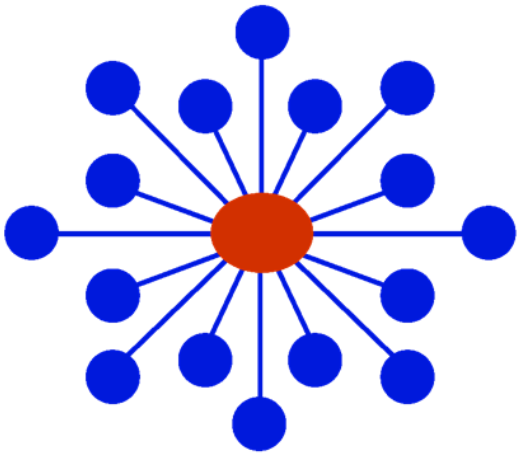

NIDA CTN Protocol 0053

Achieving Cannabis Cessation-Evaluating N-Acetylcysteine Treatment (ACCENT)

Lead Investigator (LI): Kevin M. Gray, MD

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Version 3.0

Lead Investigator:
Kevin M. Gray, MD
Southern Consortium Node
Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina
67 President Street
Charleston, SC 29425
Phone: (843) 792-6330
Fax: (843) 792-8206
graykm@musc.edu

CCTN Project Coordinator:
Udi Ghitza, PhD
Health Scientist Administrator
Center for the Clinical Trials Network
National Institute on Drug Abuse
National Institutes of Health
6001 Executive Blvd, Room 3151
Rockville, MD 20892-9557
Phone: (301) 443-9983
Fax: (301) 443-2317
ghitzau@nida.nih.gov

Project Director:
Susan Sonne, PharmD
Southern Consortium Node
Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina
67 President Street
Charleston, SC 29425
Phone: (843) 792-5221
Fax: (843) 792-8206
sonnesc@musc.edu

Clinical Coordinating Center:
Robert Lindblad, MD
Medical Officer, Clinical Coordinating Center PI
The EMMES Corporation
401 N. Washington St, Suite 700
Rockville, MD 20850
Phone: (301) 251-1161 ext. 205
Fax: (301) 576-3924
rlindblad@emmes.com

Data Coordinating Center:
Paul Van Veldhuisen, PhD
Data and Statistics Center PI
The EMMES Corporation
401 N. Washington St, Suite 700
Rockville, MD 20850
Phone: (301) 315-6152
Fax: (800) 416-2017
pvanveldhuisen@emmes.com

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
CCC	Clinical Coordinating Center
CCTN	Center for the Clinical Trials Network
CHRT-CR	Concise Health Risk Tracking-Clinician Rated
CHRT-SR	Concise Health Risk Tracking-Self Report
CI	Confidence Interval
CM	Contingency Management
CoC	Certificate of Confidentiality
CFR	Code of Federal Regulations
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
CWS	Cannabis Withdrawal Scale
DHHS	Department of Health and Human Services
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistics Manual of Mental Disorders, 4th Edition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
LI	Lead Investigator
LN	Lead Node
LOCF	Last Observation Carried Forward
MCQ	Marijuana Craving Questionnaire

Abbreviation	Definition
MedDRA™	Medical Dictionary for Regulatory Activities
MEMS	Medication Event Monitoring System
NAC	N-Acetylcysteine
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OR	Odds Ratio
PBO	Placebo
PI	Principal Investigator
PSQI	Pittsburgh Sleep Quality Index
QA	Quality Assurance
QIC	Quasi-likelihood Information Under the Independence Model Criterion
RA	Research Assistant
RRTC	Regional Research and Training Center
SAE	Serious Adverse Event
TAU	Treatment as Usual
TLFB	Timeline Follow-Back
UDS	Urine Drug Screen
USP	United States Pharmacopeia

2.0 STUDY SYNOPSIS AND SCHEMA

Study Objectives

The primary objective of this study is to evaluate the impact of N-acetylcysteine (NAC) 1200 mg versus matched placebo (PBO) twice daily, added to contingency management (CM), on cannabis use among treatment-seeking cannabis-dependent adults (ages 18-50).

Study Design

This is a Phase 3, 12-week, intent-to-treat, two-group, double-blind, randomized, placebo-controlled trial with one follow-up visit approximately 4 weeks post-treatment. Eligible participants will be randomized to NAC or PBO. Randomization will be stratified by study site and participant self-reported tobacco smoking status.

Study Population

Approximately 300 participants will be randomized into this 6-site study. The study population will include treatment-seeking cannabis-dependent adults who submit positive urine cannabinoid testing during screening. Individuals with acutely unstable medical or psychiatric disorders or substance dependence aside from cannabis or nicotine will be excluded.

Treatments

Participants will be randomized to receive orally administered NAC 1200 mg or matched placebo twice daily for 12 weeks. All participants will concurrently receive CM twice weekly during treatment, including escalating schedules of cash reinforcement with resets, targeting (a) retention, and (b) self-reported cannabis abstinence (confirmed by negative qualitative urine cannabinoid testing). Medication management will be conducted by the medical clinician weekly throughout treatment.

Assessments

Cannabis use outcome measures include self-reported use (Timeline Follow-Back) and urine cannabinoid testing (qualitative and creatinine-normalized quantitative). Secondary measures include, but are not limited to, cannabis craving (Marijuana Craving Questionnaire), cannabis withdrawal (Cannabis Withdrawal Scale), compulsive drug symptoms (Obsessive Compulsive Drug Use Scale), cannabis associated problems (Marijuana Problem Scale), depression/anxiety symptoms (Hospital Anxiety and Depression Scale), sleep quality (Pittsburgh Sleep Quality Index), and quality of life (PhenX Toolkit assessment). Medication adherence will be assessed using self-report, blister pack pill counts, and urine riboflavin testing.

Primary Analysis

The primary analysis will evaluate the impact of NAC versus PBO on cannabis use during the 12-week treatment intervention. The primary outcome measure is odds of negative urine cannabinoid tests submitted during active treatment, compared between treatment groups.

Main Secondary Analysis

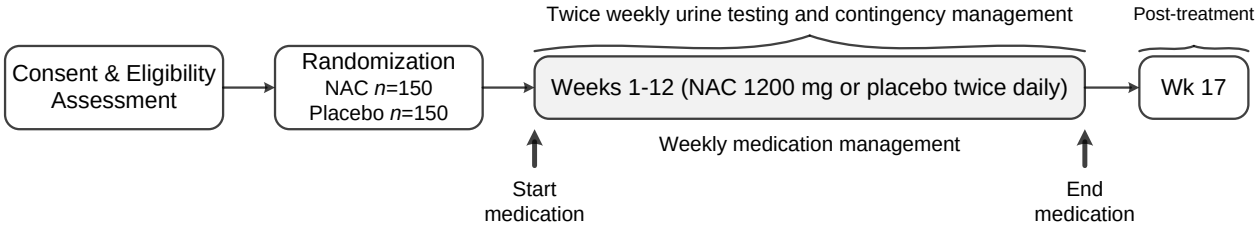
The main secondary analysis will evaluate the impact of NAC versus PBO on end-of-treatment cannabis abstinence. The main secondary outcome measure is the proportion of participants in each treatment group submitting consistently negative urine cannabinoid tests during the last two and last four weeks of treatment.

Replication Analysis

We will additionally conduct the above-described Primary and Main Secondary Analyses with consideration of only the first 8 weeks of treatment, in order to evaluate whether prior adolescent findings (8-week trial) may be replicated in adults.

3.0 STUDY FLOW CHART OR TIME AND EVENT TABLE

Figure 1: Overview of study design



4.0 INTRODUCTION

4.1 Background

Cannabis Dependence

Cannabis is the most commonly used illicit substance in the United States, and rates of use are rising (SAMHSA, 2010). In 2010, 6.9% of people age 12 or older were current cannabis users. About a quarter of current users exhibit a maladaptive pattern of use and impairment, meeting criteria for cannabis use disorders (abuse or dependence, present in 1.8% of people age 12 or older). While public perception of risks associated with cannabis use is diminishing, cannabis dependence is increasingly prevalent, is associated with substantial impairments, and frequently leads individuals to seek treatment (Budney & Moore, 2002; SAMHSA, 2007). Given a rapidly rising rate of daily cannabis use among adolescents (now 6.6% of high school seniors), the rate of cannabis use disorders is expected to continue rising, especially among young adults (Johnston et al., 2011).

While significant advances have been made in the evidence base for psychosocial treatments targeting cannabis dependence, effect sizes remain small to modest, and the majority of patients fail to achieve sustained periods of abstinence (for review, see McRae et al., 2003; Budney et al., 2007). A potential avenue to enhance outcomes is the development of pharmacological interventions to complement psychosocial treatments (Hart, 2005). This strategy has yielded success in other areas of addiction treatment (e.g., naltrexone in alcohol dependence, bupropion in nicotine dependence, and buprenorphine in opioid dependence), but an effective medication targeting cannabis dependence has not yet been identified (Benyamina et al., 2008; Levin et al., 2011).

Glutamate

Glutamate is a neurotransmitter that, while present throughout the central nervous system, is particularly prevalent in brain pathways that mediate addiction and relapse (Kalivas et al., 2008). The glutamatergic pathways thought to be important include projections from the amygdala, hippocampus, and prefrontal cortex to the nucleus accumbens (Tzschentke & Schmidt, 2003; Kalivas & O'Brien, 2008). Drugs of abuse alter glutamate transmission in the nucleus accumbens and ventral tegmental area (Carlezon et al., 2008; Kalivas et al., 2008). Glutamate and dopamine interact in the ventral tegmental area and nucleus accumbens, playing key roles in synaptic plasticity and the expression of addictive behaviors, such as drug seeking, self-administration, and behavioral sensitization (Jones & Bonci, 2005; Vezina, 2004).

A confluence of findings from multiple studies indicates that glutamate dysfunction plays an important role in addictive processes across multiple substances of abuse, including cocaine, amphetamines, opioids, nicotine, alcohol, inhalants, and cannabinoids (for review, Gass & Olive, 2008). Research utilizing the reinstatement model of drug seeking (in which animals are trained to self-administer a substance, undergo extinction training, and are induced into drug seeking by a drug-associated cue, stress, or the drug itself) has demonstrated that glutamate dysregulation in both the core and shell of the nucleus accumbens underlies drug seeking (McFarland et al., 2003, 2004; Bossert et al., 2006; LaLumiere & Kalivas, 2008; Kumaresan et al., 2009). Glutamate is thus considered a promising neurochemical focus of medication development targeting addictive behavior (Kalivas & Volkow, 2011; Olive et al., 2011).

Specific evidence suggests that cannabinoid administration disrupts glutamate. Cannabinoid (CB1) agonists hinder glutamate transmission in many brain areas, including the nucleus accumbens (Robbe et al., 2001), by preventing glutamate release from presynaptic terminals (Hoffman & Lupica, 2001; Pistis et al., 2002; Doherty & Dingledine, 2003; Robbe et al., 2003;

Schoffelemeer et al., 2006). The inhibition of glutamate transmission between the prelimbic cortex and nucleus accumbens by CB1 agonists is believed to indirectly disinhibit dopamine transmission and has been postulated as a mechanism for the reinforcing properties of cannabinoids (Robbe et al., 2001; Parolaro et al., 2005). Recent proton magnetic resonance spectroscopy studies in humans have shown decreased brain glutamate levels in adult and adolescent chronic cannabis users (Chang et al., 2006; Prescot et al., 2011).

4.2 N-Acetylcysteine

The anti-oxidant N-Acetylcysteine (NAC), an N-acetyl pro-drug of the naturally occurring amino acid cysteine, is FDA-approved as a mucolytic agent for bronchopulmonary disorders (Grandjean et al., 2000) and as an oral or intravenous antidote to treat acetaminophen poisoning (Smilkstein et al., 1988). In addition to prescription intravenous, oral, and nebulizer formulations, NAC is available as an inexpensive over-the-counter oral capsule commonly sold in nutritional supplement stores.

4.2.1 Preclinical Profile

Among potential glutamate-targeted pharmacotherapies, N-acetylcysteine (NAC) is a particularly strong candidate (Kalivas et al., 2008; Olive et al., 2011). NAC administration stimulates cystine-glutamate exchange, thereby increasing non-synaptic glial release of glutamate (Baker et al., 2003). The NAC-induced increase in extracellular glutamate stimulates inhibitory presynaptic metabotropic glutamate autoreceptors, thereby reducing vesicular glutamate release and, in turn, reducing the reinstatement of drug seeking in animal models (Baker et al., 2003; Moran et al., 2005; Madayag et al., 2007). Since drug self-administration down-regulates the cystine-glutamate exchanger (Kau et al., 2008), the up-regulation of the exchanger via NAC administratio*n* directly normalizes a drug-induced pathology (Kalivas et al., 2008; Moussawi et al., 2009). This NAC-induced normalization has been shown to provide enduring protection from relapse, even after NAC is no longer present, in multiple studies (Amen et al., 2011; Moussawi et al., 2011; Reichel et al., 2011). A recent study has also shown that NAC reduces drug seeking both early and late in the development of addictive behaviors (Murray et al., 2011). While most preclinical work in this area has focused on cocaine, studies involving nicotine and heroin have yielded consistent findings, suggesting that NAC may play a potential therapeutic role across substances (Zhou et al., 2008; Knackstedt et al., 2009).

Relative to other drugs of abuse, self-administration of cannabis is difficult to achieve in animals (Justinova et al., 2003; Martellotta et al., 1998). Therefore, although glutamate dysfunction, the target of NAC treatment, is likely a ubiquitous finding across substance use disorders (Gass & Olive, 2008), the development of a cannabis-specific animal model to replicate preclinical findings demonstrating NAC-induced effects on drug seeking may be impractical.

4.2.2 Clinical Profile

Based on promising preclinical findings, a series of preliminary clinical studies have explored the use of NAC in substance use and compulsive behavioral disorders. Case series have suggested potential utility in treatment-refractory obsessive-compulsive disorder and in chronic nail-biting (Lafleur et al., 2006; Berk et al., 2009), while controlled trials have demonstrated benefit in pathological gambling and trichotillomania (Grant et al., 2007; Grant et al., 2009). Two studies have shown NAC-associated reductions in cocaine craving in the laboratory (LaRowe et al., 2007; Amen et al., 2011), while others have demonstrated the feasibility and safety of conducting clinical trials with NAC in cocaine (LaRowe et al., 2006; Mardikian et al., 2007), nicotine (Knackstedt et al., 2009; Schmaal et al., 2011), methamphetamine (Grant et al., 2011), and cannabis (Gray et al., 2010) users.

Clinical Efficacy

Our research team recently completed an 8-week double-blind randomized placebo-controlled trial of NAC in cannabis-dependent adolescents (Gray et al., 2012). Treatment-seeking cannabis-dependent adolescents (*n*=116) were randomized, in 1:1 parallel group allocation, to receive a double-blind 8-week course of N-acetylcysteine (NAC; 1200 mg) or placebo twice daily, added to a contingency management intervention and brief (≤10 minute) weekly cessation counseling. A post-treatment follow-up visit occurred 4 weeks after treatment conclusion. The contingency management intervention, based on methods established by Carroll and colleagues (2006), included escalating cash reinforcement schedules with resets, separately reinforcing both (a) retention and adherence with study procedures, and (b) cannabis abstinence measured by qualitative urine cannabinoid testing.

The primary study hypothesis was that participants randomized to NAC would have higher odds than those randomized to placebo to submit negative weekly urine cannabinoid tests during treatment. An intent-to-treat (ITT) approach including all randomized participants was used. In all analyses, participants lost to follow up or absent for visits were coded as having a positive urine cannabinoid test at every missed visit.

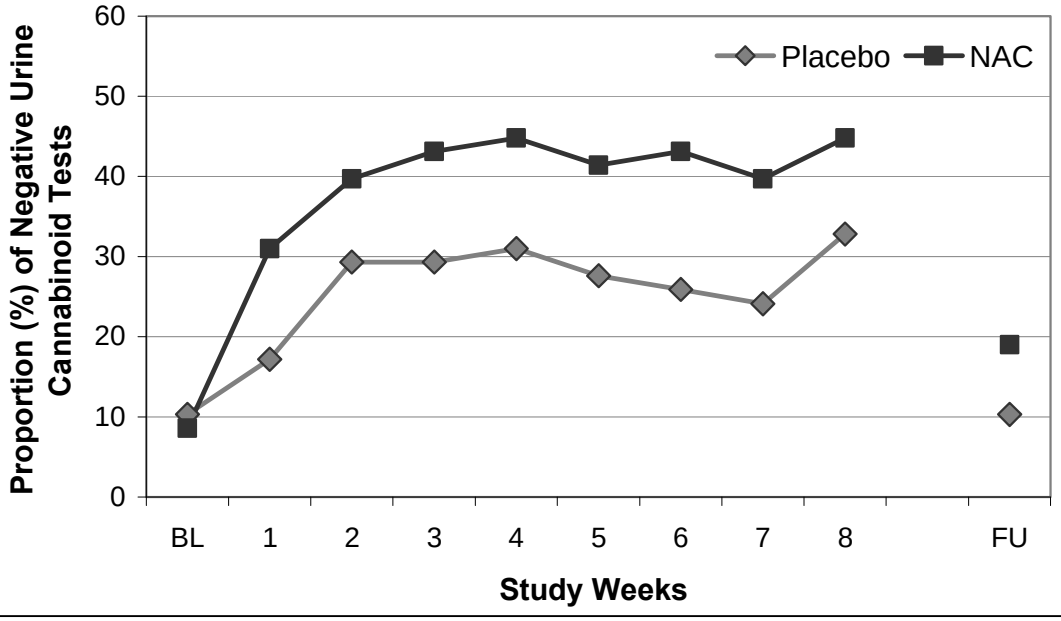
The study was powered to detect a 50% rate of negative urine cannabinoid tests in NAC participants, compared with 25% in PBO participants. These estimates were derived from a prior controlled trial of pharmacotherapy to complement contingency management targeting cocaine dependence (Moeller et al., 2007). Setting the type I error rate to 0.05, a sample of 58 participants per treatment group was deemed necessary to yield 80% power. No interim efficacy analyses were planned or conducted prior to completion of the study.

The efficacy of NAC versus placebo, each added to contingency management procedures and weekly brief cessation counseling, on abstinence from cannabis was analyzed over the 8-week active treatment and at post-treatment follow-up. A repeated measures logistic regression model using the method of generalized estimating equations (GEEs; Zeger & Liang, 1986) was applied to assess the overall treatment effect on urine cannabinoid test results during active treatment. Working correlation structures were independently compared and the final model structure was chosen using the quasi-likelihood under the independence model criterion statistic (QIC; Pan, 2001). Odds ratios and asymptotic 95% confidence intervals were computed. Additionally, a pre-planned logistic regression model was used to analyze the odds of a negative cannabinoid test at post-treatment follow-up, compared by treatment group. All models were adjusted for baseline urine cannabinoid test results and tested for possible confounding and effect modification of age, weight, gender, years of cannabis use, and number of previous quit attempts. Baseline demographic and clinical characteristics were independently tested for association with efficacy outcome (UDS) and those significantly associated were included as predictors in adjusted models. Results are presented as odds ratios with 95% confidence intervals, OR [95% CI].

The proportion of negative urine cannabinoid tests in the NAC and placebo groups at each visit (ITT sample) is shown in the figure below. Though there was no group difference in baseline years of cannabis use, this variable was an independent predictor of positive urine cannabinoid test during treatment (p=0.007) and was therefore covaried in the model. Participants randomized to NAC had more than double the odds of negative urine cannabinoid tests during treatment, compared with those randomized to placebo. In the adjusted model, the relationship between treatment and the odds of a negative urine cannabinoid test was OR=2.4 (95% CI: 1.1-5.4), p=0.021 (**Figure 2**). There was no significant differential drug effect over time (treatment x time interaction p=0.75). Through the final treatment visit, 40.9% (190/464) of the urine cannabinoid tests among participants in the NAC group were negative, compared to 27.2% (126/464) among those in the placebo group, per ITT analysis, assuming any missing urine was

positive for cannabinoids. At the post-treatment follow-up visit (four weeks after medication discontinuation), 19.0% (11/58) of the urine cannabinoid tests among participants in the NAC group were negative, compared to 10.3% (6/58) among those in the placebo group. While still numerically favoring NAC, the overall treatment effect lost statistical significance at post-treatment follow-up (OR=2.2 [95% CI: 0.7-6.5], *p*=0.155).

Figure 2: Proportion of negative urine cannabinoid tests (intent-to-treat analysis including all randomized participants, with urine cannabinoid tests assumed to be positive for all missed visits).



Negative Urine Cannabinoid Test (%)										
NAC (n=58)	8.6	31.0	39.7	43.1	44.8	41.4	43.1	39.7	44.8	19.0
Placebo (n=58)	10.3	17.2	29.3	29.3	31.0	27.6	25.9	24.1	32.8	10.3

Models were examined for the possibility of confounding and effect modification of age, weight, gender, and number of previous cannabis quit attempts. None of the variables tested were significant confounders or effect modifiers (all *p*>0.60).

A *post hoc* sensitivity analysis was performed on odds of negative urine cannabinoid tests during treatment, using multiple methods to manage missing data and participant dropouts. In addition to the ITT approach noted above (*n*=116), a modified ITT analysis that examined participants who received at least one dose of study medication (*n*=106) and a per-protocol analysis using available data (*n*=varying) were performed. Using a modified ITT analysis, participants in the NAC group had 2.2 times the odds of submitting negative urine cannabinoid tests, compared to those in the placebo group (OR=2.2 [95% CI: 1.1-4.5], *p*=0.04) during the treatment phase of the study. When only examining available data (per-protocol analysis), participants in the NAC group had 2.4 times the odds of submitting negative urine cannabinoid tests than those in the placebo group (OR=2.4 [95% CI: 1.1-4.5], *p*=0.04). Finally, combinatorial graphical methods for assessing the impact of missing data on significance of findings were also employed, in which every permutation of missing data assignment was considered, and a subsequent logistic regression performed (Hollis, 2002). For the majority of missing data assignments that could be reasonably expected, the odds ratio was still significant. In general, the selection of missing data handling had little effect on analytic outcomes.

Additional secondary analyses were conducted to explore end-of-treatment outcomes, using a sample restricted to participants with positive urine cannabinoid tests at baseline (*n*=105). While the study was not powered for these outcomes, it was felt that these were particularly relevant to evaluate meaningful clinical impact of the intervention. Criteria for four-week end-of-treatment abstinence were as follows:

For urine cannabinoid test, binary outcome defined as:

1 if the participant submitted a negative urine cannabinoid test in each of the last four weeks of the active treatment period

0 otherwise (including those who dropped out prior to the last four weeks)

For self-report, binary outcome defined as:

1 if the participant reported no marijuana use on each of the last 28 days (four weeks) of the active treatment period

0 otherwise

Table 1. Four-week end-of-treatment abstinence outcomes.

Method of Handling Missing Data	Data	Proportion Abstinent in Last Four Weeks		OR (*p*-value)
		Placebo	NAC	
Missing as Positive	UDS	8/52=0.15	17/53=0.32	2.59 (0.045)
	Self-report	6/52=0.12	12/53=0.23	2.24 (0.13)
Missing as Negative*	UDS	29/52=0.56	39/53=0.74	2.21 (0.06)
	Self-report	26/52=0.50	29/53=0.55	1.21 (0.63)
Complete Case Only	UDS	8/31=0.26	17/31=0.55	3.49 (0.015)
	Self-report	6/32=0.19	12/36=0.33	2.16 (0.18)

*Included as an extreme assumption, considered much less plausible than assuming missing as positive.

Similar methods were used to explore two-week end-of-treatment abstinence.

Table 2. Two-week end-of-treatment abstinence outcomes.

Method of Handling Missing Data	Data	Proportion Abstinent in Last Two Weeks		OR (*p*-value)
		Placebo	NAC	
Missing as Positive	UDS	10/52=0.19	20/53=0.38	2.55(.036)
	Self-report	7/52=0.14	15/53=0.28	2.54 (.063)
Missing as Negative*	UDS	32/52=0.61	40/53=0.76	1.92 (.13)
	Self-report	28/52=0.54	33/53=0.62	1.41 (.39)
Complete Case Only	UDS	10/30 =.33	20/33=.60	3.08 (.031)
	Self-report	7/31=.23	15/35=.43	2.57 (.084)

*Included as an extreme assumption, considered much less plausible than assuming missing as positive.

We additionally explored abstinence outcomes via the Number of Beyond-Threshold Weeks of Success (NOBWOS) Analysis Method (McCann & Li, 2012), quantitative self-reported marijuana use, and cumulative days abstinent during treatment (self-report), all among participants with positive baseline urine cannabinoid testing (*n*=105). We also examined concordance between UDS and self-report within the data set, yielding 88% agreement in the end-of-treatment outcome measure, and assuming all missing values are non-abstinent.

Every efficacy outcome approach explored, inclusive of both UDS and self-report data sets, consistently yielded findings numerically favoring NAC over placebo. Statistically significant differences were noted in the study's *a priori* outcome analysis (odds of negative weekly UDS over the course of treatment) and in the end-of-treatment binary UDS outcomes (last 2 and last 4 weeks). The study was powered only for the *a priori* outcome, so lack of statistical significance for some of the secondary/exploratory outcomes may be attributed to low power/limited sample size. Odds ratios were >2 for all end-of-treatment (last 2 and last 4 weeks) UDS and self-report outcomes (aside from those assuming the extremely unlikely case that all missing data were negative/abstinent). Furthermore, there was strong agreement between UDS and self-report. Overall, findings demonstrate consistently favorable outcomes for NAC versus placebo across a wide variety of approaches.

Pharmacokinetics

NAC has a complex set of metabolic pathways (Borgstrom et al., 1986). One of its main pathways is its rapid metabolism to cystine. Cystine may also be converted to glutathione, converted to inorganic sulfites, converted to sulfates, incorporated into protein, and/or converted to cysteic acid. NAC has an oral bioavailability of about 10% (De Caro et al., 1989; Holdiness et al., 1991). After oral administration, there is rapid oxidation of NAC before it reaches general circulation and extensive first pass metabolism, both contributing to the low oral bioavailability (Holdiness, 1991). As a result of this rapid and extensive first pass metabolism, it appears that even with repeated oral dosing, there is little accumulation of the drug (Moldeus et al., 1986). After an oral dose of 200 to 600 mg, the peak plasma concentration of 0.35 to 4 mg/L is achieved within 1-2 hours (Holdiness, 1991). The volume of distribution ranges from 0.33 to 0.47 L/kg (Olsson et al., 1988; Borgstrom et al., 1986), and protein binding is moderate, reaching approximately 50% four hours after the dose and decreasing to 20% twelve hours following the dose (Holdiness, 1991). Renal clearance has been reported as 0.190 to 0.211 L/h/kg. Approximately 70% of the total body clearance is non-renal. Following oral administration, NAC has a terminal half-life of 6.25 hours (Olsson et al., 1988). Studies evaluating NAC levels in the brains of humans have not been conducted. However, in an Alzheimer's disease study (Adair et al., 2001), beneficial effects of 50 mg/kg daily NAC orally in three doses suggested adequate blood-brain penetration in elderly humans.

4.2.3 Clinical Safety

Unlike many other potential candidate medications for cannabis dependence (for review, Hart 2005), NAC has a long-established safety record, with FDA approval since 1963. Given escalating concerns among the FDA, healthcare providers, and patients over potential adverse effects of psychotropic agents (Olfson et al., 2008), NAC may be particularly attractive since it has been used safely for several decades, often at doses greatly exceeding those proposed for the present study (Marzullo, 2005; Mucomyst Package Insert, 2004). A meta-analysis of studies evaluating long-term oral treatment with NAC for prevention of chronic bronchitis found that NAC was well tolerated, with generally mild, most commonly gastrointestinal adverse effects that did not require treatment interruption (Grandjean et al., 2000). Systemic allergic reactions to NAC have been observed, but only with intravenous administration (Bailey & McGuigan, 1998). Reflecting its safety profile, NAC is available over-the-counter, which further increases its potential acceptability and accessibility for patients.

4.2.4 Significance to the Field

Cannabis dependence is increasingly prevalent, and established treatments convey limited efficacy. The development of a safe and efficacious medication to complement psychosocial treatment would be a critical step in addressing a significant public health problem. Based on

the positive effect in our initial clinical trial in adolescent cannabis users and a strong safety profile, NAC is an excellent candidate for clinical evaluation in adults.

4.2.5 Study Rationale

NAC is the first medication to demonstrate intent-to-treat cessation benefit in a randomized controlled trial among cannabis users in any age group. While the results of the aforementioned adolescent study are extremely encouraging, these findings must be replicated in adult cannabis users. We have devised the proposed study to mirror methods from the adolescent study, with appropriate developmental modifications.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective of this Phase 3 study is to evaluate the impact of N-Acetylcysteine (NAC) 1200 mg versus matched placebo (PBO) twice daily, added to contingency management (CM), on cannabis use among treatment-seeking cannabis-dependent adults (ages 18-50). The primary outcome measure will be the odds of negative weekly urine cannabinoid tests during active treatment. Primary analysis will be based on an intent-to-treat evaluation of all participants randomized into the study, with missing urine specimens coded as missing and assumed to be positive. Sensitivity analyses will be performed to determine how other procedures for missing data affect results.

5.2 Secondary Objectives

See Section 8.2, for detailed Secondary Objectives.

6.0 STUDY DESIGN

6.1 Overview of Study Design

The primary objective of this Phase 3 study is to evaluate the impact of NAC 1200 mg versus matched placebo (PBO) twice daily, added to contingency management (CM), on cannabis use among treatment-seeking cannabis-dependent adults (ages 18-50). After assessment and inclusion into the study, participants will be randomized to receive a 12-week course of NAC 1200 mg or matched placebo twice daily. All participants will concurrently participate in a twice-weekly contingency management (CM) intervention. Medication management will be conducted weekly throughout treatment by the medical clinician. Urine cannabinoid testing will occur at all visits, and will be used as the primary determinant of cannabis use. Participants will return approximately four weeks after treatment conclusion for evaluation of adverse events with medication discontinuation and sustained treatment effects. Please see **Figure 1** for a design overview and **Table 5** for a summary of procedures.

We considered a 2 x 2 factorial design of NAC/placebo vs. CM/no CM, but decided against it for multiple reasons. First, CM has already demonstrated treatment efficacy for cannabis users, and it was reasoned that all participants in the study should receive some active treatment because of the serious nature of the illness being investigated. Second, given the general difficulty in recruiting treatment-seeking cannabis users for participation in research, recruitment for a four-cell study would not be feasible over the funding period. Given the primary aim of this study to examine the efficacy of NAC in cannabis-dependent adults using methods mirroring the prior adolescent trial, the proposed design is most appropriate and feasible.

Since psychosocial interventions remain the mainstay of treatment for cannabis dependence, it stands to reason that clinical pharmacotherapy trials should be conducted in the context of concurrent psychosocial treatment. Inclusion of an evidence-based psychosocial treatment among all randomized conditions addresses the ethical obligation to provide treatment for all participants. Additionally, if crafted appropriately, psychosocial and pharmacological treatments may play complementary or synergistic roles. A particularly promising psychosocial treatment for combination with pharmacotherapy is contingency management (CM). The motivating features of CM may serve to enhance treatment adherence and complement medication effect by rewarding abstinence (Carroll & Rounsaville, 2007). A recent trial of citalopram, combined with CM, in cocaine-dependent adults, demonstrated the feasibility and supported the positive effect of this approach (Moeller et al., 2007). We will additionally include a weekly medication management intervention for all participants, conducted by the medical clinician and emphasizing medication compliance, retention, and abstinence. This low-intensity intervention includes brief, non-manualized, skills-based cannabis cessation counseling provided by the medical clinician, matching the psychosocial approach used in the prior adolescent study.

Given the preliminary nature of this study and the desire to mimic closely the design of the adolescent study on which it is based, participants will not receive “treatment as usual” (TAU) at the sites. Recruitment will therefore not focus on individuals already receiving treatment at the sites. Efforts will be made to advertise/recruit in the local communities specifically for treatment-seeking cannabis users. Enrolled participants will only receive study-related interventions, and will not concurrently receive TAU from the sites.

6.2 Duration of Study and Visit Schedule

Once all sites are initiated, enrollment is expected to take place over a period of approximately 12 months.

7.0 STUDY POPULATION

Approximately 300 individuals will be randomized in this study, including males and females between 18 and 50 years of age who meet current DSM-IV criteria for cannabis dependence (**Table 3**).

7.1 Inclusion Criteria

1. Age 18 – 50 years

2. Must be able to understand the study and provide written informed consent

3. Must meet current DSM-IV criteria for cannabis dependence in the last 30 days

4. Must express interest in treatment for cannabis dependence

5. Must submit a positive urine cannabinoid test during screening

6. Women of child bearing potential must agree to use appropriate birth control methods during study participation: oral contraceptives, contraceptive patch, barrier (diaphragm or condom), levonorgestrel implant, medroxyprogesterone acetate, complete abstinence from sexual intercourse, or hormonal contraceptive vaginal ring

7.2 Exclusion Criteria

1. Allergy or intolerance to NAC

2. Women who are pregnant or lactating

3. Current use of NAC or any supplement containing NAC (must agree not to take any such supplement throughout study participation)

4. Use of carbamazepine or nitroglycerin within 14 days of randomization

5. Current enrollment in treatment for cannabis dependence

6. Any use of synthetic cannabinoids (such as K2/Spice) in the 30 days prior to screening or during the period between screening and randomization

7. Current substance dependence, other than cannabis or nicotine

8. Urine drug screen positive for any drug of abuse other than cannabis or amphetamines at the randomization visit*

9. Urine drug screen positive for amphetamines at the randomization visit without having a valid prescription for it

10. Maintenance treatment with buprenorphine or methadone

11. Recent history of asthma (within the last 3 years)

12. History of seizure disorder, bipolar disorder, schizophrenia, or other significant or unstable medical or psychiatric illness that may place the participant at increased risk in the judgment of the medical clinician

13. Significant risk of homicide or suicide

*** Only participants who have a valid prescription for amphetamines (e.g., for ADHD) may be included**

Table 3. Rationale for Inclusion and Exclusion Criteria

Criteria		Description	Rationale
Inclusion	1	Age 18 – 50 years	Definition of study sample; encompasses large majority of adults seeking treatment for cannabis use disorders (SAMHSA, 2009)
	2	Able to understand study and give consent	GCP requirement
	3	DSM-IV diagnosis of cannabis dependence	Definition of study sample
	4	Interested in treatment	To help ensure that participant will provide useful data
	5	Positive urine cannabinoid test during screening	To ensure enrollment of individuals who might benefit
	6	Agree to use birth control	NAC safety during pregnancy not established
Exclusion	1	Allergy or intolerance to NAC	Safety
	2	Pregnancy or lactation	NAC safety during pregnancy/lactation not established
	3	Use of NAC or NAC-containing supplements	Safety; integrity of randomization
	4	Use of hazardous concurrent medications	Safety—potential high-risk drug-drug interactions
	5	Current treatment enrollment	Concurrent treatments may confound trial results
	6	Use of synthetic cannabinoids	Safety; Possible confound
	7	Other substance dependence	Definition of study sample
	8	UDS positive aside from cannabinoids	To help ensure that cannabis is primary substance
	9	UDS positive for amphetamines without valid prescription	To allow individuals receiving pharmacotherapy for co-occurring ADHD to participate
	10	Buprenorphine or methadone maintenance	Definition of study population
	11	Recent history of asthma	Safety
	12	High risk medical or psychiatric illness	Safety
	13	Risk of homicide or suicide	Safety

7.3 Subject Recruitment

Approximately 300 participants will be randomized into this multicenter study. Individuals who are likely to meet DSM-IV criteria for cannabis dependence and are likely to meet other study requirements will be recruited for the study. Participants will not receive treatment as usual at the site while they are participating in the study. Thus, participants must be willing to have the study intervention serve as their sole treatment during study participation. Upon study completion, participants may enroll in treatment as usual at the site or with another provider.

Participants may be recruited from a variety of sources, including advertising approved by the site's Institutional Review Board (IRB). An attempt will be made to randomize approximately 35% female participants, consistent with the female proportion of current cannabis users in the U.S. (SAMHSA, 2011). In addition, efforts will be made to recruit a study sample that reflects, or exceeds, the proportion of minorities in the community where the site is located.

Federal regulations require that IRBs give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, and pregnant women. Research involving women who are or may become pregnant receive special attention clinical studies because of women's additional health concerns during pregnancy and because of the need to avoid unnecessary risk to the fetus. NIH policy requires the inclusion of women and minorities in research study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study. To safeguard children's interests and to protect them from harm, special ethical and regulatory considerations are in place for research involving children. Regulations provided in Title 45 CFR Part 46 by the Office of Human Research Protection describe special protections for such population groups.

7.4 Site Characteristics

Participating sites should:

1) Have access to a medical clinician (e.g., N.P., P.A., M.D., etc.); the degree and licensing requirements depend on the regulations of the state in which the site is located) to perform medical assessments (e.g., medical history, physical examination, concomitant medications, etc.), determine participant eligibility, regulate the medication dose appropriately, evaluate severity and relatedness of adverse events, and provide the medication management intervention.
2) Have access to, or the ability to contract with, a pharmacy/pharmacist (or other appropriately qualified entity based on local/state regulations) to store/dispense study medications.
3) Be able to provide after-hours clinical backup for study-related emergencies.
4) Provide adequate space to accommodate research staff and study protocol procedures including on-site urine collection/testing and space to conduct study assessments.
5) Be willing to provide cash incentives for contingency management purposes.
6) Be able to recruit enough individuals with cannabis dependence to meet study recruitment goals.

7.5 Rationale for Site Selection

Study sites should have the appropriate resources to conduct the study safely and efficiently. All sites must have the ability to require study staff to follow all procedures associated with the study and ensure that good clinical practices are followed.

8.0 OUTCOME MEASURES

8.1 Primary Outcome Measures

The primary outcome measure will be the odds of negative urine cannabinoid tests during treatment, which will be compared by treatment group (NAC versus PBO). This primary outcome measure will be collected serially throughout treatment.

8.2 Secondary Outcome Measures (see 10.2 for support/justifications)

Additional measures of cannabis use (self-report, creatinine-normalized quantitative urine cannabinoid testing, quantitative testing dichotomized using methods described in Schwilke et al., 2011) will be used as secondary cannabis use outcomes. We will also evaluate the following:

The effect of NAC versus PBO, each added to CM, on:

1) End-of-treatment cannabis abstinence, measured by negative cannabinoid testing throughout the last two and last four weeks of treatment.
2) Odds of negative weekly urine cannabinoid tests during the first 8 weeks of active treatment (to assess for replication of prior adolescent study findings).
3) Two- and four-week abstinence, based on urine cannabinoid tests, anchored at week 8 (to assess for replication of prior adolescent study findings).
4) Two- and four-week end-of-treatment abstinence assessed via self-reported abstinence confirmed by negative urine cannabinoid tests.
5) Other cannabis-related measures (e.g., craving [Marijuana Craving Questionnaire], withdrawal [Cannabis Withdrawal Scale], compulsive use [Obsessive Compulsive Drug Use Scale], cannabis-associated problems [Marijuana Problem Scale]).
6) Other substance use (e.g., cigarettes per day [Timeline Follow-Back] among tobacco smokers).
7) Nicotine dependence among tobacco smokers (Fagerström Test for Nicotine Dependence)
8) Quality of life (PhenX Toolkit assessment).
9) The above outcomes will also be tested among the subgroup of participants that meet criteria for medication compliance (pill count and self-report, confirmed by riboflavin measurement).

The effect of change in cannabis use on:

10) Depressive and anxiety symptoms (Hospital Anxiety and Depression Scale).
11) Sleep quality (Pittsburgh Sleep Quality Index).
12) Quality of life (PhenX Toolkit asessment).

The relationships between measures of cannabis use:

13) Self-report (Timeline Follow-Back), qualitative urine cannabinoid testing, quantitative urine cannabinoid testing (continuous measure), quantitative urine cannabinoid testing dichotomized using methods described in Schwilke et al., 2011.

9.0 STUDY PROCEDURES

9.1 Pre-Screening Assessment

Individuals responding to recruitment materials or otherwise referred to the study will be pre-screened on the phone or in person to ascertain preliminary eligibility status. A series of questions will determine preliminary eligibility, and formal screening appointments will be scheduled for those who meet these eligibility criteria. No information obtained during the pre-screening will be used as research data.

9.2 Informed Consent Procedures

Prior to the initiation of any study procedures, written informed consent and HIPAA authorization will be obtained by the designated site research staff. Potential participants will be given a copy of the IRB-approved consent form and asked to read it either on site or at home in accordance with the consent process approved by the local IRB. Those who remain interested after receiving an explanation of the study will be given a short quiz to test their understanding of the project, the purpose and procedures involved, and the voluntary nature of their participation. Those who cannot successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form and proceed with the screening assessments. As part of the informed consent procedures, participants will be asked to provide or decline consent to be contacted for future studies.

9.3 Screening/Baseline Assessment

After consenting to participate in the study, participants will start the screening/baseline assessment phase. Ideally, the screening/baseline assessment procedures will be completed in one visit, but they can be completed in more visits if necessary. The screening/baseline assessment procedures should be completed within a one-week timeframe, but the allowable time for completion is within two weeks of signing consent.

9.4 Randomization

Following completion of screening/baseline assessments and determination of study eligibility, participants who return for the randomization visit and continue to be eligible will be randomly assigned to one of the two conditions (NAC or PBO) for 12 weeks of treatment. Random assignment will be on a 1:1 ratio to one of the two conditions. Randomization will be stratified by study site and self-reported tobacco smoking status. The randomization procedure will be conducted centrally through the CTN Data and Statistics Center (DSC), and randomization assignments will not be conveyed to staff or participants. The DSC statistician will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. The DSC statistician will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization slot, once used, will not be re-allocated.

9.5 Treatment

9.5.1 Study Interventions

Psychosocial Intervention

All participants will receive psychosocial intervention in the form of once-weekly medication management and twice-weekly contingency management (CM).

Medication Management

In order to ensure that each site is providing consistent but minimal support and encouragement to study participants, non-manualized medication management will be performed by the medical clinician weekly throughout treatment. This is a low intensity intervention that emphasizes medication compliance, retention, and abstinence, but does not incorporate more intensive modalities, such as cognitive behavioral therapy or twelve-step facilitation. It is the expectation that the weekly medication management will be conducted by the medical clinician. However, if for some reason the medical clinician is unavailable, an experienced member of the research staff may do it with consultation from the medical clinician or the lead team.

Contingency Management

After review of prior studies of CM in cannabis users (Kamon et al., 2005; Budney et al., 2006; Carroll et al., 2006; Kadden et al., 2007; Stanger et al., 2009), we devised a CM intervention for all participants in our prior adolescent study to encourage (a) retention in the study, and (b) cannabis abstinence, and will use similar methods in the present study. Among psychosocial treatments, CM may be ideally suited as a platform for pharmacological trials for substance use disorders (Carrol & Rounsaville, 2007).

In addition to providing contingent reward for cannabis abstinence (negative urine cannabinoid dipstick tests), we propose providing contingent reward for visit attendance (i.e., keeping scheduled study visits). This "two-tiered" CM approach was used with significant effect on both study retention and cannabis abstinence in a prior young adult CM trial (Carroll et al., 2006). An additional potential benefit of the "two-tiered" approach is that it increases early exposure to contingent rewards. Among regular cannabis users, urine cannabinoids may take two to four weeks to test negative after initiation of abstinence. In the context of a CM procedure that only rewards negative urine testing, several participants, even if abstaining from use, would potentially not be eligible for rewards for two to four weeks after achieving abstinence. It is felt that rewarding attendance may help to sustain motivation among participants initiating a quit attempt. We are particularly interested in this two-tiered method of reinforcement given the lack of single-tiered CM (reward only for substance abstinence) effect on study retention in our prior adolescent smoking cessation study (Gray et al., 2011).

An escalating reinforcement schedule, in which participants are able to earn increasing contingent rewards over successive displays of desired behavior (study visit attendance, cannabis abstinence), will be used (**Table 4**). For attendance, the initial contingent reward is $10 (cash). For each successive visit at which the participant keeps his/her scheduled study visit, the reward increases by $2 ($12, then $14, and so on), up to a maximum of $30. If participants attend all scheduled visits, they will receive a total of $610 during the 12-week treatment period. If a participant subsequently fails to attend a study visit, he/she does not receive an attendance-contingent reward at that visit, and the attendance-contingent reward value for the next session is "re-set" at the baseline of $10. For abstinence, the initial contingent reward is $5. For each successive visit at which the participant is abstinent, the reward increases by $2 ($7, then $9, and so on), up to a maximum of $25. If participants have a negative urine cannabinoid dipstick test at each visit during the 12-week treatment period, they will receive a total of $490. If a participant tests positive for cannabinoids at a subsequent visit, he/she does not receive an abstinence-contingent reward at that visit, and the abstinent-contingent reward value for the next negative urine cannabinoid test is "re-set" at the baseline of $5. If, at a given visit, a participant tests positive but adheres with study procedures, he/she may still collect the attendance reward as scheduled, but is not eligible for abstinence reward. The rate of contingent reward escalation and the total potential contingent reward are comparable to those in previous cannabis cessation studies (Kamon et al., 2005; Budney et al., 2006; Carroll et al., 2006; Kadden et al., 2007; Stanger et al., 2009). The escalating

reinforcement schedule with "re-set" contingency has been shown to be more effective than fixed schedule or escalating schedule without "re-set" contingency (Roll & Higgins, 2000).

Contingent rewards will be delivered in the form of cash payment. Prior research indicates that this form of contingent compensation, when compared with the use of gift cards or vouchers, is associated with improved research follow-up and retention rates and does not increase drug use or perception of coercion (Croft et al., 2007; Festinger et al., 2008).

We considered alternative CM designs, such as prize-based reinforcement, which has demonstrated improved cost-effectiveness in some settings (Olmstead & Petry, 2009). However, we were unable to find any controlled trials supporting the efficacy of prize-based CM targeting cannabis cessation. Additionally, given the positive primary outcome noted in our adolescent study when NAC versus PBO was added to an escalating CM schedule with resets, we determined that it would be wisest to closely mirror that trial's CM design. If the present study yields positive findings, future studies could explore the efficacy of NAC in the context of alternative CM strategies and/or other psychosocial interventions.

Table 4: Contingency management reward schedule

Maximum possible CM compensation values if a participant attends and is abstinent at each visit																									
	1	**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**		**EOT**	***CM Total Possible***
	b	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**	**a**	**b**		
Attendance	$10	$12	$14	$16	$18	$20	$22	$24	$26	$28	$30	$30	$30	$30	$30	$30	$30	$30	$30	$30	$30	$30	$30	$30	$610
Abstinence	$5	$7	$9	$11	$13	$15	$17	$19	$21	$23	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25	$490
CM Total Possible	$15	$19	$23	$27	$31	$35	$39	$43	$47	$51	$55	$55	$55	$55	$55	$55	$55	$55	$55	$55	$55	$55	$55	$55	$1100

EOT = End of Treatment

Pharmacological Intervention

United States Pharmacopeia (USP) grade NAC powder will be encapsulated in 600 mg quantities (two 600 mg capsules per dose). Matched placebo capsules will also be prepared. All capsules will be packaged in blister packs, with individual labels for time/date of each dose (e.g., Tuesday morning October 5th). This date- and time-labeled blister pack method has demonstrated superior participant adherence, compared to traditional packaging, and offers the additional advantage of tracking the timing of any missed doses (Wright et al., 1999; Huang et al., 2000; Simmons et al., 2000). We successfully used identical methods for medication/placebo preparation and dispensing in our adolescent study.

If assessment procedures reveal that a participant meets inclusion criteria and none of the exclusion criteria, the participant will be randomized to NAC or matched placebo in a double-blind fashion. The participant will be given a two-week supply of medication to take home, with instruction to take 1200 mg twice daily, in approximately twelve-hour intervals. This dose was chosen due to its demonstrated tolerability and evidence of effect on cannabis use in cannabis-dependent adolescents (see 4.2.2 Clinical Profile section). Giving two weeks of medication the first week will allow participants to have an additional seven-day supply of medication for use in the event that they are unable to make it to the next clinic visit in which medication is dispensed. For each subsequent week, medication will be given out a week in advance to decrease the risk of the participant running out of study medication. Participants will be expected to continue taking study medication until they come in for the End of Treatment Visit.

Study personnel will review medication logs and perform pill counts weekly throughout treatment to monitor medication adherence. Medication tolerability and effects will be systematically assessed. Medication supply will be refreshed for ongoing use over the following week. Participants will be encouraged to contact study personnel between visits to address any immediate concerns regarding adverse effects. If a participant experiences intolerable medication-related adverse effects at any point during the study, a dose reduction to 600 mg twice daily may be undertaken. The dosage may be increased back to 1200 mg twice daily at the discretion of the medical clinician. However, if a participant is unable to tolerate the reduced dose, medication will be discontinued, and the participant will continue to come in for study visits.

Subject Discontinuation/Stopping Rules

Every effort will be made to retain participants in the trial. If a participant experiences intolerable adverse effects with study medication that are not remedied by a dose reduction, the medication may be discontinued while the participant continues to participate in all non-medication study interventions and procedures.

Clinical Deterioration “Rescue” Plan

A clinical deterioration “rescue” plan will be in place for participants that experience psychiatric or substance use deterioration during the study. Symptoms will be monitored closely throughout the trial to assess for deterioration. Appropriate intervention will be arranged for any participant demonstrating gross clinical deterioration. The rescue measures will include immediate assessment by the site medical clinician for a comprehensive psychiatric and substance abuse evaluation and referral for appropriate clinical intervention.

Referral for Participants Needing Continuing Treatment

At the end of study participation, if a participant requires or requests continuing treatment for cannabis dependence, an appropriate treatment referral will be made.

9.6 Follow-Up

A post-treatment follow-up visit will be conducted at Week 17 (may occur +/- one week).

9.7 Blinding

9.7.1 Type of Blinding

This study is a double-blind, placebo-controlled trial.

9.7.2 Maintenance of Blind

With the exception of specified individuals at the DSC, safety staff at the CCC and the NIDA contract research pharmacist preparing study medications, all other study personnel and participants will remain blind to medication status until completion of the trial, nationwide. A Data and Safety Monitoring Board (DSMB) will review study data. DSMB reports will be blinded, though the blind may be broken in the closed session upon request.

9.7.3 Breaking the Blind

In rare cases, it may be necessary to break the blind for a particular study participant before completion of the trial (e.g., pregnancy or other medical necessity). The request to break the study blind for an individual participant will be made by the medical clinician after consultation with the Lead Investigator. Unblinding the participant should occur only in cases of medical emergency when knowledge of the treatment group investigational agent may be necessary for

clinical management and decision-making. The decision to break the blind for a participant will be made jointly by the CCC Medical Monitor and at least one of the Lead Investigators.

9.8 Participant Reimbursement

Participants will be compensated $30 for completing the Screening Visit (if screening requires multiple sessions to complete, partial compensation amounts may be provided at each session, with total compensation of $30 for all screening procedures), $20 for completing the Randomization Visit (Week 1a), and $40 for completing the Follow-Up (Week 17) Visit. Participants who are willing to provide an optional blood sample (see section 10.2.4) will receive an additional $20 at the time of sample collection. Compensation for the Week 1b through End of Treatment visits (active treatment phase) will be based on a contingency management intervention (see **Table 4**). Participants who attend all visits, and who have a negative urine cannabinoid test at each week 1-12 visit, may be compensated a maximum of $1210 ($1100 from CM procedures during the active treatment phase, $20 for the optional blood draw, and $90 compensation for Screening Visit, Randomization Visit, and Follow-Up Visit) over the course of study participation. Those who attend all visits and provide an optional blood sample, but do not attain any negative urine cannabinoid tests, may be compensated a maximum total of $720 ($610 from CM procedures during Weeks 1-12 and $110 compensation for Screening/Baseline Visit, Randomization Visit, and Follow-Up Visit and blood sample).

10.0 STUDY ASSESSMENTS

10.1 Study Timetable (Table 5: Study Procedures)

	Time	SC	Double-Blind Medication Phase													FU
Week →	(min)	0	1[ø]	2	3	4	5[&]	6	7	8	9[&]	10	11	12	EOT	17
Informed Consent	20	X														
Locator Form and Updates	2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PhenX Toolkit Core Tier 1[#]																
Demographics	2	X														
Body Mass Index (weight, height)	2	X														
Treatment Status Form	2	X														
Quality of Life	2	X					X				X				X	X
Self-Report of HIV Testing	1	X														
Tobacco, Alcohol, and Substance Use History	15	X														
Medical Assessments																
History and Physical	20	X[%]														
Weight, Blood Pressure, and Pulse	5	X	X				X				X				X	X
Adverse Events	2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Meds	2	X	X[$]	X	X	X	X	X	X	X	X	X	X	X	X	X
Penetration of Blind Assessment	1						X				X				X	X
Psychological Assessments																
DSM-IV Checklist	10	X														
M.I.N.I. 6.0	30	X[%]														
HADS	2	X					X				X				X	X
Pittsburgh Sleep Quality Index	2	X	X	X	X	X	X				X				X	X
CHRT-SR Suicidal Behavior Eval[# †]	2	X	X[$]	X	X	X	X	X	X	X	X	X	X	X	X	X
Substance Self-Report																
TLFB/Substance Use Diary	15	X[%]	X[$]	X	X	X	X	X	X	X	X	X	X	X	X	X
Cannabis Withdrawal Scale	2	X	X	X	X	X	X				X				X	X
Marijuana Craving Questionnaire	2	X	X	X	X	X	X				X				X	X
Marijuana Problem Scale	2	X					X				X				X	X
Obsessive Compulsive Drug Use Scale	2	X					X				X				X	X
Fagerström Test for Nicotine Dependence	2	X													X	X
Lab Samples/Testing																
UDS (dipstick)[*]	2	X[^]	2x[^]	2x	2x	2x	2x	2x	2x	2x	2x	2x	2x	2x	X	X
Urine Cannabinoids & Creatinine	•	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Synthetic Cannabinoid Test	•		*Performed at first negative cannabinoid dipstick test after randomization*													
Urine Riboflavin Test	•		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[‡]	•	X	X[$]				X				X				X	
Genetics Blood Sample[#]	5		X													
Psychosocial Procedures																
Contingency Management[*]	2		X[ø]	2x	2x	2x	2x	2x	2x	2x	2x	2x	2x	2x	X	
Med Compliance Assessment (Pill Count and Med Log Review)	2			X	X	X	X	X	X	X	X	X	X	X	X	
Medication Management	10		X	X	X	X	X	X	X	X	X	X	X	X		
Medication Dispensation	2		X	X	X	X	X	X	X	X	X	X	X	X		
Estimated Visit Length (hours) →		2-2.5	1	.75	.75	.75	1	.75	.75	.75	1	.75	.75	.75	1	1

SC=Screening/Assessment, EOT=End of Treatment, FU=Follow-Up

ø the week 1a visit is the Randomization Visit (contingency management will not be provided at the week 1a [Randomization] visit, but will be provided at the week 1b visit), ♯required by NIDA/CCTN, **†**CHRT-CR will be performed by the medical clinician only if a participant answers any of questions 14-16 on the CHRT-SR as agree or strongly agree, **‡** females only, ***** twice weekly during treatment (one at full clinic visit ["a" visit] and the other at "drop-in" UDS/CM-only visit ["b" visit] - the UDS/CM-only visit ["b" visit] will be about 15 minutes long), **^** UDS (including buprenorphine dipstick) should be performed at screening/baseline and again before randomization to ensure eligibility, **$** should

be completed prior to randomization to ensure eligibility. & If either monthly visits 5 or 9 are missed, assessments that are only completed at those visits should be performed at the next attended visit, as long as the window for the next monthly visit has not yet opened. % These assessments may be performed at the randomization visit, as long as they occur prior to randomization to ensure eligibility.

10.2 Protocol Specific Assessments

Study measures were chosen to minimize the research burden on participants yet collect adequate data to support analyses and assure safety. Similar to other pharmacotherapy and behavioral treatment research, measures have been included to ensure a comprehensive assessment of pertinent status and functioning variables. Measures were selected to obtain information usually included in treatment studies, and include assessments of drug abuse and dependence diagnoses, psychological status, quality of life, and measures of craving. Safety is assessed at each visit. Additional forms are used to collect and document study-specific information such as enrollment, study medication dosing, CM schedule, and contact information. The above study timetable provides a representation of study assessments. On average, screening assessments will be completed in 2-2.5 hours, and the randomization visit will take approximately 1 hour. Weekly clinic assessments will be completed in approximately 45 minutes and monthly assessments will take approximately 1 hour. Weekly brief contingency management-only visits will take approximately 10-15 minutes. The follow-up visit is expected to take approximately 1 hour.

10.2.1 Locator Form

A locator form will be used to obtain information to assist in finding participants during treatment and at follow-up. This form will collect participants' current address, email address, and phone numbers, as well as names, addresses and phone numbers of family/friends who may know how to reach the participant if direct contact efforts are unsuccessful. Subject to local IRB approval, the research team will have a Facebook page with no reference to the study site, substance abuse, or research. Privacy settings will be such that only the research team will be able to see the list of "friends" associated with the account, no one can post on the "wall", and the research team will not post on the walls of any "friends" associated with the account. The research team will use private messages to contact participants through Facebook. Locator information will be collected at screening, and will be updated weekly during the active treatment phase, and at the End of Treatment visit. No information from this form will be used in data analyses.

10.2.2 Demographics Form

The PhenX Toolkit demographics form will collect information about demographic characteristics of the participant, including sex, date of birth, ethnicity/race, education, employment pattern, and marital status. This form will be completed at screening.

10.2.3 Treatment Status Form

This form will ask if the individual is currently receiving maintenance treatment for opioid dependence, if s/he is currently enrolled in treatment for cannabis dependence, and if s/he is currently interested in cutting down or stopping his/her marijuana use. These questions will aid in determining study eligibility. This form will be completed at the screening visit.

10.2.4 Laboratory Tests

Urine Pregnancy Test

For safety purposes, a urine pregnancy test will be performed at screening, at randomization, at weeks 5 and 9, and at End of Treatment for all women, and at any other visit if a woman suspects she is pregnant. If a woman is found to be pregnant at any point during the study, she will be allowed to continue in the study but be withdrawn from study medications, given an appropriate referral, and followed until resolution of the pregnancy. If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

Urine Drug Screen (UDS)

A qualitative urine drug dipstick test will be performed at each visit to test for substance use (benzodiazepines, amphetamine, cannabis, methamphetamine, opiates, cocaine, ecstasy, oxycodone, methadone, and barbiturates—panel typically used in CTN studies) for CM and clinical assessment purposes. Adulterant testing will occur as well, with assessment of temperature and pH. One of the two weekly urine samples will additionally be sent to a central lab for quantitative cannabinoid testing and creatinine level (to assess creatinine-normalized quantitative urine cannabinoid level). Central laboratory testing qualitative results (rather than dipstick results) will be used for the primary analysis. Urine drug testing is an essential measure in this study, providing a biological indication of substance use versus abstinence. The dipstick UDS performed at both the screening/baseline visit and the randomization visit will also include a separate, specific test for buprenorphine to determine eligibility criteria.

Urine Creatinine-Normalized Tetrahydrocannabinol Test (Huestis & Cone, 1998; Schwilke et al., 2011)

This will be conducted by the central laboratory and will be used to reliably compare quantitative urine marijuana metabolite levels across visits. We will obtain a quantitative level of marijuana metabolites as well as a urine creatinine concentration. A creatinine-normalized tetrahydrocannabinol level will be obtained by dividing the marijuana metabolite level by the urine creatinine level.

Urine Synthetic Cannabinoid Test (Moran et al., 2011)

This will be administered upon the first negative urine cannabinoid dipstick test that occurs after randomization for each participant, to ensure that cannabis cessation is not achieved via substitution of synthetic cannabinoids (e.g., K2, Spice). This will be conducted by a central laboratory with capability/expertise in synthetic cannabinoid testing.

Genetic Sampling

The NIDA CCTN has requested that blood samples for genetic analysis be obtained for all new CTN pharmacotherapy trials. Participants will be asked to consent to having a single blood draw of approximately 10 mL (2 teaspoons). All randomized participants will be asked to provide a blood sample for genetic testing, but individuals may decline the blood draw and still participate in the ACCENT study. Ideally, blood will be collected at the randomization visit, but it may be collected at any visit after consent, based on the availability of a phlebotomist. The blood sample will be sent to the Rutgers University Cell and DNA Repository for storage and future analysis. The blood samples will be coded and only the local investigators will know the identity of the participant providing the sample.

10.2.5 Clinical Assessments

Timeline Follow-Back (TLFB)

The Timeline Follow-Back procedure (Sobell et al., 1988) will be used to elicit the participant's self-reported use of substances at screening/baseline and throughout study participation. For staff/participant convenience, this may be done at the Randomization visit as long as it is completed prior to randomization. During the screening process, this form will be used to assess substance use for the 30-day period prior to consent. Since standard TLFB procedures do not account for precise quantity and potency measures of cannabis, an additional cannabis quantification procedure will take place at screening only to supplement the TLFB. Participants will be asked to quantify cannabis use by weighing out amounts of an inert cannabis surrogate and reporting on potency through dollar values. These procedures have been used previously (Mariani et al., 2011) and provide superior estimates for TLFB assessments. The TLFB will be administered weekly throughout the active treatment phase and through the end of the follow up period to document the participant's self-reported use of substances for each day since the previous TLFB assessment. We plan to use the TLFB to track self-reported use of all substances. Participants will be given a diary card to document daily use of marijuana and other substance use while enrolled in the study. Participants will be asked to bring the card to study visits to help them remember their substance use. The diary card will only be used as a tool for participant recall and will not be collected as data.

DSM-IV Checklist

The DSM-IV Checklist will be administered to determine the participant's Axis I substance abuse and dependence diagnoses, based on DSM-IV criteria, prior to enrollment. It will be administered during the screening/baseline assessment visit by research staff trained in the DSM-IV Checklist.

Mini International Neuropsychiatric Interview Plus (M.I.N.I. 6.0)

The MINI (Sheehan et al., 1996) is a semi-structured interview designed to ascertain a current, past, or lifetime history of the major Axis I psychiatric disorders in DSM-IV and ICD-10. Based on the original MINI, an expanded version (M.I.N.I. 6.0) has been developed and validated. The M.I.N.I. 6.0 will be administered by trained staff and used to evaluate for psychiatric disorders. Equivocal diagnoses will be confirmed by the medical clinician.

Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983)

The HADS is a brief, validated instrument that screens for both depression and anxiety (Bjelland et al. 2002). It will be administered at screening, weeks 5 and 9, End of Treatment, and Follow-Up. Given the known links between cannabis use and mood/anxiety symptoms, it will be critical to track mood and anxiety over the course of a cessation trial (Cheung et al., 2010). If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

The Pittsburgh Sleep Quality Index (PSQI)

Sleep changes (e.g., insomnia, vivid dreams) are common with reduction and cessation of cannabis use, but have been understudied in the context of cannabis cessation clinical trials (Vandrey et al., 2011). The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) will be used to complement standard AE assessment of sleep changes. The PSQI is a relatively brief, validated instrument that measures sleep quality. The PSQI will be completed following the schedule outlined in the study timetable. The standard (past month) version will be used at the screening visit, and a modified (past week) version will be used at all subsequent administrations. If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

Concise Health Risk Tracking—Self Report (CHRT-SR) Suicidal Behavior Evaluation

The CHRT-SR (Trivedi et al, 2011) is a 16-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). The CHRT-SR will be assessed at screening, prior to randomization (week 1a), once weekly during study weeks 2-12, at End of Treatment, and again at the week 17 follow up visit. The CHRT-SR will assess high risk suicide ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of, thoughts of how and/or a specific plan to commit suicide) and prompt a clinician assessment for suicide risk before leaving the clinic.

Concise Health Risk Tracking – Clinician Rated (CHRT-CR) (Trivedi et al, 2011)

This assessment will be performed by the medical clinician only if a participant answers any of questions 14-16 on the CHRT-SR as agree or strongly agree as described above.

Cannabis Withdrawal Scale (CWS; Allsop et al., 2011)

The CWS is a valid instrument for assessment of cannabis withdrawal symptoms. It will be clinically important to monitor these symptoms during cannabis reduction and cessation, and to evaluate whether they are impacted by study interventions. The CWS will be administered following the schedule outlined in the study timetable. If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

Marijuana Craving Questionnaire (MCQ; Heishman et al., 2001, 2009)

The MCQ is a valid and reliable Likert-based self-assessment of cannabis craving. The 12-item MCQ, containing the three items from each factor of the full 47-item MCQ that exhibited the most within-factor reliability, will be administered following the schedule outlined in the study timetable. Craving is a prevalent and clinically important phenomenon among cannabis users that should be tracked in the context of a cannabis cessation trial (Heishman & Singleton, 2006). If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

Marijuana Problem Scale (Stephens et al., 2000)

This self-report measure assesses problems related to cannabis use, and will be administered at screening, weeks 5 and 9, End of Treatment, and Follow-Up, to track changes over the course of study participation, which may serve as important secondary outcomes. If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

Obsessive Compulsive Drug Use Scale (Franken et al., 2002)

This questionnaire has been adapted to specify cannabis as the primary substance, and be used to assess obsessive and compulsive cannabis use-related symptoms. Given NAC's potential effect on compulsive drug seeking, this scale may help uncover behavioral changes underlying treatment effects. If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

Fagerström Test for Nicotine Dependence (FTND)

The Fagerström Test for Nicotine Dependence (FTND) is used for assessing nicotine use and dependence (Heatherton et al., 1991) and will be administered to each participant at screening/baseline, End of Treatment, and Follow-Up.

Penetration of Blind Assessment

Participants and the primary study personnel who interact with the participant (medical clinician and study coordinator/RA) will be asked whether they think the participant is receiving NAC or PBO. This will be conducted at weeks 5 and 9, End of Treatment, and Follow-Up. If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

10.2.6 Efficacy Assessments

Qualitative urine cannabinoid testing (with standard cutoff of 50 ng/mL) conducted by the central laboratory (at baseline, at randomization, weekly throughout treatment, and at post-treatment follow-up) will be the foundation of the efficacy assessments. Other laboratory and clinical assessments described above will be used as secondary efficacy assessments (see **8.0 Outcome Measures**).

10.2.7 Safety Assessments

History and Physical

A medical history and physical exam will be performed by appropriately credentialed medical personnel (e.g., physician, physician's assistant, nurse practitioner) at the screening visit to assess whether individuals are medically stable for study inclusion. For staff/participant convenience, this may be done at the Randomization visit as long as it is completed prior to randomization.

Vital Signs

Vital signs including height (screening visit only), weight, and blood pressure will be recorded at screening, every fourth week during active treatment, and at the follow-up visit. If either visits 5 or 9 are missed, this assessment will be performed at the next attended visit.

Prior and Concomitant Medications

For safety purposes, all medications taken by the participant for the 30 days prior to screening/baseline, during screening/baseline, and during the study will be documented on a Prior/Concomitant Medications assessment. All medications taken by the participant while in the study should ideally be pre-approved by the medical clinician.

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

Appropriately qualified and trained study personnel will assess for any medical or psychiatric side effects, by asking: "How have you been feeling since your last visit?" AEs will be recorded at each visit according to the adverse event reporting definitions and procedures outlined in the protocol. If a reported AE suggests medical or psychological deterioration, it will be brought to the attention of the study medical clinician for further evaluation. SAEs will be medically managed, reported, and followed in accordance with applicable regulatory requirements.

Concise Health Risk Tracking—Self Report (CHRT-SR) Suicidal Behavior Evaluation

The CHRT-SR (Trivedi et al, 2011) is a 16-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). The CHRT-SR will be assessed at screening, prior to randomization (week 1a) and once weekly during study weeks 2-12, End of Treatment, and again at the week 17 follow up visit. The CHRT-SR will assess high risk suicide ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of,

thoughts of how and/or a specific plan to commit suicide) and prompt a clinician assessment for suicide risk before leaving the clinic.

Concise Health Risk Tracking – Clinician Rated (CHRT-CR) (Trivedi et al, 2011)

This assessment will be performed by the medical clinician only if a participant answers any of questions 14-16 on the CHRT-SR as agree or strongly agree as described above.

10.2.8 Treatment Compliance

Study medication compliance will be measured primarily by blister pack pill count and self-report (via medication diaries). Riboflavin measurement will be used for biological confirmation, with 25 mg of riboflavin in each NAC or placebo capsule, and urine riboflavin level >1500 ng/mL considered consistent with compliance (Malcolm et al., 2000). We considered additional methods to assess compliance, such as the Medication Event Monitoring System (MEMS), but opted against them due to added cost with unclear added benefit (Farmer, 1999). There have been studies of pill count combined with patient self-report demonstrating good concordance with MEMS cap data in primary care populations (Matsuyama et al., 1993). By assessing compliance via pill count, one is able to obtain the *extent* of compliance, and the use of blister packs with labeled day/time of individual doses provides added benefit in assessment and enhancement of compliance (Wright et al., 1999; Huang et al., 2000; Simmons et al., 2000).

Compliance will be defined as taking 80-120% of prescribed study medication per study week, confirmed by urine riboflavin level >1500 ng/mL. Individuals who miss more than two consecutive weeks of study treatment will be considered non-compliant.

Urine riboflavin levels will be assessed at the randomization visit to determine baseline riboflavin levels. This value will be subtracted from subsequent urine riboflavin results to determine the amount of riboflavin attributed to taking study medication.

Participants taking multivitamins at study entry will be asked not to change their multivitamin usage during the course of the study.

10.2.9 Projected Timetable

Study enrollment will occur over a 12-month period. The study intervention and follow-up phase will go on for a total of 16 months.

10.3 Validity and Reliability of Outcome Measures

See above.

11.0 STUDY TREATMENTS

11.1 Study Interventions

All participants will receive medication management and contingency management interventions.

11.1.1 Active Group

Participants randomized to NAC will receive double-blind NAC 1200 mg to be taken twice daily throughout the 12-week active treatment. Individuals experiencing intolerable adverse effects may undergo a dose reduction to 600 mg twice daily or the medication may be discontinued altogether, based on the judgment of the study medical clinician.

11.1.2 Control Group

Participants randomized to placebo (PBO) will receive double-blind PBO to be taken twice daily throughout the 12-week active treatment. As with those in the active treatment group, individuals experiencing intolerable adverse effects may undergo a dose reduction to 600 mg twice daily or the medication may be discontinued altogether, based on the judgment of the study medical clinician.

11.1.3 Dispensing of Study Medications

United States Pharmacopeia (USP) grade NAC powder will be encapsulated in 600 mg quantities (two 600 mg capsules per dose). Matched placebo capsules will also be prepared. Riboflavin 25 mg will be added to all capsules as a biomarker for medication compliance. All capsules will be packaged in blister packs, with individual labels for time/date of each dose (e.g., Tuesday morning October 5th). This date- and time-labeled blister pack method has demonstrated superior participant adherence, compared to traditional packaging, and offers the additional advantage of tracking the timing of any missed doses (Wright et al., 1999; Huang et al., 2000; Simmons et al., 2000). We successfully used identical methods for medication/placebo preparation and dispensing in our adolescent study.

11.1.4 Provisions for Access to Investigational Treatment After Study

NAC is readily available over-the-counter and may be accessed by participants after the study if desired.

11.2 Drug Packaging/Handling/Storage/Accountability

NAC and matched placebo will be packaged and distributed by the appropriate agency contracted by NIDA. It will be stored at each site in compliance with all state and institutional policies. While at each site, study drug will be refrigerated, and temperatures should be between 36 and 46 degrees Fahrenheit (2 – 8 degrees Celsius). A temperature log will be maintained to ensure study drug is maintained at the correct temperature. Drug-accountability records will be maintained at all times. These will include a record of the quantity of medications transferred between areas of the study site (from pharmacy to clinic and back, for example), and those dispensed to and returned by an individual participant.

11.3 Training Procedures

Medication Management

Given that medical clinicians already provide medication management as part of routine clinical care, significant training for the medical clinicians will not be necessary. Medical clinicians will be trained in medication management during the national training.

Contingency Management

Research staff will be trained in contingency management during the national training. Training will include basic principles of contingency management as well as training on the use of the incentive calculator (to be developed by the Lead Team).

Fidelity of Contingency Management

Contingency management for both attendance and abstinence will be tracked on a running log for each participant. The Contingency Management Tracker will capture visit date, compliance (yes/no), presence of cannabinoids in the urine (yes/no), incentive earned based on the incentive calculator, as well as actual incentive provided to the participant. This information will be reviewed by the local QA monitor at each monitoring visit for accuracy.

12.0 CONCOMITANT THERAPY

12.1 General Considerations

Concomitant medications that either pose a safety risk or may confound the primary efficacy measure will not be allowed.

The local site medical clinician should examine the acceptability of all concomitant medications not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that study participants be instructed not to take any medication (either self-administered non-prescription products or prescription medication prescribed by another physician) without prior consultation with the research staff.

The generic name, start date, end date, dosing information and indication for any medication (prescription or non-prescription) will be recorded on the prior/concomitant medication form.

Each participant will be instructed not to consent to any elective medical procedure without prior consultation with the research staff. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc.) that might require hospitalization or anesthesia should be deferred until after the study whenever clinically appropriate.

12.2 Medications Prohibited Before/During the Trial

Due to potential interactions with NAC, participants may not take nitroglycerin or carbamazepine 14 days before randomization or any time during participation in the study. Individuals receiving maintenance buprenorphine or methadone treatment will be excluded from the study. Participants will be asked not to use synthetic cannabinoids (e.g., K2/Spice) or take cannabinoid medication (e.g., dronabinol/oral tetrahydrocannabinol) during the course of the study, as these substances may confound outcomes. Participants will be asked not to start taking multivitamins containing riboflavin during study participation to avoid interference with medication compliance tracking. However, participants should continue to take any multivitamins they were on at the screening/baseline assessment.

Additionally, participants will be advised not to take non-study NAC or NAC-containing products throughout study participation.

12.3 Medications Allowed During the Trial

Aside from the above-mentioned exclusionary medications, participants may take other medications as deemed appropriate by the study medical clinician.

13.0 STATISTICAL ANALYSIS

13.1 General Design

CTN-0053 is a two-armed, multisite, randomized controlled trial comparing NAC to PBO, built upon a platform of CM, in terms of abstinence over the 12 weeks of treatment. The target sample size is 300. The Statistical Analysis Plan will contain detailed information regarding randomization, power, and sample size calculations, planned analyses and content for reporting results.

13.1.1 Study Hypothesis

It is hypothesized that cannabis abstinence rates in the NAC-treated participants will be greater than in the participants randomized to receive PBO.

13.1.2 Primary and Secondary Outcomes (Endpoints)

The primary outcome of CTN-0053 is the abstinence rate over the 12 weeks of treatment. Abstinence is based on a weekly urine drug screen (UDS) analyzed by central laboratory testing and defined as a negative cannabinoid result. The first UDS contributing to the primary outcome will be collected at Week 2, since the Week 1a Visit UDS sample is collected prior to randomization. The last UDS contributing to the primary outcome will be collected at the End of Treatment (Week 13) Visit. Thus, each participant contributes 12 indicators of abstinence, one for each week of treatment, and the primary outcome measure for each participant is then a vector of binary variables of length 12. The primary end result will indicate whether the likelihood of a negative urine cannabinoid test in NAC participants is statistically different than in PBO participants over the entire 12 weeks of treatment.

The CTN TEAM Task Force recommends testing for a treatment effect only in the last four weeks of the active treatment phase. This study will instead consider the entire treatment period because we are seeking to replicate, within a preliminary Phase III design, findings from the adolescent study, which also considered the entire treatment period. We nonetheless assessed the feasibility of using the CTN TEAM Task Force recommendation within this study and found that, with the proposed sample of 300 participants, we are reasonably powered (see Section 13.2) for a four-week end-of-treatment abstinence outcome. This will be used as the main secondary outcome, and we will additionally explore two-week end-of-treatment abstinence.

One objective of the proposed study is to replicate the findings from the adolescent study previously conducted by the LN. For this reason, additional analyses will be performed that mimic those conducted for the adolescent study. The first analysis will be the comparison of the odds of a weekly cannabinoid-negative urine drug screen during the first 8 weeks of treatment across treatment assignments. In addition, a modified end-of-treatment analysis will be used that is based on the first 8 weeks of treatment such that one outcome variable is defined by UDS-based abstinence in weeks 6-9 (corresponding to four-week “end-of-treatment”) and another will be defined as UDS-based abstinence in weeks 8-9 (corresponding to two-week “end-of-treatment”). Conducting these analyses will allow direct comparison of results with the adolescent study which utilized only 8 weeks of active treatment.

All of the end-of-treatment analyses will be repeated using a different definition of abstinence that requires both negative urine drug screens as well as self-reported abstinence on TLFB. An additional secondary abstinence outcome will be to use the methodology developed by Huestis and colleagues to utilize urine cannabinoid and creatinine testing to distinguish cannabis

abstinence versus new use (Schwilke et al., 2011). This methodology uses the actual quantitative results of the UDS, whereas the primary outcome measure assesses abstinence using the qualitative UDS results from the central laboratory. Another secondary outcome will be abstinence defined solely through self-report, which is collected via Timeline Follow-Back. Potential secondary outcomes other studies have used: longest period of continuous abstinence, and number of negative urines.

Additional secondary outcomes include: (i) other cannabis-related measures of craving, withdrawal, and compulsive use; (ii) cannabis-related problems; (iii) other substance use; and (iv) overall quality of life.

13.1.3 Factors for Stratification

Participants will be randomized to one of two arms, NAC or PBO, in a 1:1 fashion. Randomization will be stratified by site and self-reported tobacco smoking status. Prior research indicates that cannabis users who also smoke tobacco may have more difficulty with cannabis cessation than those who do not smoke tobacco (Peters et al., 2012).

13.1.4 Statistical Methods for Primary and Secondary Outcomes

Please note that the Randomization Visit where participants first receive study drug is Week 1a. Thus, 12 weeks of active treatment will go through week 13 (End of Treatment).

For the primary outcome measure, a longitudinal logistic model will be used to analyze the odds of a negative UDS as an indicator of abstinence across all 12 weeks of treatment (measured at weeks 2-13 [End of Treatment]). At each week, the primary outcome will be an indicator of whether the urine drug screen at that visit was negative for cannabinoids. Since each participant will contribute up to 12 outcomes to the model, generalized estimating equations (GEEs; Liang and Zeger, 1986) will be used to adjust for this correlation. The primary analysis will assess various correlation structures between observations and select the best fitting structure using the QIC criterion. The longitudinal model will include the main effect of treatment, the main effect of time, site effects, the effect of being a tobacco smoker at baseline and a time-by-treatment interaction. These terms may be dropped from the final model depending on evidence of an effect; however, the following terms are always included: treatment assignment, baseline tobacco smoking status, and site. Testing of the treatment difference will evaluate whether the coefficient of the main effect of treatment assignment is significantly different from zero.

Let y_{it} denote the indicator of abstinence for participant i (i=1, …, 300) and t indexes week (t=2, …, 13), that is y_{it} = 1 for a cannabinoid negative urine drug screen and 0 for a positive result. Missing UDS will be coded as missing (and counted as positive/non-abstinent) for the primary analysis, but sensitivity analyses will be performed, as described in **Section**

13.3. The longitudinal model is given by:

$$\text{logit } P(y_{it} = 1) = \alpha + \eta^{*}I\{\text{Smoker}\} + \beta\, I\{\text{NAC}\} + \varphi_t \times I\{t\} + \gamma_t \times I\{\text{NAC}\} \times I\{t\} + \Sigma_{sites}\, \theta_{sites} \times I\{\text{site}\}$$

where I{} is an indicator function defined in a qualitative manner using (k-1) indicator variables to capture k categories, where k=2 (two treatments) for I{NAC}, k=12 (12 weeks) for I{t} and k=X (X sites) for I{site}. For example, if there are four sites then I{site} would be defined using three indicator variables. Entering time in the model this way allows for a different abstinence rate at each week. The odds ratio (OR) capturing the main effect of treatment is e^{β}, thus the null hypothesis is $\beta = 0$, and the alternative is $\beta \neq 0$. Should there be evidence of a time-by-treatment interaction, secondary tests of treatment effect will also evaluate whether $\gamma_t = 0$.

13.2 Sample Size and Statistical Power

As per CCTN's recommendation for CTN-0053 to closely mimic the adolescent study, we conducted the sample size calculation using the approach described below. Please note that the adolescent study numbering for weeks began with randomization at week 0, and subsequent weekly observations during treatment at weeks 1-8 (8-week trial). However, in contrast, the current study begins with randomization at week 1, and subsequent weekly observations during treatment at weeks 2-13 (12-week trial). As such, for example, week 1 in the adolescent study corresponds to week 2 in the current study.

Sample Size Calculation Approach:

1. Obtain the proportions of negative UDS in each week in the Placebo + CM arm from the adolescent study. Only 52/105 participants with positive baseline UDS in the Placebo + CM were used and missing UDS were not imputed while calculating these proportions.

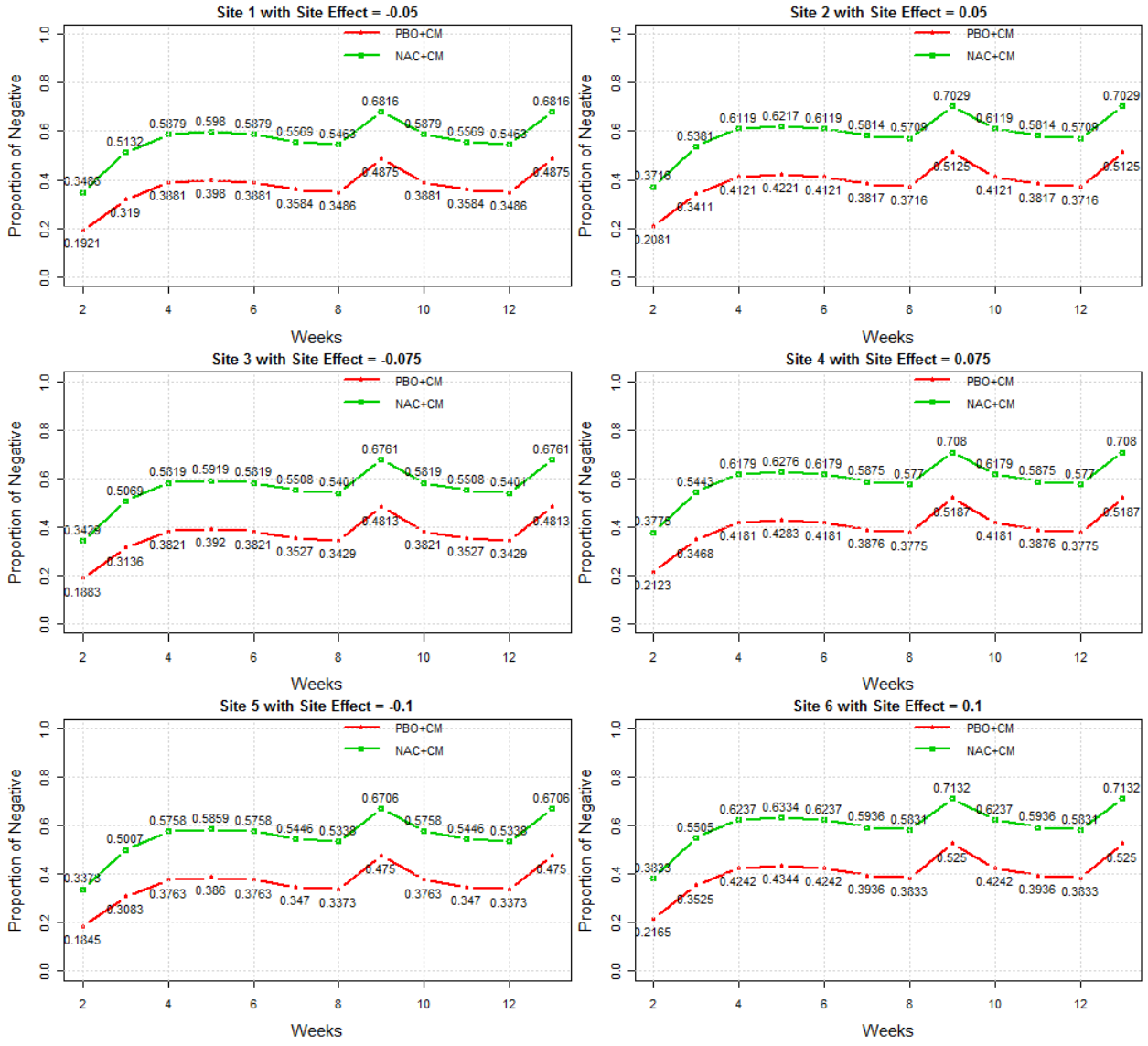
Week	1	2	3	4	5	6	7	8
Proportion	.20	.33	.40	.41	.40	.37	.36	.50

2. The following missing data patterns were observed in the 105 participants from the adolescent study. Here 0 represents missing UDS and 1 represents UDS present. For example, 00000000 denotes that all 8 UDS are missing.

UDS	Pattern	Frequency	Percent
All Missing	00000000	26	25%
Monotone Missing	10000000	4	11%
	11000000	2	
	11100000	1	
	11111000	2	
	11111100	1	
	11111110	2	
Intermittent Missing	00100000	1	20% of participants had
	01011111	1	23% of UDS missing intermittently
	01100000	1	
	01110100	1	
	01110111	1	
	10111111	2	
	11011111	3	
	11110111	3	
	11111011	6	
	11111101	2	
All Observed	11111111	46	44%
Total		===	
		105	

3. Assume two different odds ratios (OR = 2.25 and 2) as effect size measures. We assumed auto-regressive (AR(1)) correlations of 0.75 for the within-participant correlation in weekly scores over time, and a baseline tobacco smoking rate of 57% obtained from the adolescent study.

4. Impose fixed site effect (6 sites) that would change the proportion of negative UDS in each of the sites. This will induce the site variability. Below are the proportions of negative UDS in the two arms with treatment effect, OR = 2.25. Similar plots can be obtained for OR = 2, as well as 4 and 5 sites.



5. Simulate the data assuming the proportions from Step 4 and that abstinence rates in weeks 10-13 are the same as weeks 6-9.

6. Impose the missing UDS pattern (from Step 2) to the simulated data. Here we assumed that the missing percentage and missing pattern in weeks 2-13 are similar to weeks 2-9 (obtained from adolescent study and shown in Step 2).

7. Impute the missing UDS to be positive in the simulated data.
8. Test the effect of the treatment, NAC + CM compared to Placebo + CM, in weeks 2 through 13. Analyze the simulated data using a GEE (generalized estimating equation) model incorporating overall main treatment effect, week effect, site effects and week-by-treatment interaction effect and baseline tobacco smoking effect.

Following are the sample sizes versus power for the primary outcome measure over 12 weeks (weeks 2-13), at 5% level of significance, under various combinations of assumptions about the main effects of treatment (OR) and the number of sites.

Overall Sample Size	Number of Sites	Power	
		OR = 2.25	OR = 2
300	6	.93	.84
300	5	.94	.86
304	4	.94	.86
252	6	.88	.77
250	5	.89	.79
256	4	.90	.80

In order to ensure sufficient power for the analysis replicating the adolescent study, additional power simulations were conducted for the odds of a cannabinoid-negative weekly urine drug screen over the first 8 weeks of active treatment (weeks 2-9). These power analyses follow exactly as the approach outlined above, but no data was generated for weeks 10-13.

Below are the sample sizes versus power with a 5% level of significance:

Overall Sample Size	Number of Sites	Power	
		OR = 2.25	OR = 2
300	6	.88	.78
300	5	.90	.80
304	4	.90	.80
252	6	.83	.71
250	5	.84	.72
256	4	.85	.73

From both tables above, a sample size of 300 provides sufficient power (>79%) to detect the treatment difference corresponding to effect size, odds ratio = 2 with 6 sites, for both the 12-week (weeks 2-13) and 8-week (weeks 2-9) analyses. While a sample size of 252 would be sufficient to detect an OR of 2 for the primary outcome analysis, it does not allow for sufficient power in replicating the adolescent which is a vital component of the proposed study.

Power and Sample Size for End-of-Treatment Abstinence

As per the CCTN's recommendation, we also looked at the power to detect similar effects based on a complete abstinence outcome using UDS over the last 4 weeks of treatment (weeks 10-13). From the adolescent study, 15% of the participants were completely abstinent in the weeks 5-8 in the Placebo + CM arm. All missing urine drug screens were imputed as positive while calculating this proportion. It was assumed that the odds of four cannabinoid-negative urine drug screens in weeks 10-13 was the same as that observed in week 5-8 in the adolescent study.

The simulation study generated data for the Placebo + CM arm using parameter estimates from a logistic regression analysis of the adolescent study, and then the rate in the NAC + CM arm was calculated based on the assumed OR (2.6, 2.5, 2.25 and 2.0) as an effect size measure. The OR of 2.6 is the value estimated from the adolescent study using only those with a positive baseline UDS. From the adolescent study, we assumed 57% of participants would be self-reported tobacco smokers at baseline. To adjust for site heterogeneity, we implemented an approach similar to the sample size calculations for the primary outcome described above. For the set of simulations where there are six sites, site 1 has a 10% increase in odds of end of treatment abstinence, site 2 a 5% increase, site 3 a 10% decrease and site 4 a 5% decrease, and sites 5 and 6 have an 8% and 7% increase and decrease, respectively. The simulations for 4 and 5 sites are set up in a similar fashion. Once the data have been generated, they are analyzed using a logistic regression model with the following covariates: indicator of randomization to NAC + CM, tobacco smoking status and indicators of site. All simulations assume an equal number of participants enrolled per site.

Following are the sample size versus power, at 5% level of significance, for four different odds ratios (ORs). We have also included the estimate from the adolescent study (OR=2.6).

Overall Sample Size	Number of Sites	Power			
		OR = 2.6	OR = 2.5	OR = 2.25	OR = 2.0
304	4	.93	.91	.82	.68
300	5	.94	.91	.82	.68
300	6	.93	.91	.81	.68
256	4	.89	.86	.76	.61
250	5	.88	.85	.75	.60
252	6	.88	.86	.76	.60

For all three numbers of sites, the power to detect a difference for this outcome measure is <80% for an odds ratio of 2, but there will be sufficient power with approximately 300 participants to detect an OR of 2.25 for 4, 5 and 6 sites, which is deemed a clinically significant effect size.

13.2.1 Projected Number of Sites

We anticipate that six sites will be used in this study.

13.2.2 Projected Number of Participants per Site

We anticipate that each site will enroll and randomize approximately 50 (between 40-60) participants over the 12-month recruitment period.

13.3 Missing Data and Dropouts

A sensitivity analysis will be performed to determine how the missing data mechanism affects the results. One approach that will be used within the sensitivity analysis is to impute missing urine test results based on completed tests just before and after the missing test, which is common in substance use research.

13.4 Significance Testing

The primary outcome will be evaluated using a two-sided test with a type I error rate of 5%. There are several secondary outcomes; however, multiple comparisons will not be adjusted for since these are not part of the study's primary objective.

13.5 Interim Analyses

In coordination with the centralized Data and Statistics Center, a DSMB will monitor the progress of the trial. If recruitment progresses slowly enough to allow interim analysis to impact a substantial proportion of future recruitments, then interim analysis will be conducted. One interim check would focus on the nuisance parameters for the primary abstinence outcome measure in order to assess the adequacy of the projected study sample size. This check would not reveal the treatment effect observed in the trial at the time of this interim analysis. The parameters to be considered could include the missingness pattern and the within-participant correlation in consecutive weekly urine drug screens. If either is substantially different from the assumed values, there may be a need to adjust the sample size. This analysis would be conducted when approximately half of the participants (n=150) have been enrolled and have completed the active treatment phase of the study. The results of this analysis would be presented to the DSMB, who will then provide a recommendation to the NIDA CCTN regarding whether the target sample size should be modified. A decision regarding any such modification would be made subsequently by the CCTN, taking into consideration the recommendation of the DSMB.

In addition, formal statistical interim analyses for efficacy and futility may be performed. For an interim efficacy analysis we would use two-sided, symmetric O'Brien-Fleming type boundaries (O'Brien & Fleming, 1979) generated using the flexible Lan-DeMets approach to group sequential testing (Lan & DeMets, 1983). The monitoring guidance for early stopping in a futility analysis would be based upon an approach of conditional power (Jennison & Turnbull, 2000). 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.

13.6 Types of Analyses

All analyses will follow the intent-to-treat principle, where all subjects are analyzed and the covariate of interest is the treatment assignment, not the treatment received. Analysis of the safety population can be performed upon request. Further analyses may consider the amount of NAC received based on treatment compliance, or the amount of incentives earned.

13.7 Exploratory Analyses

Exploratory analyses will focus on two areas. First, the fit of the proposed model will be assessed and development of the most parsimonious model will be undertaken. Second, subgroup analyses will be performed. For example, we will explore whether abstinence rates differ across race, ethnicity, or gender, as well as whether they are effect modifiers for the relationship between NAC and abstinence.

13.8 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 means and standard deviations. 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 will be more informal. In case differences between treatment 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.

13.9 Safety Analysis

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by system organ class and preferred term using MedDRA™ (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, system organ class, and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available. Treatment arm differences will be monitored by the DSMB.

14.0 REGULATORY COMPLIANCE AND SAFETY MONITORING

14.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. An Operations Manual will be provided as a reference guide and study quality assurance tool.

14.2 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, 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 local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

14.3 Confidentiality

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. 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 federal office that issues the CoC will be advised of changes in the CoC application information. Participating 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 storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. At most, the web site will include a summary of the results. Additionally, data from this study will be available to researchers on another website, http://datashare.nida.nih.gov/, after the study is complete and the data analyzed. These websites will not include information that can identify participants, and may be viewed at any time.

14.3.1 Health Insurance Portability 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.

14.3.2 Investigator Assurances

Each site 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.

14.3.3 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 must comply with their institution's policy regarding conflict of interest.

14.3.4 Inclusion of Women and Minorities

A diverse group of study sites will be involved so that these sites can attract a diverse study population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and or treatment programs that serve a large number of women or minorities, advertising in newspapers or radio stations with a high female or minority readership/listening audience, etc.

14.3.5 IND Requirements

An IND application will be submitted to the FDA for this study. Any subsequent amendments to this clinical trial submitted to the FDA for review will reflect awareness of and compliance with U.S Code of Federal Regulations 45 CFR 46 and its subparts, as well as the International Conference on Harmonization Good Clinical Practice (ICH E6). This IND study will also be conducted in accordance with all applicable FDA regulations and will comply with all applicable laws and regulations at clinical research sites.

14.3.6 Regulatory Files

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

14.3.7 Records Retention and Requirements

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

14.3.8 Audits

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

14.3.9 Reporting to Sponsor

The site Principal Investigator agrees to submit accurate, complete, legible, and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event reporting and Serious Adverse Event reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

14.3.10 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 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 IRB and institutional policies and that is accessible to the study monitors.

Prior to signing the informed consent form, research staff knowledgeable about the study will explain the study to the potential participant and provide him/her with a copy of the consent to read. If the potential participant is interested in participating in the study, a researcher who is authorized to obtain informed consent by the PI and (if applicable) by the IRB, will review each section of the informed consent form in detail, answer any of the participant's questions, and determine if the participant comprehends the information provided by administering the comprehension tool. The participant will document agreement to participate by signing and dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document. The consent must be properly executed and complete to be valid. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Persons delegated by the PI to obtain informed consent must be listed on the Site Staff Delegation of Responsibilities and Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training. A copy of the informed consent document will be provided to the participant, and this action will be noted in the participant's record.

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. Those who cannot successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Those who demonstrate understanding of the study and voluntarily agree to

participate will be asked to sign the Informed Consent Form. 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 participant's participation in the trial. All participants affected by the change will be re-consented (based on local IRB policy). The participants will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty.

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.

14.3.11 Clinical Monitoring

The monitoring of the study site will be conducted on a regular basis using a combination of NIDA-contracted monitors and RRTC (Regional Research and Training Center) site managers. 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.

NIDA contract monitors will monitor study compliance and study procedures to assess compliance with the protocol, GCP, and applicable regulations. NIDA contract monitors will assess accurate submission of data and that data are in agreement with source documentation and will review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and principal investigator supervision and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA.

Qualified node personnel (Node Protocol Managers and/or 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 Node, 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 staff 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 Quality Assurance Monitoring Plan.

14.3.12 Study Documentation

Study documentation includes all case report forms, data correction forms, participant diaries, source documents, monitoring logs and appointment schedules, Sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Board 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.

14.4 Safety Monitoring

14.4.1 Data and Safety Monitoring Board (DSMB)

NIDA has appointed a CCTN DSMB in accordance with NIH requirements to provide independent oversight of CTN trials. The DSMB will review the research protocol and plans and make recommendations to assure that subject safety, trial validity and data integrity are addressed appropriately. Throughout this trial, the DSMB will periodically assess at regularly scheduled meetings trial progress, factors that can affect study outcome, safety and outcome data, critical efficacy endpoints and factors or scientific discoveries external to the study that may have ethical considerations or may affect the risk benefit analysis of this study. After review of the trial data and other factors, the DSMB will make recommendations to NIDA on whether to continue, stop or modify the trial or an individual participant's participation in the trial.

14.4.2 Protocol Deviations Reporting and Management

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor 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. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the site's IRB. All protocol deviations 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 major or minor protocol deviation will be made by the protocol's Lead Investigator in conjunction with the CCC and DSC.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviations CRF. Additionally, each site is responsible for tracking and reporting protocol deviations to their IRB as required. Site staff should contact the DSC, CCC, and Lead Investigator immediately if an unqualified/ineligible participant is randomized into the study.

14.4.3 Adverse Events (AEs)

Each participating site will appoint a medical clinician (MD, PA, NP, etc.) for this study, who will review or provide consultation for each serious event as needed. These reviews will include an assessment of the severity and causality to the study drug or study procedures. The Medical 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 site Principal Investigators a Safety Letter when necessary. The medical monitor will determine which safety events require expedited reporting to NIDA, the DSMB, and regulatory authorities. This will include all suspected adverse reactions that are serious and unexpected. The study staff will be trained to monitor for and report adverse events and serious events.

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

14.4.4 Definitions of Adverse Events and Serious Adverse Events

Standard definitions for adverse events and serious adverse events, their identification, characterization regarding severity and relationship to therapy and processing are described in Section 18.0 and Appendix A.

14.4.5 Reportable Adverse Events and Serious Adverse Events

Adverse Events

For the purpose of this study, the following AEs will not require reporting in the data system but will be captured in the source documentation as medically indicated:

- Grade 1 (mild) and unrelated adverse events
- This would typically include physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Serious Adverse Events

For the purpose of this study, admission to a hospital or freestanding residential facility for drug detoxification will not be recorded as an SAE in the data system and will be reported to local IRBs per local IRB guidelines.

14.4.6 Known Potential Toxicities of Study Drug/Intervention

NAC has a generally benign adverse effect profile. A meta-analysis of studies evaluating long-term oral treatment with NAC for prevention of chronic bronchitis found that NAC was well tolerated, with generally mild, most commonly gastrointestinal adverse effects that did not require treatment interruption (Grandjean et al., 2000).

Some patients who have taken intravenous NAC for the treatment of acetaminophen overdose have had more serious reactions. Allergic reactions have occurred in about 5% of patients taking intravenous NAC (Bailey & McGuigan, 1998). These reactions may be mild, consisting of flushing, rash, and itching. Less common side effects include trouble breathing, low or high blood pressure, fever, and hives. If untreated, such a reaction could lead to death. Even more rare serious side effects of intravenous NAC are irritability, confusion, and seizures. These reactions (severe allergic reaction or seizures) have never been reported when NAC is taken orally, as it will be in this study. As a precaution, we will exclude individuals with a recent history of asthma, as they are believed to possess a higher risk of allergic reaction to NAC. We will also exclude individuals with a history of seizure disorder.

14.4.7 Known Potential Adverse Events Related to the Underlying Clinical Condition and/or Study Populations

Several withdrawal symptoms are common during cannabis cessation, including irritability, cannabis craving, vivid dreams, insomnia, and reduced appetite.

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. AdvantageEDC, a web-based distributed data entry system, 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 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in the AdvantageEDC User's Guide.

15.3 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 Collection

Data will be collected at the study sites either on source documents, which will be entered at the site into eCRFs, or through direct electronic data capture. The eCRFs will be supplied by the DSC. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. Paper CRFs and eCRFs should be completed according to the CRF instruction manual and relevant instructions in the study operations manual. 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.

15.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into the AdvantageEDC system in accordance with the AdvantageEDC User's Guide. Only authorized individuals shall have access to eCRFs.

15.6 Data Editing

Completed data will be entered into AdvantageEDC. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into AdvantageEDC.

15.7 Data Transfer/Lock

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.

15.8 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of AdvantageEDC.

15.9 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 SIGNATURES

SPONSOR'S REPRESENTATIVE (CCTN DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version **3.0** of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- 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 personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Site Name _____

Node Affiliation _____

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18.0 APPENDIX A

Adverse Events - Definition of Adverse Event and Serious Adverse Event

Adverse Event: An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. (Any change from baseline in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the medical clinician are considered AEs.)

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

Serious Adverse Event (SAE): A serious adverse event (SAE) refers to all serious events including serious adverse events or serious suspected adverse reaction or serious adverse reaction as determined by the medical clinician or the sponsor is any event that results in any of the following outcomes:

1. Death: A death occurring during the study or which comes to the attention of the site research personnel during the protocol-defined follow-up after the completion of the study, whether or not considered treatment-related, must be reported.

2. Life-threatening AE (Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.)

3. Inpatient hospitalization or prolongation of existing hospitalization.

4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

5. Congenital abnormality or birth defect.

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Unexpected Adverse Event: Any adverse event, the specificity or severity of which is not consistent with the investigator brochure or the package insert. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy: All pregnancies that occur on study will be captured on a pregnancy CRF and not separately reported as an AE or a serious event. Women who become pregnant during the study period will be discontinued from further study drug/intervention referred for medical care, and the pregnancy followed until an outcome is known. Women who terminate the pregnancy

may be reinitiated on study medication based on the judgment of the medical clinician. Women who become pregnant will be eligible to continue study assessments.

Medical History: A thorough medical history during the eligibility assessment phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, or symptoms of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site's Role in Eliciting and Reporting Adverse Events: Appropriately qualified and trained research personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Research personnel will obtain as much information as possible about the reportable AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local site staff is responsible for reporting serious events to their IRB, per their IRB's guidelines.

Site staff is required to enter reportable AEs and SAEs in to the study's data capture system. Additional information may need to be gathered to evaluate the SAE and to complete the appropriate CRFs. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stabilized at the time of initial reporting or if new information becomes available, follow-up information must be submitted as soon as possible.

Reportable AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization even beyond the end of the study.

Assessment of Severity and Causality

A designated medical clinician will review reportable AEs and SAEs for seriousness, severity, and causality on at least a weekly basis.

Guideline for Assessing Severity:

The severity of an adverse event refers to the intensity of the event.

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 required, hospitalization possible.

Guideline for Determining Causality:

The designated medical clinician will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study drug/intervention caused the event?

Reporting and Management Procedures of AE/SAEs

Site AE/SAE Monitoring: Protocol monitors as well as local node staff will review the study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately by the research staff. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

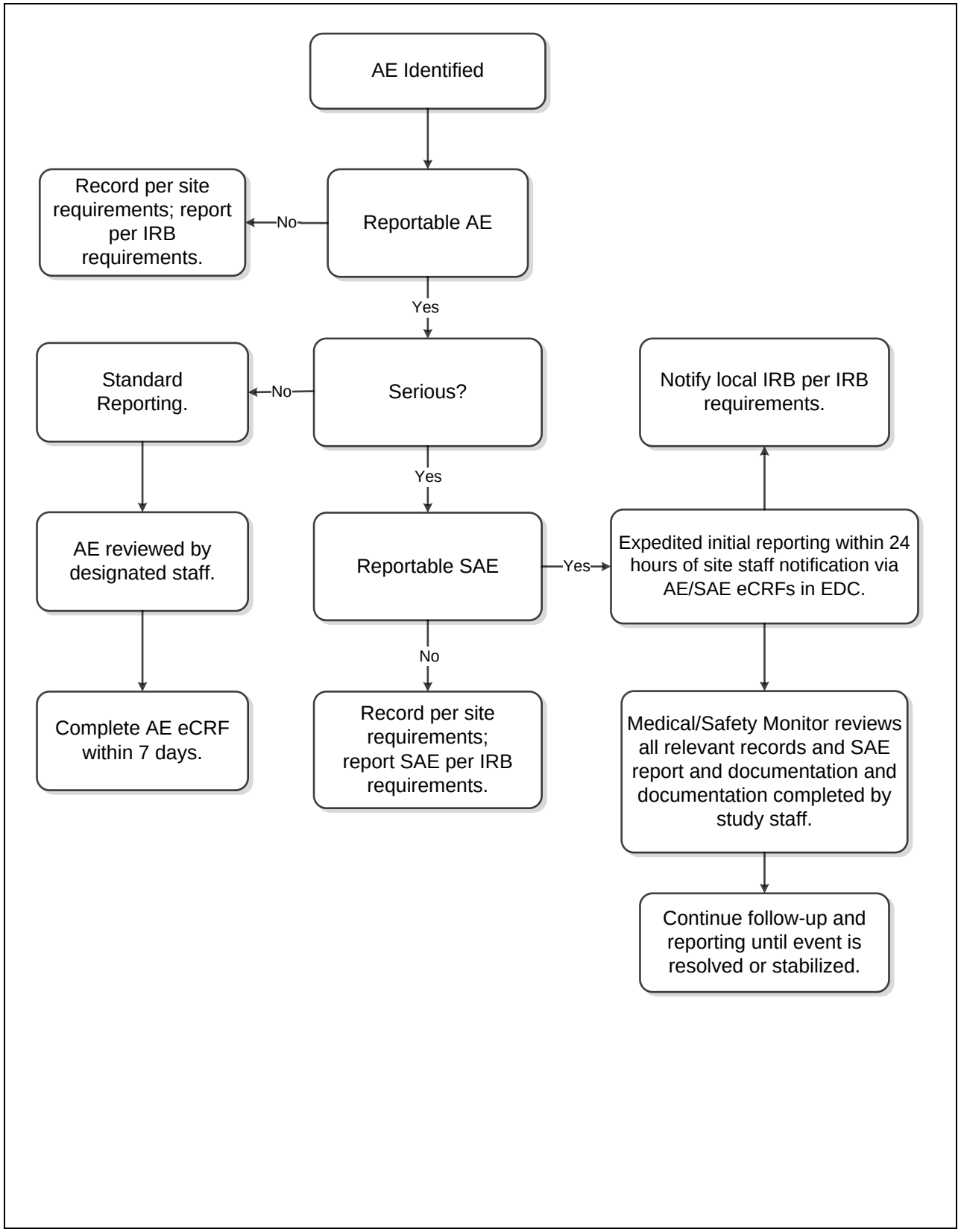
Sponsor's Role in Safety Management Procedures of AEs/SAEs: A NIDA-assigned Medical Monitor is responsible for reviewing all SAE reports. All reported SAEs will generate an e-mail notification to the Medical Monitor. All SAEs will be reviewed by the Medical Monitor in the study's data capture system and, if needed, additional information will be requested. The medical monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA assigned Medical Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the medical monitor in writing for review by the sponsor and DSMB. Subsequent review by the Medical Monitor, DSMB, FDA and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor, DSMB and FDA retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Reporting to the Data and Safety Monitoring Board: The DSMB will receive listing of reportable AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Regulatory Reporting for an IND study:

All serious and unexpected suspected adverse reactions are reported by IND sponsor to the FDA in writing within 15 calendar days of notification. Suspected adverse reactions that are unexpected and meet the criteria for death or immediately life-threatening also require notification of the FDA as soon as possible but no later than 7 calendar days of notification of the event, with a follow-up written report within 15 calendar days of notification of the event. The medical monitor will prepare the expedited report (MedWatch Form 3500A or similar) and forward it to the IND sponsor for submission to the FDA and other regulatory authorities. CCC will distribute copies of the expedited report to all participating sites and DSMB. Expedited reports will be placed in the site regulatory files upon receipt. A copy of all expedited reports will be forwarded to the site's local IRB, as applicable.

Participant Withdrawal: The site investigator in consensus with a medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be discontinued from study drug/intervention. The site investigator should consult with the Lead Investigator and/or Medical Monitor as needed. If necessary, a site investigator may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant should be asked to complete an End of Treatment Visit and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or their condition becomes stable.


AE Identified
Reportable AE
No
Record per site requirements; report per IRB requirements.
Yes
Serious?
No
Standard Reporting.
Yes
Reportable SAE
Yes
Expedited initial reporting within 24 hours of site staff notification via AE/SAE eCRFs in EDC.
Notify local IRB per IRB requirements.
AE reviewed by designated staff.
No
Record per site requirements; report SAE per IRB requirements.
Medical/Safety Monitor reviews all relevant records and SAE report and documentation and documentation completed by study staff.
Complete AE eCRF within 7 days.
Continue follow-up and reporting until event is resolved or stabilized.

19.0 APPENDIX B

Data and Safety Monitoring Plan

19.1 Brief Study Overview

The primary objective of this study is to evaluate the impact of N-acetylcysteine (NAC) 1200 mg versus matched placebo (PBO) twice daily, added to contingency management (CM), on cannabis use among treatment-seeking cannabis-dependent adults (ages 18-50). The primary outcome measure will be the odds of negative urine cannabinoid tests during active treatment. Primary analysis will be based on an intent-to-treat evaluation of all participants randomized into the study, with missing urine specimens coded as missing and assumed to be positive. Secondary outcomes include end-of-treatment abstinence and other cannabis-related measures. Details for the definitions and reporting of safety events are found in the protocol (Appendix A).

19.2 Oversight of Clinical Responsibilities

A. Site Principal Investigator

Each participating site's PI 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.

Regarding safety and in accordance with FDA reporting requirements, all Adverse Events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol. The assessment of Adverse Events (medical and/or psychiatric) will commence at the time of participant consent and will continue through 30 days post last active treatment visit.

The occurrence of AEs and Serious Adverse Events (SAEs) will be assessed at each clinic visit during the study. Serious adverse events will be followed until resolved or considered stable, with reporting to the CCC Safety Monitor/Medical Monitor through the follow-up period.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events).

B. Medical Monitor/Safety Monitor

The NIDA Clinical Coordinating Center (CCC) Safety Monitor/Medical Monitor is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed at the time they are reported in the EDC. The Medical Monitor will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed the Safety Monitor/Medical Monitor will discuss the event with the site. Reviews of SAEs will be conducted in the AdvantageEDC data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.
The CCC Safety Monitor/Medical Monitor will in turn report events to the sponsor and regulatory authorities if the event meets the definition of an expedited event. All SAEs that meet expedited reporting based on federal regulations will be reported to the FDA in writing within 15 calendar days of notification of the CCC. If the SAE meets the criteria for death or immediately life-threatening, the CCC will notify the FDA electronically, by phone or by fax as soon as possible but no later than 7 calendar days of notification of the CCC, with a follow-up written report within 15 calendar days of notification of the CCC. The CCC will prepare an expedited report

(MedWatch Form 3500A or similar) for the FDA and copies will be distributed to all site investigators.

Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings.

C. Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. The DSMB will make recommendations to the NIDA as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication detailing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site will be conducted on a regular basis using a combination of NIDA CCC contract monitors and the local RRTC site managers. Investigators will host periodic visits for the NIDA CCC contract monitors and RRTC site managers. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the sites to identify issues and re-train the site as needed to enhance research quality.

Site Visit Reports will be prepared by the NIDA CCC contract monitors following each site visit. These reports will be forwarded to the site Principal Investigator, the study Lead Investigator and NIDA.

E. Management of Risks to Participants

<u>Confidentiality</u>

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations.

<u>Information Meeting Reporting Requirements</u>

The consent form will specifically state the types of information that are required to be reported and the fact that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

<u>Subject Protection</u>

The site medical clinician will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. Adverse events (AEs) and concomitant medications will be assessed and documented at each clinic visit. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration and provided referrals for other treatment or to specialized care for management of the AE. Study personnel will request that the participant complete an End of Treatment Visit to assure safety and to document end-of-medication

outcomes. Participants who discontinue medication will be encouraged to remain in the study for all non-medication procedures.

Pregnancy

Pregnancy is an exclusion criterion for study participation. A positive pregnancy test post-randomization will result in the cessation of study medication. Participants who discontinue medication will be expected to continue with study visits and non-medication study procedures. Pregnancy test results and related outcome information will be collected on a Pregnancy and Outcome CRF. The site staff will follow the participant until an outcome of the pregnancy is known.

Study Specific Risks

Risks to participants include adverse effects from NAC administration and blood drawing. A meta-analysis of studies evaluating long-term oral treatment with NAC for prevention of chronic bronchitis found that NAC was well tolerated, with generally mild, most commonly gastrointestinal adverse effects that did not require treatment interruption (Grandjean et al., 2000). Systemic allergic reactions to NAC have been observed, but only with intravenous administration (Bailey & McGuigan, 1998). Blood drawing risk include mild pain upon needle stick and possible bruising. Fainting could occur. The study interviews and behavior intervention to be administered involve no specific risks or discomforts beyond those of a standard clinical interview/therapy situation, such as feeling upset at the review of one's psychiatric status or fatigue.

19.3 Data Management Procedures

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture system (AdvantageEDC) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

19.4 Data and Statistics Center Responsibilities

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (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) prepare instructions for the use of AdvantageEDC and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, 6) perform data cleaning activities prior to any interim analyses and prior to the final study database lock.

19.5 Data Collection and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in AdvantageEDC, or will be collected via direct entry into the eCRF. In the event that AdvantageEDC is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into AdvantageEDC in accordance with the instructions provided during project-specific training and guidelines established by the DSC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

The investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

19.6 Data Monitoring, Cleaning and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in AdvantageEDC. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in AdvantageEDC on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into AdvantageEDC.

As described above, the CCC will conduct regular visits to sites during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding RRTC (node), the Lead Investigator, the coordinating centers, and NIDA to monitor the sites' progress on the study.

19.7 Data Lock and Transfer

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.