strictly prohibited. To maintain subject privacy, all study forms and reports will be identified by a coded study identification number only. No subject identifying information will be included in any presentations or publications resulting from the study.

Study records may be inspected by the sponsor and its authorized representatives, other government agencies such as the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), authorized Node Staff, or the local IRB for quality assurance purposes.

14.13.4 Adverse Events (AEs) and Serious Adverse Events (SAEs)

The Lead Investigator (LI) may appoint a Study Clinician (MD, PhD, or PI) for this study, who will review or provide consultation for each Serious Adverse Event (SAE) as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary. The medical monitor will determine which safety events require expedited reporting to NIDA, the DSMB and regulatory authorities. The study staff will be trained to monitor for and report Adverse Events and Serious Adverse Events.

Each of the CTPs has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each CTP will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

14.13.5 Definitions of Adverse Event and Serious Adverse Event

Standard definitions for Adverse Events and Serious Adverse Events, their identification, characterization regarding severity and relationship to the study intervention and processing are described in Appendix 1.

14.13.6 Non-Reportable Adverse Event and Serious Adverse Events

Adverse Events

For the purpose of this study, the following AEs will not require reporting in the data system and will not be captured:

- Grade 1 (mild) unrelated event.
- Grade 2 (moderate) unrelated event.

This would typically include physical events such as headache, cold, etc that was considered unrelated to study participation by the Site PI and/or Study Medical Monitor.

Serious Adverse Events

For the purpose of this study, the following SAEs will not be recorded in the data system but will be documented:

- Admission to a hospital/surgery center for preplanned/elective surgeries (captured in the Visit Summary/Progress Note).
- Admission to a hospital for scheduled labor and delivery (captured in the pregnancy CRF).
- Admission to a hospital or freestanding residential facility for drug detoxification (captured in the Visit Checklist/Progress Note).

Local documentation and reporting guidelines should also be followed based on local IRB requirements.

15.0 DATA MANAGEMENT AND PROCEDURES

15.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. 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.

15.2 Data Collection Forms

The data collection process consists of direct data entry at the study sites into the EDC system(s) provided for the protocol. In the event that the EDC system(s) are not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data entry into the eCRFs should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant. The DSC is not responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

15.3 Data Acquisition and Entry

Data entry into electronic CRFs (eCRFs) shall be performed by authorized individuals. Selected eCRFs may also require the investigator's written signature or electronic signature, as appropriate. Electronic CRFs will be monitored for completeness, accuracy, and attention to detail throughout the study.

15.3.1 Site Responsibilities

The data management responsibilities of each individual CTP will be specified by the DSC and outlined in the data management plan.

15.3.2 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF 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 cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

15.4 Data Editing

Completed data will be entered into the EDC system. If incomplete or inaccurate data are found, a data query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the EDC system in accordance with the data management plan.

15.5 Data Transfer

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

15.6 Data QA

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

16.0 HUMAN SUBJECTS PROTECTION

All requirements relating to obtaining institutional review board (IRB) review and approval and informed consent will be met. Written informed consent will be obtained from each study participant utilizing the local IRB-approved informed consent form. Appropriate research personnel will explain all aspects of the study to each participant, answering all questions and ensuring that all basic elements of the informed consent process are covered.

All study personnel will be required to complete Human Subject Protection, Good Clinical Practice and HIPAA training (as required) and will be instructed to act under those guidelines at all times when working with participants, participants data or protected participant health information.

17.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____
CCTN Designee		

INVESTIGATOR (S)

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

Typed Name	Signature	Date
_____	_____	_____
Principal Investigator		
_____	_____	_____
Sub-Investigator		
_____	_____	_____
Sub-Investigator		

18.0 REFERENCES

- Anderson GH, Woodend D. Consumption of sugars and the regulation of short-term satiety and food intake. *American Journal of Clinical Nutrition*. 2003; 78:S843-S849.
- Babyak M, Blumenthal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med*. 2000; 62:633–8.
- Ball SA, Martino S, Nich C, et al. Site matters: Multisite randomized trial of motivational enhancement therapy in community drug abuse clinics. *J Consult Clin Psychol*. 2007; 75:556-567
- Blair SN, Connelly JC. How much physical activity should we do? The case for moderate amounts and intensities of physical exercise. *Research Quarterly for Exercise and Sport*. 1996; 67:193-205.
- Blair JR, Spreen O. Predicting premorbid IQ: a revision of the National Adult Reading Test. *Clin Neuropsychol*. 1989; 3:129-136.
- Blomquist KB, Danner F. Effects of physical conditioning on information-processing efficiency. *Perceptual Motor Skills*. 1987; 65:175-86.
- Blumenthal JA, Babyak MA, Doraiswamy PM. et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007; 69:587–96.
- Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older participants with major depression. *Arch Intern Med*. 1999; 159:2349–56.
- Bock BC, Marcus BH, King TK, Borrelli B, Roberts MR. Exercise effects on withdrawal and mood among women attempting smoking cessation. *Addictive Behaviors*. 1999; 24(3), 399-410.
- Bolla KI, Rothman R, Cadet JL. Dose-related neurobehavioral effects of chronic cocaine use. *J Neuropsychiatry Clin Neurosci*. 1999; Summer;11(3):361-9.
- Breus MJ, O'Connor PJ. Exercise induced anxiolysis: a test of the "time out" hypothesis in high-anxious females. *Medicine and Science in Sports and Exercise*. 1998; 30: 1107-1112.
- Broocks A, Bandelow B, Pekrun G, George A, Meyer T, Bartmann U. et al Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder. *American Journal of Psychiatry*. 1998; 155(5), 603-609.
- Brown RA, Evans DM, Miller IW, Burgess ES, Mueller TI. Cognitive behavioral treatment for depression in alcoholism. *J Consult Clin Psychol*. 1997; Oct;65(5):715-26.
- Brown RA, Abrantes AM, Read JP, Marcus BH, Jakicic J, Strong DR, Oakley JR, Ramsey SE, Kahler CW, Stuart GG, Dubreuil ME, Gordon AA. Aerobic Exercise for Alcohol Recovery: Rationale, Program Description, and Preliminary Findings. *Behav Modif*. 2009; Mar;33(2):220-49.
- Cacciola JS, Alterman AI, McLellan AT, et al. Initial evidence for the reliability and validity of a "Lite" version of the Addiction Severity Index. *Drug Alcohol Depend*. 2007; Mar 16;87(2-3):297-302.
- Canadian Society for Exercise Physiology (CSEP). (2002). Physical Activity Readiness Questionnaire (PAR-Q). <http://www.csep.ca/forms.asp>.
- Carlson NR. (1991) *Physiology of behavior*. Boston: Allyn & Bacon.

- Carroll KM, Ball SA, Nich C. Motivational interviewing to improve treatment engagement and outcome in individuals seeking treatment for substance abuse: A multisite effectiveness study. *Drug and Alcohol Dependence*. 2006; 80:301-312.
- Carroll KM, Sinha R, Nich C. Contingency management to enhance naltrexone treatment of opioid dependence: A randomized clinical trial of reinforcement magnitude. *Exp and Clin Psychopharmacology*. 2002;10:54-63.
- Carta MG, Hardoy MC, Pilu A, Sorba M, Floris AL, Mannu FA, Baum A, Cappai A, Velluti C, Salvi M. Improving physical quality of life with group physical activity in the adjunctive treatment of major depressive disorder. *Clinical Practice and Epidemiology in Mental Health*. 2008; 4: 1
- Chaouloff F. Effects of acute physical exercise on central serotonergic systems. *Medicine and Science in Sports and Exercise*. 1997; 29:58-62.
- Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA*. 2007; May 16;297(19):2081-91.
- Clark PJ, Brzezinska WJ, Thomas MW, et al. Intact neurogenesis is required for benefits of exercise on spatial memory but not motor performance or contextual fear conditioning in C57BL/6J mice. *Neuroscience*. 2008; Sep 9;155(4):1048-58.
- Collingwood TR, Reynolds R, Kohl HW, Smith W, Sloan S. Physical fitness effects on substance abuse risk factors and use patterns. *Journal of Drug Education*. 1991; 21(1), 73-84.
- Collingwood TR, Sunderlin J, Kohl HW. The use of a staff training model for implementing fitness programming to prevent substance abuse with at-risk youth. *American Journal of Health Promotion*. 1994; 9, 20-23, 33.
- Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci*. 2002; 25:295-301.
- Crews DJ, & Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. *Med Sci Sports Exerc*. 1987; 19(5 Suppl), S114-120.
- Cronan TL, & Howley ET. The effect of training on epinephrine and norepinephrine excretion. *Medicine in Science and Sports*. 1974; 5, 122-125.
- Daniel JZ, Cropley M, Fife-Schaw C. Acute exercise effects on smoking withdrawal symptoms and desire to smoke are not related to expectation. *Psychopharmacology*. 2007; 195: 125-129.
- Daniel JZ, Cropley M, Fife-Schaw C. The effect of exercise in reducing desire to smoke and cigarette withdrawal symptoms is not caused by distraction. *Addiction*. 2006;101:1187-1192.
- Daniel J, Cropley M, Ussher M, West R. Acute effect of a five minute bout of moderate versus light intensity exercise on tobacco withdrawal symptoms in sedentary smokers *Psychopharmacology*. 2004; 174: 320-326.
- DiLorenzo TM, Bargman EP, Stucky RR, Brassington GS, Frensch PA, LaFontaine T. Long-term effects of aerobic exercise on psychological outcomes. *Preventive Medicine: An International Journal Devoted to Practice and Theory*. 1999; 28, pp. 75–85.
- Dunn AL, Trivedi MH, Kampert JB, et al. Exercise treatment for depression: efficacy and dose response. *Am J Prev Med*. 2005; 28:1–8.
- Dunn AL, Trivedi MH, Kampert JB, et al. The DOSE study: a clinical trial to examine efficacy and dose response of exercise as treatment for depression. *Control Clin Trials*. 2002; 23:584–603.

- Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. *Medicine and Science in Sports and Exercise*. 2001; 33 (Suppl) S587-S597.
- Dutra L, Stathopoulou G, Basden SL, et al. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry*. 2008; Feb;165(2):179-87.
- Elavsky S, McAuley E. Lack of perceived sleep improvement after 4-month structured exercise programs. *Menopause*. 2007; 14:535-540.
- Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993; 29(2):321-326.
- Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *J Consult Clin Psychol*. 2000; Feb;68(1):134-44.
- Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *J Clin Psychiatry*. 2006; 67:1754-1759.
- Fava M, Iosifescu DV, Pedrelli P, Baer L. Reliability and validity of the Massachusetts general hospital cognitive and physical functioning questionnaire. *Psychother Psychosom*. 2009; 78:91-97.
- Fletcher GF, Balady G, Froelicher VF et al. Exercise standards. A statement for healthcare professionals from the American Heart Association. Writing Group. *Circulation* 1995; 91:580-615.
- Frankel A, Murphy J. Physical fitness and personality in alcoholism. *Quarterly Journal of Studies on Alcohol*. 1974; 35, 1272-1278.
- Franken IHA, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: Further validation of the Snaith-Hamilton pleasure scale (SHAPS). *J Affective Disorders*. 2007; 99:83-89.
- Froelich JC. Opioid peptides. *Alcohol Health and Research World*. 1997; 21, 132-135.
- Galper DI, Trivedi MH, Barlow CE, Dunn AL, Kampert JB. Inverse association between physical inactivity and mental health in men and women. *Med Sci Sports Exerc*. 2006; 38: 173-178.
- Golden CJ. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Wood Dale, Ill: Stoelting Co.; 1978.
- Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. *Eur J Neurosci*. 2008; Dec;28(11):2278-87.
- Greenwood BN, Strong PV, Foley TE, Fleshner M. A behavioral analysis of the impact of voluntary physical activity on hippocampus-dependent contextual conditioning. *Hippocampus*. 2008; Dec 29. [Epub ahead of print].
- Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. American College of Sports Medicine; American Heart Association. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007b; Aug 28;116(9):1081-93. [Epub 2007 Aug 1].
- Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for

adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007a; Aug;39(8):1423-34.

Hattori S, Naoi M, Nishino H. Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. *Brain Res Bull.* 1994; 35(1):41-9.

Heatherton TF, Kozlowski LT, Frecker RC and Fagerstrom K. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *British Journal of Addiction.* 1999; 86:1119-1127.

Heinz A, Mann K, Weinberger DR, Goldman D. Serotonergic dysfunction, negative mood states, and response to alcohol. *Alcohol: Clinical and Experimental Research.* 2001; 25: 487-495.

Hill JS. Effects of a program of aerobic exercise on the smoking behavior of a group of adult volunteers. *Canadian Journal of Public Health.* 1985; 76:183-186.

Hill RD, Rigdon M, Johnson S. Behavioral smoking cessation treatment for older chronic smokers. *Behavior Therapy.* 1993; 24:321-329.

Hughes JR. Psychological effects of habitual aerobic exercise: A critical review. *Preventive Medicine.* 1984; 13: 66-78.

Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, Epperson LE. Reliability and validity of the Cocaine Selective Severity Assessment. *Addict Behav.* 1998; Jul-Aug;23(4):449-61.

Kawatchi I, Troisi RJ, Rotnitzky AG, Coakley EH, Colditz MD. Can physical activity minimize weight gain in women after smoking cessation? *American Journal of Public Health* 86. 1996; pp. 999–1004.

King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial *JAMA* 1997; 277: pp 32–37.

Kozlowski LT, Porter CQ, Orleans CT, Pope MA, Heatherton T. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HIS. *Drug and Alcohol Dependence.* 1994; 34: 211–16.

LIFE Study Investigators, Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, Guralnik JM, Hadley EC, King AC, Kritchevsky SB, Maraldi C, Miller ME, Newman AB, Rejeski WJ, Romashkan S, Studenski S. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. *J Gerontol A Biol Sci Med Sci.* 2006; Nov;61(11):1157-65.

Marcus BH, Albrecht AE, King TK, Parisi AF, Pinto BM, Roberts M. Exercise effects on withdrawal and mood among women attempting smoking cessation. *Archives of Internal Medicine.* 1999; 159, pp. 1229–1234.

Marcus BH, Albrecht AE, Niaura RS, Abrams DB, Thompson PD. Usefulness of physical exercise for maintaining smoking cessation in women. *American Journal of Cardiology.* 1991; 68:406-407.

Marcus BH, Albrecht AE, Niaura RS, Taylor ER, Simkin LF, Feder SI. Exercise enhances the maintenance of smoking cessation in women. *Addictive Behaviors.* 1995; 20, pp. 87–95.

Marcus BH, Lewis BA, Hogan J, King TK, Albrecht AE, Bock B, Parisi AF, Niaura R, Abrams DB. The efficacy of moderate-intensity exercise as an aid for smoking cessation in women: a randomized controlled trial. *Nicotine and Tobacco Research.* 2005; 7: 871-880.

Marlatt GA, Gordon JR. Relapse prevention: Maintenance strategies in the treatment of addictive behaviors. New York: Guilford Press. 1985.

Martin JE, Calfas KJ, Patten CA, Polarek M, Hofstetter CR, Noto J, Beach D. Prospective evaluation of three smoking interventions in 205 recovering alcoholics: One-year results of project SCRAP-Tobacco. *Journal of Consulting and Clinical Psychology*. 1997; 65, pp. 190–194.

Martin JE, Dubbert PM. Exercise applications and promotion in behavioral medicine: Current status and future directions. *Journal of Consulting and Clinical Psychology*. 1982; 50 pp. 1004–1017.

Mather AS, Rodriguez C, Guthrie MF et al. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomized controlled trial. *Br J Psychiatry* 2002; 180:411–5.

McAuley E, Courneya KS, Lettunich J. Effects of acute and long-term exercise on self-efficacy responses in sedentary, middle-aged males and females. *The Gerontologist*. 1991; 31, 534-542.

McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. *J Nerv Ment Dis*. 1980 Jan;168(1):26-33.

Meeusen R. Exercise and the brain: insight in new therapeutic modalities. *Ann Transplant*. 2005; 10:49-51.

Meeusen R, Smolders I, Sarre S, de Meirleir K, Keizer H, Serneels M, Ebinger G, Michotte Y. Endurance training effects on neurotransmitter release in rat striatum: an in vivo microdialysis study. *Acta Physiol Scand*. 1997; Apr;159(4):335-41.

Morss GM, Jordan AN, Skinner JS, Dunn AL, Church TS, Earnest CP, Kampert JB, Jurca R, Blair SN. Dose Response to Exercise in Women aged 45-75 yr (DREW): design and rationale. *Med Sci Sports Exerc*. 2004; Feb;36(2):336-44.

Murphy TJ, Pagano RR, Marlatt GA. Lifestyle modification with heavy alcohol drinkers: effects of aerobic exercise and meditation. *Addict Behav*. 1986; 11, (2), 175-86.

Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C. American College of Sports Medicine; American Heart Association. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007b; Aug 28;116(9):1094-105. [Epub 2007 Aug 1].

Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007a; Aug;39(8):1435-45.

NIH Consensus Development Panel on Physical Activity and Cardiovascular Health. Physical activity and cardiovascular health. *JAMA*. 1996; 276: 241-46.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979; 35(3):549-556. PMID:497341.

O'Malley SS, Jaffe A J, Chang G, Rode S, Schottenfeld R, Meyer RE, et al. (1996). Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Arch Gen Psychiatry*. 1996; 53, 217-224.

Paliwal P, Hyman SM, Sinha R. Craving predicts time to cocaine relapse: Further validation of the now and brief versions of the cocaine craving questionnaire. *Drug and Alcohol Dependence*. 2008; 93:252-259.

Palmer J, Palmer LK, Michiels K, Thigpen B. Effects of type of exercise on depression in recovering substance abusers. *Perceptual and Motor Skills*. 1995; 80, pp. 523–530.

Palmer J, Vacc N, Epstein J. Adult inpatient alcoholics: Physical exercise as a treatment intervention. *Journal of Studies on Alcohol*. 1988; 49, pp. 418–421.

Pate RR, Pratt M, Blair SN et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine *JAMA*. 1995; 273: 402-407.

Petry NM, Alessi SM, Marx J, Austin M, Tardiff M. Vouchers versus prizes: Contingency management treatment of substance abusers in community settings. *Journal of Consulting and Clinical Psychology*. 2005; 73:1005-1014.

Petry NM, Tedford J, Austin M, Nich C, Carroll KM, Rounsaville BJ. Prize reinforcement contingency management for treatment of cocaine abusers: How low can we go and with whom? *Addiction*. 2004; 99:349-360.

Pilkington K, Kirkwood G, Rampes H, Richardson J. Yoga for depression: The research evidence. *J Affect Disord*. 2005; Dec;89(1-3):13-24.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007; 164:1035-1043.

Rapaport MH, Clary C, Fayyad R, Endicott J. Quality-of-life impairment in depressive and anxiety disorders. *Am J Psychiatry*. 2005; Jun;162(6):1171-8.

Radak Z, Kaneko T, Tahara S et al. Regular exercise improves cognitive function and decreases oxidative damage in rat brain. *Neurochem Int*. 2001; 38: 17-23.

Rawson RA, McCann MJ, Flammio F et al. A comparison of contingency management and cognitive behavioral approaches for stimulant-dependent individuals. *Addiction*. 2006; 101:267-274.

Read JP, Brown RA. The role of physical exercise in alcoholism treatment and recovery. *Professional Psychology: Research and Practice*. 2003; 34: 49-56.

Rejeski WJ, Fielding RA, Blair SN, Guralnik JM Gill TM, Hadley EC, King AC, Kritchevsky SB, Miller ME, Newman AB, Pahor M. The lifestyle interventions and independence for elders (LIFE) pilot study: design and methods. *Contemp Clin Trials*. 2005; Apr;26(2):141-54.

Rejeski WJ, Gregg E, Thompson A, Berry M. The effects of varying doses of acute aerobic exercise on psychophysiological stress responses in highly trained cyclists. *Journal of Sport and Exercise Psychology*. 1991; 13, pp. 188–199.

Rush AJ, Bernstein IH, Trivedi MH, Carmody TJ, Wisniewski S, Mundt JC, Shores-Wilson K, Biggs MM, Woo A, Nierenberg AA, Fava M. An evaluation of the quick inventory of depressive symptomatology and the Hamilton rating scale for depression: A sequenced treatment alternatives to relieve depression trial report. *Biological Psychiatry*. 2006; 59(6), 493-501.

Rush AJ, Carmody TJ, Ibrahim HM, Trivedi MH, Biggs MM, Shores-Wilson K, Crismon ML, Toprac MG, Kashner TM. Comparison of self-report and clinician ratings on two inventories of depressive symptomatology. *Psychiatric Services*. 2008; 57(6), 829-837.

Rush AJ, Carmody TJ, & Reimitz PE. The Inventory of Depressive Symptomatology (IDS): Clinician (IDS-C) and Self-Report (SR) rating of depressive symptoms. *International Journal of Methods in Psychiatric Research*. 2000; 9(2), 45-59.

Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, Trivedi MH et al. Texas Medication Algorithm Project, phase 3 (TMAP-3): rationale and study design. *J Clin Psychiatry*. 2003; 64(4), 357-369.

Rush AJ, et al. One-year clinical outcomes of depressed public sector outpatients: A benchmark for subsequent studies. *Biological Psychiatry*. 2004; 56(1): p. 46-53.

Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G, STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004a; 25(1), 119-42.

Rush AJ, Trivedi MH, Fava M et al. (2006). A comparison of bupropion-SR, sertraline, and venlafaxine-XR following SSRI failure for depressed outpatients: a STAR*D report. *N Engl J Med*. 2006; 354(12),1231-42.

Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003; Sep 1;54(5):573-83. Erratum in: *Biol Psychiatry*. 2003; Sep 1;54(5):585.

Russell PO, Epstein LH, Johnston JJ, Block DR, and Blair E. The effects of physical activity as maintenance for smoking cessation. *Addictive Behaviors*. 1988; 13: 215-218.

Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum*. 2003; 49: 156-163.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K. et al. Reliability and Validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. *European Psychiatry*. 1997; 12:232-241.

Singh NA, Clements KM, Fiatarone MA. Sleep, sleep deprivation, and daytime activities; a randomized controlled trial of the effect of exercise on sleep. *Sleep*. 1997; 20:95-101.

Sinyor D, Brown T, Rostant L, Seraganian P. The role of a physical fitness program in the treatment of alcoholism. *Journal of Studies on Alcohol*. 1982; 43, pp. 380–386.

Smith SC, Jr, Blair SN, Criqui MH et al. AHA consensus panel statement. Preventing heart attack and death in patients with coronary disease. The Secondary Prevention Panel. *J Am Coll Cardiol*. 1995; 26: 292-94.

Smith E, Meyers RJ. The community reinforcement approach. In: R.K. Hester and W.R. Miller, Editors, *Handbook of alcoholism treatment approaches: Effective alternatives*. 1995; pp. 251–266.

Smolander J, Blair SN, Kohl HW 3rd. Work ability, physical activity, and cardiorespiratory fitness: 2-year results from Project Active. *J Occup Environ Med*. 2000; Sep;42(9):906-10.

Snaith RP, Hamilton M, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone: The Snaith-Hamilton Pleasure Scale. *British Journal of Psychiatry*. 1995; 167, 99-103.

Sobell LC, Sobell MB. Timeline follow-back: A technique for assessing self-reported alcohol consumption. In R.Z. Litten & J.P. Allen (Eds.), *Measuring alcohol consumption*. 1992; pp. 41-72.

Sobell LC, Sobell MB. Timeline follow-back: A technique for assessing self-reported ethanol consumption. In J. Allen & R. Litten (Eds.), *Techniques to Assess Alcohol Consumption*. (In press).

Stewart AL, Hays RD, Wells KB, et al. Long term functioning and well-being outcomes associated with physical activity and exercise in patients with chronic conditions in the medical Outcomes Study. *J Clin Epidemiol*. 1994; 47: 719-30.

Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643-62

Sugaya K, Nishijima S, Owan T, Oda M, Miyazato M, Ogawa Y. Effects of walking exercise on nocturia in the elderly. *Biomedical Research*. 2007; 28: 101-105.

Sussner BD, Smelson DA, Rogrigues S, et al. The validity and reliability of a brief measure of cocaine craving. *Drug and Alcohol Dependence*. 2006; 83:233-237.

Taylor AH, Ussher MH, Faulkner G. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect and smoking behavior: a systematic review. *Addiction*. 2007; 102: 534-543.

Taylor CB, Houston-Miller N, Haskell WL, DeBusk RF. Smoking cessation after acute myocardial infarction: The effects of exercise training. *Addictive Behaviors*. 1988; 13:331-335.

Taylor CB, Sallis JF, Needle R. The relation of physical activity and exercise to mental health. *Public Health Reports*. 1985; 100, pp. 195–201.

Thoren P, Floras JS, Hoffmann P, Seals DR. Endorphins and exercise: Physiological mechanisms and clinical implications. *Medicine and Science in Sports and Exercise*. 1990; 22, 417-428.

Tiffany ST, Carter BL. Is craving the source of compulsive drug use? *Journal of Psychopharmacology*. 1998; 12:23-30.

Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, Ritz L, Nierenberg AA, Lebowitz BD, Biggs MM, Luther JF, Shores-Wilson K, Rush AJ. Medication Augmentation after the Failure of SSRIs for Depression. *New England Journal of Medicine*. 2006c; 354:1243-52.

Trivedi MH, Greer TL, Grannemann B, Church TS, Galper DI, Sundarajan P, Wisniewski SR, Chambliss HO, Jordan AN, Finely C, Carmody TJ. TREAD: Treatment with exercise augmentation for depression: study rationale and design. *Clinical Trials*. 2006b; 3: 291-305.

Trivedi MH, Greer TL, Grannemann BD et al. Exercise as an augmentation strategy for treatment of major depression. *J Psychiatr Pract*. 2006a; 12:205–13.

Trivedi MH, et al. Clinical results for patients with major depressive disorder in the Texas medication algorithm project. *Archives of General Psychiatry*. 2004a; 61(7): p. 669-680.

Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, Crismon ML, Shores-Wilson K, Toprac MG, Dennehy EB, Witte B, Kashner TM. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders, a psychometric evaluation. *Psychological Medicine*. 2004b; 34:73-82.

Trivedi MH, Rush AJ, Wisniewski SR et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006d; 163(1):28-40.

US Department of Health and Human Services (USDHHS). Physical activity and health: a report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease

Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. 1996.

Ussher M, Nunziata P, Cropley M, West R. Effects of a short bout of exercise on tobacco withdrawal symptoms and desire to smoke. *Psychopharmacology*. 2001; Vol. 158, p66-7.

Ussher M, Sampuran AK, Doshi R, West R, Drummond DC. Acute effect of a brief bout of exercise on alcohol urges. *Addiction*. 2004; 99(12), 1542-1547.

Ussher M, West R, McEwen A, Taylor A, Steptoe A. Efficacy of exercise counseling as an aid for smoking cessation: a randomized controlled trial. *Addiction*. 2003; Vol. 98, p523-532.

Vaynman S, Gomez-Pinilla F. Revenge of the "sit": how lifestyle impacts neuronal and cognitive health through molecular systems that interface energy metabolism with neuronal plasticity. *J Neurosci Research*. 2006; 84: 699-715.

Veale D, Le Fevre K, Pantelis C et al. Aerobic exercise in the adjunctive treatment of depression: a randomized controlled trial. *J R Soc Med*. 1992; 85:541-4.

Ware JE Jr. Conceptualization and measurement of health-related quality of life: comments on an evolving field. *Arch Phys Med Rehabil*. 2003; 84(4 Suppl 2): S43-51.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992; Jun;30(6):473-83.

Ware JE, Snow KK, Kosinski M, Gandek B. SF-36[®] Health Survey Manual and Interpretation Guide. Boston, MA: New England Medical Center. The Health Institute. 1993.

Wechsler D. Wechsler test of adult reading. San Antonio, TX. *Psychological Corporation*. 2001.

Weicker H, Struder HK. Influence of exercise on serotonergic neuromodulation in the brain. *Amino Acids*. 2001; 20:35-47.

Weinstock J, Barry D, Petry NM. Exercise-related activities are associated with positive outcome in contingency management treatment for substance use disorders. *Addictive Behaviors*. 2008; (in press).

Wetzel H, Szegedi A, Scheurich A, et al. Combination treatment with nefazodone and cognitive-behavioral therapy for relapse prevention in alcohol-dependent men: A randomized controlled study. *J Clin Psychiatry*. 2004; 65:1406-1413.

Weuve J, Hee Kang J, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA*. 2004; 292: 1454-1461.

Williams PA, Cash TF. *A controlled study of the effects of circuit weight training on body image*. Paper presented at the Annual meeting of the Association for the Advancement of Behavior Therapy, Toronto, Ontario. 1999.

Wilson WM, Marsden CA. Extracellular dopamine in the nucleus accumbens of the rat during treadmill running. *Acta Physiol Scand*. 1995; Dec;155(4):465-6.

Wojtowicz JM, Askew ML, Winocur G. The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. *Eur J Neurosci*. 2008; Mar;27(6):1494-502.

Wyrwich K, Harnam N, Revicki DA, Locklear JC, Svedsäter H, Endicott J. Assessing health-related quality of life in generalized anxiety disorder using the Quality Of Life Enjoyment and Satisfaction Questionnaire. *Int Clin Psychopharmacol*. 2009; Nov;24(6):289-95.

APPENDIX 1

Adverse Event Reporting Definitions and Procedures

1.0 Definitions of Adverse Events and Serious Adverse Events

1.1 Adverse Event (AE)

An adverse event (AE) is defined as any reaction, side effect, or untoward event including any new illness, symptom, sign or worsening of a pre-existing condition or abnormality that occurs during the course of an individual's participation in a clinical trial, *whether or not* the event is considered related to the clinical trial intervention.

Stable chronic conditions, such as arthritis, which are present prior to an individual's enrollment in a clinical trial and that do not worsen during the course of their participation are not considered AEs. In order to avoid the reporting of pre-existing conditions as new AEs, and to assist with the assessment of a condition that may have worsened in intensity or severity, a thorough medical history should be performed during the eligibility assessment phase to record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs.

An AE case report form (CRF) is used to capture reported AEs (as defined by the protocol) and may also be used to record follow-up information for unresolved or ongoing events that were reported previously.

A site study investigator is responsible for reviewing and characterizing each AE that is reported, and is expected to follow appropriate reporting procedures.

Adverse events and their resolution outcome should be elicited from study participants at each study related contact. The site must actively seek information about the AE until it is resolved or medically stable or until the participant is lost to follow-up and terminated from the study.

1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is an adverse event that is deemed serious by a study investigator because it meets one or more of the following criteria (although the event may meet more than one of the criteria below, investigator's should choose only the most serious when reporting the event):

An adverse event is serious if it results in:

- Death: A death that occurs either during the course of the clinical trial or that comes to the attention of the investigator during the protocol-defined follow-up period and after the completion of therapy, whether or not it is considered treatment-related must be reported.
- Life threatening: Any adverse event that when it occurs places the participant at immediate risk of death (i.e., it does not include a reaction that had it occurred in a more serious form, might have caused death).
- Admission to the hospital or is responsible for the prolongation of an existing hospitalization.
- A persistent or significant disability or incapacity.
- A congenital anomaly or birth defect.
- Requiring a medical intervention to prevent one of the above outcomes.

A SAE case report form is used to capture reported SAEs and may also be used to record follow-up information for unresolved or ongoing events that were reported previously.

A site study investigator at the site is responsible for reviewing and characterizing each SAE that is reported, and is expected to follow appropriate reporting procedures, including the reporting of the event to their IRB as per local IRB guidelines.

Serious adverse events will be followed until resolved or considered stable, with reporting to the NIDA appointed Safety Monitor through the follow-up period. The site must actively seek information about the SAE as appropriate until the SAE is resolved or medically stable or until the participant is lost to follow-up and terminated from the study.

In the event that a FDA MedWatch form is generated and distributed by the NIDA appointed Safety Monitor as a result of a related and unexpected event, the site staff will be responsible for reporting this to their IRB as per local IRB guidelines and for maintaining this information in their regulatory binders.

1.3 Pregnancy

All pregnancies that are reported during the course of the clinical trial will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Pregnancies will be followed through resolution, regardless of the outcome.

1.4 Laboratory Results

In clinical trials where laboratory results are collected in the database for the purpose of data analysis or for monitoring participant safety, laboratory results will be captured on specific laboratory result CRFs. A site study investigator is responsible for reviewing abnormal lab results in order to determine if they are clinically significant or not clinically significant. Abnormal lab results that are determined to be clinically significant should be reported as AEs.

2.0 Eliciting and Monitoring Adverse Events

The assessment of Adverse Events will begin once a participant has signed consent and will continue through last study visit or the participant's study termination date, whichever comes first. Follow up of an event will continue for up to 30 days past the Adverse Event assessment date. Qualified research staff is responsible for consistently and thoroughly eliciting medical and/or psychiatric AEs/SAEs from participants during every study assessment visit in order to complete the AE/SAE CRFs in a timely manner. This may require consent in the form of a release of information (ROI) from the participant in order to request medical records, hospital discharge summaries, etc.

Qualified research staff is responsible for reviewing all clinician progress notes and checklists following each participant contact in order to ensure that all AEs/SAEs have been appropriately reported. Reported AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and related AEs/SAEs will be followed until resolution or stabilization, even beyond the end of the study. Each participating site's study principal investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Protocol monitors from the Clinical Coordinating Center (CCC) and local node staff will regularly review each study site's documentation and study data to ensure that any unreported or unidentified SAEs discovered during their visits are promptly reported by the site to the Safety Monitor, NIDA (sponsor), the Node or Protocol PI or designee, the lead investigator for the study

and the IRB per local IRB requirements to ensure that the reported SAEs are being followed appropriately by the research staff and also to advise site staff to report any previously unreported safety issues. The CCC monitor or node staff will also make reference to these unreported events on the monitoring report and cite protocol violations as they occur. Staff education, re-training or appropriate corrective action plans will be implemented at the participating site when unreported or unidentified reportable AEs or SAEs are discovered, to ensure future identification and timely reporting by the site. The NIDA CTN Data Safety Monitoring Board (DSMB) will also review data related to safety monitoring for this trial periodically at regularly scheduled meetings.

3.0 Assessment of Severity and Relatedness

A study investigator is responsible for reviewing all reported AEs on a weekly basis in order to characterize their seriousness, severity, and relatedness to the study intervention.

3.1 Severity

The seriousness of an event is determined by whether or not it meets one or more of the criteria for a serious adverse event. The severity of an event refers to the intensity of the event.

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

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

3.2 Relatedness

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

Relationship to intervention is defined as:

- **Definitely related:** An adverse event that follows a temporal sequence from administration of the test intervention and/or procedure and follows a known response pattern to the test intervention and/or procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the test intervention and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.
- **Probably related:** An adverse event that follows a reasonable temporal sequence from administration of the test intervention and/or procedure and follows a known response pattern to the test intervention and/or procedure 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 intervention and/or procedure and follows a known response pattern to the test intervention and/or procedure, but could have been produced by the participant's clinical state or by other therapies.
- **Unrelated:** An adverse event that does not follow a reasonable temporal sequence after administration of the test intervention and/or procedure and is most likely explained by the participant's clinical disease state or by other therapies.

4.0 Reporting Procedures of AE/SAEs

Standard reporting, or the process of reporting an event within 7 days of the site becoming aware of the event, is required for all reportable AEs, whether or not they are considered related to the clinical trial participation.

Expedited reporting, or the process of reporting an event within 24 hours of the occurrence of the event and/or the site's knowledge of the event, is required for all SAEs, including deaths. The SAE case report form and a progress note summary as well as any other relevant documentation related to the event should also be submitted with the initial report. If complete information about the event is not available at the time of the initial report, the event should still be reported with as much information as possible within the 24 hour window. The site staff is then responsible for gathering as much additional information as possible, and submitting this information within 14 days to the electronic database. Any documentation related to the event that cannot be entered into the electronic data base should be sent directly to the NIDA-appointed Safety Monitor via fax. If the SAE is not resolved or medically stable at this time or if new information becomes available after the SAE form is submitted, follow-up SAE information must be submitted as soon as possible, but at most within 14 days after the site learns of the information.

Additional information may need to be gathered in order for the site research staff and investigator to evaluate the SAE and to complete the AE and SAE case report forms. This information is necessary to provide a complete and clear picture of the SAE and of the events preceding and following the event and may include obtaining hospital discharge reports, physician records, autopsy records or other types of records or information.

A NIDA-assigned Safety Monitor is responsible for reviewing all serious adverse events reported during a clinical trial. The safety monitor will in turn report these events to the study sponsor and the NIDA CTN DSMB. The DSMB will receive and review summary reports of all reportable adverse events associated with a clinical trial at least annually.

The DSMB or the NIDA-assigned Safety Monitor may also request additional and updated information. Details regarding adverse events, if requested by the NIDA-assigned Safety Monitor, DSMB, local ethics Committee/IRBs or regulatory authorities, should be summarized in writing by the site Lead Investigator and should include the treatment and resolution.

5.0 Discontinuation of Participant From a Clinical Trial Related to a Reported AE/SAE

The site study investigator must apply his/her clinical judgment in order to determine whether or not an AE/SAE is of sufficient severity to require that a participant be removed from the study intervention. The site study investigator may consult with the NIDA-assigned Safety Monitor as needed. If necessary, an Investigator may suspend any trial treatments and institute the necessary medical therapy or refer a participant to appropriate medical care in order to protect a participant from any immediate danger.

Subsequent review of the event(s) by the Medical Monitor, DSMB, ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor and DSMB retain the authority to suspend additional enrollment and treatments for an individual study site or the entire study as applicable.

A participant also has the right to 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 participant should be asked to continue (at least limited) scheduled evaluations, complete an end-of-study evaluation and be referred to appropriate care for medical supervision until the symptoms of any adverse event resolve or until their condition becomes stable.

