CTN-0031 Ancillary Study (CTN-0031-A): An evaluation of neurocognitive function, oxidative damage, and their association with treatment outcomes in methamphetamine and cocaine abusers

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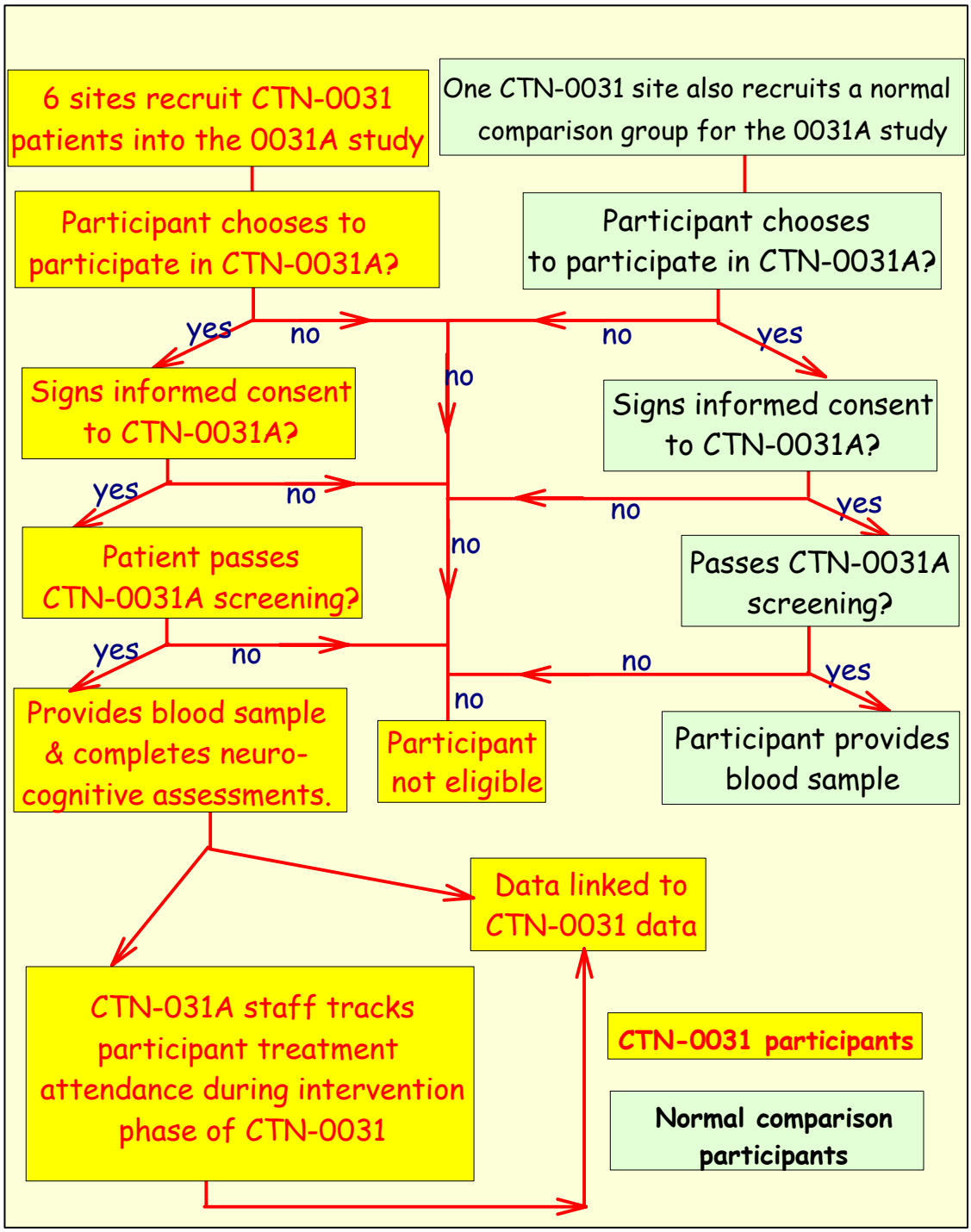
1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AI	Attentional impulsiveness
BIS-11	Barratt Impulsiveness Scale version-11
CAT	catalase
CCC	Clinical Coordinating Center
CDMC	Centralized Data Management Center
CRF	Case report form
CTN	Clinical Trials Network
CTP	Community treatment program
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSMB	Data Safety and Monitoring Board
FrSBe	Frontal Systems Behavior Scale
GCP	Good Clinical Practice
GSH-Px	glutathione peroxide
GT	Iowa Gambling Task
IRB	Institutional review board
ITT	Intent-to-Treat
LI	Lead Investigator
LN	Lead Node
MCI	mild cognitive impairment
MDA	malondialdehyde concentration
METH	Methamphetamine
MI	Motor impulsiveness
NIDA	National Institute on Drug Abuse
NP	Non-planning impulsiveness
OVN	Ohio Valley Node
PI	Principal Investigator
QA	Quality Assurance
RA	Research assistant
RAVLT	Rey Auditory-Verbal Learning Test
ROS	Reactive oxygen species
RT	Reaction time
SOD	superoxide dismutase
STAGE-12	Stimulant Abuser Groups to Engage in 12-step
TAC	Total antioxidant capacity
TAU	Treatment as usual
TBI	Traumatic brain injury
WURS	Wender Utah Rating Scale
WCST	Wisconsin Card Sorting Task

2.0 STUDY SCHEMA

Figure 1: Study Schema



3.0 STUDY SYNOPSIS

STUDY BACKGROUND. Previous research has found significant neurocognitive deficits in both cocaine and methamphetamine (METH) abusers and it has been suggested that these deficits have important implications for treatment outcome in these populations. There is also strong pre-clinical evidence to suggest that the neurotoxic effects of cocaine and METH are the result of oxidative stress, which is an imbalance between free radical production and antioxidant defense. It has therefore been suggested that neurocognitive deficits observed in METH/cocaine-abusing individuals may be the consequence of oxidative stress.

STUDY OBJECTIVES. The primary objective of this study is to replicate the finding that performance on the Stroop color-word interference task is predictive of treatment completion in participants with cocaine use disorders and to extend this finding to participants with METH use disorders. Secondary objectives include evaluating whether: 1. performance on various neurocognitive measures, including the Stroop, Rey Auditory-Verbal Learning Test (RAVLT), Iowa Gambling Task (GT), Wisconsin Card Sorting Task (WCST), the Barratt Impulsiveness Scale version -11 (BIS-11), and the Frontal Systems Behavior Scale (FrSBe) is predictive of treatment attrition and stimulant use outcomes in METH/cocaine abusers; 2. neurocognitive test performance is associated with oxidative damage, a severe consequence of oxidative stress, in METH/cocaine abusers; 3. oxidative damage is predictive of treatment attrition and substance use outcomes in METH/cocaine abusers, 4. oxidative damage in METH/cocaine abusers is significantly greater than that of a normal comparison group and 5. exploratory analyses reveal a significant relationship among oxidative stress, neurocognitive function, and treatment outcomes in METH/cocaine abusers.

STUDY DESIGN. The present protocol is an ancillary study to CTN-0031, a randomized controlled trial of Stimulant Abuser Groups to Engage in 12-Step (STAGE-12). It is estimated that approximately six of the nine sites participating in CTN-0031 will participate in the present study. At the participating sites, participants who are randomized into CTN-0031 will be eligible to be screened for the present study and, if eligible, will complete a research visit in which neurocognitive testing is performed and a blood sample is obtained for the assessment of oxidative stress/damage. In addition, the CTN-0031-A staff will use clinic records to record the participant's treatment attendance during the eight-week intervention phase of CTN-0031. The substance use data collected for CTN-0031, as well as other data (e.g., sample characteristics, etc.), will be used in analyses for the present study. A blood sample for the assessment of oxidative stress/damage will be obtained from approximately 30 normal comparison participants from a single site.

STUDY POPULATION. The METH/cocaine abusing sample for this study is a sample of convenience and, thus, the final sample size will be determined to some degree by the participant flow at the CTN-0031 study sites. Each of the CTN-0031 study sites has a target enrollment of 40-50 participants. It is estimated that approximately 27 participants per site from 6 of the CTN-0031 sites will participate in the present study, yielding an approximate total sample size of 164. Inclusion criteria include (1) meeting DSM-IV criteria for abuse or dependence for METH and/or cocaine, and (2) endorsing METH or cocaine as the primary drug of choice. Exclusion criteria include having a seizure disorder or having a history of stroke. The normal comparison group will be comprised of approximately 30 individuals who currently screen negative for depression, anxiety, and ADHD, who do not meet current or lifetime history of DSM-IV criteria for substance abuse or dependence (except nicotine dependence and/or a history of alcohol abuse), have a negative urine screen, and screen negative for a history of traumatic brain injury, HIV, seizure disorder, and stroke.

ASSESSMENTS. The neurocognitive measures included in the study each yield more than a single test result. While exploratory analyses will be conducted for many of these tests, the following test results will be used to test the primary and secondary study hypotheses: the derived interference reaction time (RT) from the Stroop, the interference recall score from the RAVLT, number of advantageous vs. disadvantageous cards from the GT, the number of perseverative errors from the WCST, and the total scores from the BIS-11 and FrSBe. The measures of oxidative damage that will be used to test the secondary hypotheses include tail length from the comet assay, and malondialdehyde concentration (MDA) from the malondialdehyde assay. For the analyses testing hypotheses related to treatment completion, the treatment attendance data will be used to classify participants as treatment completers or non-completers. For the analyses related to stimulant use, self-reported days of stimulant use will be utilized.

ANALYSIS. The analysis of the single primary and multiple secondary measures will largely utilize logistic regression. Statistical tests will be two-sided at a 5% level alpha Type I error rate.

4.0 BACKGROUND AND RATIONALE

4.1 Overview

Both pre-clinical and clinical research suggests that repeated use of drugs of abuse result in significant brain alterations (Baer and Volkow, 2006) and multiple studies have found impaired neurocognitive functioning in methamphetamine (METH; Salo et al., 2002; Simon et al., 2002; Hoffman et al., 2006; Gonzalez et al., 2007; Salo et al., 2007) and cocaine abusers (Jovanovski et al., 2005; Verdejo-Garcia et al., 2007) relative to normal control participants. It has been suggested that the brain changes and neurocognitive impairments associated with stimulant abuse are likely to have important treatment implications (Kalechstein et al. 2003; Yücel et al., 2007). Indeed, recent studies have revealed that poorer performance on neurocognitive measures is predictive of treatment attrition in cocaine dependent individuals (Aharonovich et al., 2006; Streeter et al., 2007), and that brain imaging assessments are correlated with performance on neurocognitive measures (Volkow et al., 2001, Salo et al., 2007) and are predictive of relapse in METH abusers (Paulus et al., 2005).

The mechanisms involved in the neurotoxic effects of METH and cocaine have received increasing attention in the past decade. There is strong pre-clinical evidence to suggest that the neurotoxic effects of METH result from the damage caused by oxidative stress, which is an imbalance between free radical production and antioxidant defense (Yamamoto & Bankson, 2005; Tata & Yamamoto, 2007, see section 4.3 for details). There is also compelling evidence that the neurotoxic effects of cocaine involve oxidative stress (Poon et al., 2007). Outside of the substance abuse field, there is a substantial amount of research indicating that oxidative stress plays a critical role in neurodegenerative diseases such as Alzheimer's (Mariani et al., 2005), and Parkinson's (Hung et al., 2007) disease; the consequence of severe oxidative stress, oxidative damage, is of particular interest in this regard. Consequently, a significant amount of resources have been devoted to identifying compounds to decrease oxidative stress/damage (Tan et al., 2003; Rodrigo et al., 2007). Should it be demonstrated that METH and cocaine abusers evidence oxidative stress/damage then they, too, would be candidates for effective compounds identified; these compounds could specifically be used to protect against further neuronal damage.

The present study, which is an add-on to the CTN-0031: "Stimulant Abuser Groups to Engage in 12-Step" protocol, will evaluate the relationships among neurocognitive functioning, oxidative damage, and substance abuse treatment outcomes, including treatment attrition and substance use, in METH/cocaine abusers. The present study will also assess oxidative damage in a normal comparison group to allow a comparison of the oxidative damage level in the METH/cocaine abusers to that of a non-substance-abusing comparison group. It should be noted that neurocognitive testing will not be conducted with the normal comparison group since past research has repeatedly demonstrated that METH/cocaine abusers have neurocognitive deficits relative to normal controls and it is not the goal of the present study to demonstrate these group differences once again. Rather, the goal of the present study is to explore the potential impact that neurocognitive deficits have on substance abuse treatment outcomes and to explore the relationship among oxidative damage level, neurocognitive deficits, and treatment outcome in METH/Cocaine abusers. METH/cocaine abusers randomized into the CTN-0031 study will be recruited for the present study; eligible participants will complete neurocognitive assessments and provide a blood sample for the assessment of oxidative stress/damage. CTN-0031-A staff will use clinic records to record the participant's treatment attendance during the eight-week intervention phase of CTN-0031. The substance use, as well as other data (e.g., sample characteristics, etc.) collected for CTN-0031, will be used in analyses for the present study.

4.2 Rationale for specific neurocognitive measures

4.2.1 The Comalli-Kaplan version of the Stroop Color Word Task

Disinhibition is an aspect of impulsivity that describes the inability to suppress a prepotent, or habitual, response when the behavior is no longer advantageous to the individual. Clinically, disinhibition may manifest when addicted individuals continue to think about using substances (perceptual impulsiveness) or when they actually abuse substances after being triggered by cues (motor impulsiveness) (Adinoff et al., in press). Given the inherent difficulty in measuring internal thought processes, research has focused on behavioral inhibition. A number of cognitive measures have been utilized to measure response inhibition, including the Stroop task (Stroop, 1935). Though numerous versions of the Stroop task are available (for review, see MacLeod, 1991), the test has generally been characterized as assessing selective attention and cognitive flexibility (Strauss et al., 2006) and response inhibition (Archibald et al., 1999; Strauss et al., 2006). Of primary importance is the *interference trial*, or the time it takes the participant to read colored words printed in incongruently colored inks. In the original Stroop task, the participant is required to name the color of the ink in which a word is printed while inhibiting the overlearned response of reading the word (e.g., the word ‘‘red’’ might be printed in blue ink). Stroop found that normal people can read color words printed in colored ink as quickly as when the words were presented in black ink. However, they take significantly longer to name the ink color of incongruently colored words (e.g., the participant must state, “green” for the word blue printed in green ink). The phenomenon of decreased color-naming speed has become known as the “color-word interference effect.”

Abnormally slowed performance on the interference trial has been interpreted to reflect difficulty with response inhibition and has been associated with frontal lobe dysfunction (Milner 1964; Golden 1976; Mesulam 1985). Increased Stroop interference has been demonstrated in patients addicted to METH (Simon et al., 2000 Salo et al. 2002; Salo et al., 2007) and cocaine (Strickland et al., 1993; Roselli et al., 2001; Jovanovski et al., 2005; Hester et al., 2006), although not all investigators have observed a difference (Goldstein et al., 2001, Bolla et al., 2004). Of particular relevance to our proposed study is the observation by Streeter et al. (2007) that performance on the Comalli-Kaplan version of the Stroop task predicted treatment attrition in a cocaine treatment trial. Specifically, Streeter et al. (2007) found that, compared to treatment completers, non-completers took significantly more time to complete the interference trial; these results were unchanged when age, past alcohol abuse/dependence, and Hamilton Depression Score were included as covariates in the statistical model. In addition, drug use at the time of testing, as measured by urine toxicology results, was not significantly associated with Stroop performance.

4.2.2 The Rey Auditory Verbal Learning Test (RAVLT)

As noted in section 4.1., it has been suggested that the neurocognitive impairments associated with stimulant abuse are likely to have important treatment implications (Kalechstein et al., 2003; Yücel et al., 2007). Currently, there are no FDA approved medications for the treatment of stimulant abuse/dependence and, thus, psychosocial approaches are the gold standard treatment. Since psychosocial approaches depend upon the ability of the patient to learn and remember new information, frequently given in verbal form during the course of group or individual sessions, it is predicted that individuals who have difficulty with learning and remembering verbal information will have more difficulty benefiting from treatment and, thus, will have worse treatment outcomes. The RAVLT is a widely-used neuropsychological measure of verbal learning and memory. Prior research has shown that performance on the RAVLT, relative to normal controls, is impaired in METH dependent patients (Hoffman et al., 2006) and is significantly correlated with striatal dopamine transporters in METH dependent patients (Volkow et al., 2001). Impaired performance on the RAVLT has also been reported for cocaine abusers, with those self-reporting more cocaine in the past having poorer performance on the RAVLT (Bolla et al., 2000). Finally, research in Alzheimer’s patients has found that

baseline RAVLT performance predicted the ability to benefit from a cognitive/social group intervention, with those having more impaired RAVLT performance being significantly less likely to improve (Haddad and Nussbaum, 1989).

4.2.3 The Iowa Gambling Task

Two broad categories of neurocognitive functioning are often considered in the assessment of decision-making, particularly in substance use disorders. The first process involves risk and delay. This process requires that the value of a reward or punishment, the time it takes before the selected outcome is experienced, and/or the likelihood of the outcome occurring must be weighted prior to making a decision (see discussion in Monterosso et al., 2001). The selection of smaller, immediate rewards with postponed but heightened punishments instead of early losses accompanied by larger, deferred rewards has been referred to as a "myopia for the future" (Bechara et al., 2000). One of the identifying features of addiction is the persistence of addictive behaviors despite the likelihood of seriously negative long-term effects. Alternately, a riskier choice may reflect the discounting of risk: punishments carry less weight than rewards (Kahneman et al., 1979; Cloninger, 1987). Two common tests of delay and risk are the Delayed Discounting Procedure (DDP; Bickel et al. 1999) and the Gambling Task (GT; Bechara et al., 1998). In the GT, subjects must choose between decks of cards offering high payments with occasional high penalties or decks offering low payments but more frequent lower penalties; the optimal, long-term strategy is the low pay/low penalty deck. Research has found that, compared to normal controls, both cocaine (Verdejo-Garcia et al., 2007) and methamphetamine (Gonzalez et al., 2007) abusers perform significantly worse than normal controls on the GT.

4.2.4 The Wisconsin Card Sorting Task

Response reversal, or set shifting, is a major process involved in decision-making. Response reversal is required when response contingencies, such as the amount of reward, direction of reward (win or lose), or the time it takes to obtain a reward, are altered. When a response that previously produced a positive outcome suddenly becomes aversive, a reversal in cognitive and behavioral strategies is required to suppress the course of action that is now no longer appropriate. Thus, response reversal considers the positive and negative attributes of a potential response, followed by a decision to either maintain or change the present direction of responding. In the addicted individual, impaired response reversal becomes evident during the development of the addiction. Initially, a drug user will experience the substance as highly rewarding and without an associated downside. As drug use becomes progressively less pleasurable and accompanied by increasingly negative consequences, an intact response reversal process should dictate a change in behavior. The drug-addicted individual, however, will persist in using drugs. Thus, a previously rewarded behavior is not adaptively reversed following a change in contingencies.

The Wisconsin Card Sorting Test (WCST; Heaton et al., 2001, Fisk et al., 2004) is a traditional test of response reversal. The WCST assesses this type of flexibility as it requires the examinee to shift his or her behavior in response to environmental feedback (i.e., set shifting). Impaired performance on the WCST has been reported in participants with both METH (Kim et al., 2005) and cocaine (Roselli et al., 1996, Ardila et al., 1991, Beatty et al., 1995, Bechara et al., 2001, Roselli et al., 2001) dependence, although not all investigators have observed differences (Hoff et al., 1996, Gillen et al., 1998). Impaired performances have also been demonstrated in individuals susceptible to executive functioning impairments, such as those with autism (Ozonoff, 1995; Minshew et al., 2002), multiple sclerosis (Arnett et al., 1994, Beatty et al., 1996), Parkinson's disease (Paolo et al., 1995; Green et al., 2002), obsessive-compulsive disorder (Lacerda et al., 2003), Korsakoff's syndrome (Leng et al., 1988; Brokate et al., 2003), attention deficit hyperactivity disorder (impulsive type; Gansler et al., 1998) and alcohol abuse (Adams et al., 1995; Brokate et al., 2003). The WCST has strong evidence of predictive validity in non-substance use disorders, correlating well with

patients' functional ability at the time of discharge from hospitalization (Greve et al., 1999), and their ability to manage independently (Heinrichs, 1990) or to return to gainful employment (Kibby et al., 1998; Nybo et al., 1999).

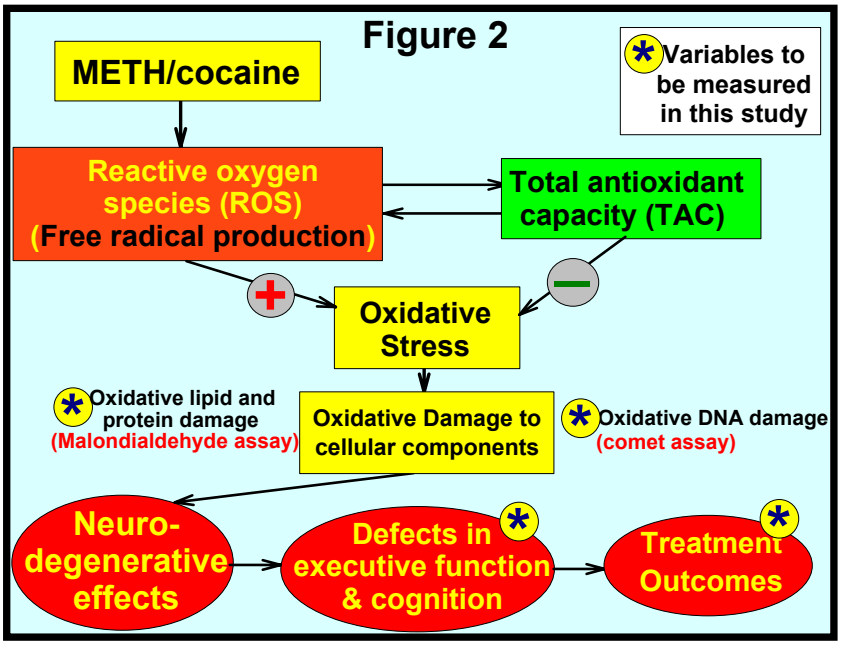
4.2.5 Barratt Impulsiveness Scale version-11 (BIS-11)

The BIS-11 is designed to assess the personality/behavioral construct of impulsiveness and has been used extensively in psychological, sociological, and educational research. The BIS-11 assesses impulsiveness in three domains: Attentional impulsiveness (AI), Motor impulsiveness (MI), and Non-planning impulsiveness (NP). AI evaluates actions precipitated by lack of attention; it can be exacerbated in anxious situations. MI evaluates hyperactivity due to need of movement, which is exacerbated by stress. NP evaluates attitudes and conclusions precipitated by lack of reflection. BIS-11 scores are significantly correlated with self reported daily use of cocaine and cocaine withdrawal symptoms (Moeller et al., 2001). Patients with cocaine addiction demonstrate increased scores on the BIS-11 relative to controls (Patkar et al., 2004), even in the absence of antisocial personality disorder and after controlling for aggression (Moeller et al., 2002). Participants with high BIS-11 are also more likely to relapse to cocaine use and leave treatment (Moeller et al., 2001; Moeller et al., 2002).

4.2.6 Frontal Systems Behavior Scale (FrSBe)

Past research indicates that traditional neurocognitive assessments can fail to detect deficits in individuals with frontal lobe damage whose behavior in natural settings is clearly impaired (Grace and Malloy, 2001). The FrSBe is a brief, valid, and reliable assessment of three areas of functioning associated with the pre-frontal cortex: apathy, disinhibition, and executive dysfunction (Grace and Malloy, 2001). The FrSBe scores of both METH and cocaine addicted individuals, relative to normal comparison participants, suggest that they evidence significant behavioral problems associated with the areas of the pre-frontal cortex assessed by the FrSBe (Verdejo-Garcia et al., 2006). Since the FrSBe is a 10-minute self-administered assessment, it is an instrument that could be utilized by substance abuse community treatment programs should it be found to be predictive of treatment attrition and/or substance use outcomes.

4.3 Rationale for oxidative stress/damage measures



As noted in section 4.1, there is substantial preclinical evidence to suggest that oxidative stress plays an important role in the neurotoxic effects of METH/cocaine. These data suggest that administration of METH/cocaine results in an increased formation of reactive oxygen species (ROS) which mediate the drug's toxicity to dopamine and/or serotonin nerve terminals (Yamamoto et al., 2005; Cadet et al., 2007; Poon et al., 2007). Under normal physiological conditions, a group of antioxidant enzymes and antioxidants (e.g., glutathione peroxide (GSH-Px), superoxide dismutase (SOD), catalase (CAT), ascorbic acid), collectively known as total antioxidant capacity (TAC), in the body are able to detoxify ROS. However,

in certain diseases, such as Alzheimer's or Parkinson's disease, or after the abuse of drugs such as METH or cocaine, an increased release of ROS through dysfunction of the mitochondrial oxidative phosphorylation results in "oxidative stress." Under these conditions, the ROS released are not entirely detoxified but react with cellular proteins, lipids and DNA bases to form oxidized products with impaired functionality. The present study will primarily focus on the consequence of severe oxidative stress, oxidative damage, in which there is damage to cellular components. Specifically, oxidative damage will be assessed using the malondialdehyde assay, which measures oxidative lipid and protein damage (Nielson et al., 1997), and the comet assay which assesses DNA damage caused by oxidative stress (Migliore et al., 2005; Frenzilli et al, 2006). In addition, measures of oxidative stress will be obtained through assessments of antioxidant parameters, including SOD, GSH-Px, CAT and TAC. For individuals with oxidative damage, these parameters will be abnormally low while for individuals with oxidative stress that has not yet reached the severity of oxidative damage, these parameters will be abnormally high. The oxidative stress measures will be evaluated in exploratory analyses. All assessments can be completed with approximately 23 ml of blood.

While measures of oxidative damage might appear to be too global of an assessment to be associated with specific behavioral outcomes, such as neurocognitive functioning, a study by Migliore et al. (2005) suggests otherwise. Specifically, Migliore et al. (2005) used the comet assay to assess oxidative DNA damage in patients with Alzheimer's disease (AD), patients with mild cognitive impairment (MCI), and normal controls. The results of the study revealed significantly greater oxidative DNA damage in both the AD and MCI groups compared to normal controls (Migliore et al., 2005). In addition, it has been suggested that the comet assay might be suitable for assessing the neurotoxicity and genotoxicity in drugs of abuse (Frenzilli et al, 2006). The hypothesized relationships among METH/Cocaine use, ROS, TAC, oxidative damage, neurocognitive functioning and substance abuse treatment outcomes are delineated in Figure 2.

It should be noted that since the present study is an add-on, the extent to which we can assess for potential confounding factors that could impact oxidative stress/damage, such as diet, exercise, and environment, is limited. Hence, should we find the hypothesized greater oxidative damage in the METH/cocaine abusers, relative to the normal comparison participants, we will not be able to conclude that the increased stress/damage was due to METH/cocaine abuse. Still, the finding of greater oxidative stress/damage in METH/cocaine abusers, relative to normal comparison participants, would be of interest in terms of the potential treatment needs of METH/cocaine abusers. Of even greater interest would be findings indicating significant relationships between oxidative stress/damage and neurocognitive functioning and/or treatment outcomes in METH/cocaine abusers, regardless of the causes of the oxidative stress/damage. Should these hypothesized significant relationships be found, future research, in which potential confounds are evaluated, could be conducted to delineate the factors contributing to oxidative stress/damage in METH/cocaine abusers.

5.0 STUDY OBJECTIVES

5.1 Primary Objective

1. To replicate the finding that performance on the Stroop color-word interference task is predictive of treatment attrition in cocaine abusers and to extend this finding to METH abusers.

5.2 Secondary Objectives

1. To evaluate whether performance on the RAVLT, GT, WCST, BIS-11, and FrSBE is predictive of treatment attrition in METH/cocaine abusers.

2. To evaluate whether performance on the Stroop, RAVLT, GT, WCST, BIS-11, and FrSBE is predictive of stimulant use outcomes in METH/cocaine abusers.

3. To evaluate whether performance on the Stroop, RAVLT, GT, WCST, BIS-11, and FrSBE is associated with oxidative damage level in METH/cocaine abusers.

4. To evaluate whether oxidative damage level is predictive of treatment attrition and stimulant use outcomes in METH/cocaine abusers.

5. To evaluate whether oxidative damage level in METH/cocaine abusers is significantly higher that that of a normal comparison group.

6. To conduct exploratory analyses of the relationship among oxidative stress, neurocognitive functioning, and treatment outcomes in METH/cocaine abusers as well as to compare oxidative stress levels in METH/cocaine abusers and normal comparison participants.

6.0 STUDY DESIGN

6.1 Overview of Study Design

The present protocol is an ancillary study to CTN-0031, a randomized controlled trial of Stimulant Abuser Groups to Engage in 12-Step (STAGE-12). It is estimated that approximately six of the nine sites participating in CTN-0031 will participate in the present study. At the participating sites, participants who are randomized into CTN-0031 will be eligible to be screened for the present study. Within two weeks of randomization into CTN-0031, eligible participants will be scheduled to complete a research visit in which neurocognitive testing is performed and a blood sample is obtained for the assessment of oxidative stress/damage. In addition, the CTN-0031-A staff will use clinic records to record the participant's treatment attendance during the eight-week intervention phase of CTN-0031. The substance use, as well as other data (e.g., sample characteristics, etc.) collected for CTN-0031 will be used in analyses for the present study. A blood sample for the assessment of oxidative stress/damage will be obtained from approximately 30 normal comparison participants recruited at a single site.

6.2 Site and Participant Selection – METH/Cocaine Abusers

6.2.1 Number of Sites and Participants – METH/Cocaine Abusers

The sample for this study is a sample of convenience and, thus, the final sample size will be determined to some degree by the participant flow at the CTN-0031 study sites. Each of the CTN-0031 study sites has a target enrollment of 40-50 participants. It is estimated that approximately 27 participants per site from 6 of the CTN-0031 sites will participate in the present study, yielding a total sample size of approximately 164 for the METH/Cocaine group. As delineated in section 9.3, this sample size will provide more than 80% power for the primary analysis.

6.2.2 Site Selection – METH/Cocaine Abusers

The sites eligible to participate in the current study are the approximately nine sites that will participate in the CTN-0031 study. Of the nine sites, the goal is to recruit approximately six sites for participation in the present study. If more than six sites express an interest in participating, priority will be given to sites that treat a substantial number of individuals with METH abuse/dependence and/or sites that have a strong track record in completing clinical trials.

6.2.3 Participant Selection – METH/Cocaine Abusers

6.2.3.1 Inclusion Criteria

Potential participants must:
1. be randomized into the CTN-0031 (STAGE-12) trial
2. meet DSM-IV criteria for current (as defined in CTN-0031) abuse or dependence for METH and/or cocaine
3. endorse METH and/or cocaine as the primary drug of choice
4. be willing to sign appropriate documentation to allow access to CTN-0031 study records
5. be able to understand the study, and having understood, provide written informed consent in English
6. be able to correctly distinguish the colored stimuli on the Stoop task.

6.2.3.2 Exclusion Criteria
Potential participants must not:

1. have a history of stroke
2. have a history of a seizure disorder; individuals who have experienced only isolated seizures (e.g., febrile, withdrawal, acute stimulant intoxication, etc.) are eligible

6.2.3.3 Rationale for Eligibility Criteria
The rationale for each inclusion and exclusion criterion is provided in Table 1.

Table 1: Rationale for Study Eligibility Criteria– METH/Cocaine Abusers

Criterion#	Criterion Description	Criterion Rationale
I1	Randomized into CTN-0031	The present study is an add-on to CTN-0031
I2	Meet DSM-IV criteria for abuse or dependence on METH/cocaine	Definition of Study Sample
I3	Endorse METH/cocaine as primary drug of choice	
I4	Grant permission to access CTN-0031 records	The present study is an add-on to CTN-0031 and requires access to CTN-0031 study data
I5	Understand study and give consent	GCP Requirement
I6	Distinguish the colored stimuli on the Stoop task	Required for a valid Stroop assessment
E1	History of seizure disorder	Is fairly rare in the population of interest and could significantly impact neurocognitive function and/or oxidative stress/damage level, thus skewing the results
E2	History of stroke	

6.3 Site and Participant Selection – Normal Comparison Participants

6.3.1 Number of Sites and Participants – Normal Comparison Participants
The assessments of oxidative damage obtained from the comet and malondialdehyde assays are associated with a significant amount of inter-lab variability and there are currently no normative standards for these tests. Consequently, a blood sample will be obtained from a small number of normal comparison participants to provide a comparison point for the oxidative stress/damage assessments obtained for the METH/Cocaine group. It should be noted that a large normal comparison group that is perfectly matched to the

METH/Cocaine group is beyond the resources available for the present study. The goal, then, is to recruit a small normal comparison group and to include the factors that have been found to be related to oxidative damage, namely gender, smoking status, and age (Migliore et al., 2005), as covariates in the statistical analyses comparing the METH/Cocaine and normal comparison groups. One method for defining sample size states that ten participants need to be enrolled for each covariate to be included in the statistical model (Harrel, 2001). Based on this method, and our need to include three covariates (i.e., gender, smoking status, and age) in the statistical model, approximately 30 normal comparison participants will be enrolled in the present study. The normal comparison group will include both men and women, individuals who smoke and non-smokers, and will be approximately the same age as the METH/Cocaine group. For efficiency, the approximately 30 normal comparison participants will be recruited at the Maryhaven site, located in Columbus, Ohio. This site was selected based on its outstanding track record in recruiting a variety of participant populations, including non-substance abusing populations, in an efficient and cost-effective manner.

The proposed sample size for the normal comparison group (N=30) raises the question of whether a Type II error is likely to occur in the analyses comparing the METH/Cocaine and normal comparison groups. To address this issue, we conducted a power analysis, which revealed that enrolling 30 normal comparison participants will provide 80% power to detect a moderate effect size (D=.42; Cohen, 1988) at a significance level of .05 (two-sided). It should be noted that this effect size (D=.42) is much smaller than that found by Migliore et al. (2005) in comparing MCI (n=15) and normal control (n=15) groups on tail length from the comet assay (D=1.75). Hence, our proposed sample sizes should be sufficient to detect differences in oxidative damage between the METH/Cocaine and normal comparison groups.

6.3.2 Participant Selection – Normal Comparison Participants

6.3.2.1 Inclusion Criteria

Potential normal comparison participants must:

1. be 18 years of age or older
2. be in the age range set for the normal comparison participants (see section 8.2)
3. be able to understand the study, and having understood, provide written informed consent in English

6.3.2.2 Exclusion Criteria

Potential normal comparison participants must not:

1. have a history of stroke
2. have a history of a seizure disorder; individuals who have experienced only isolated seizures (e.g., febrile, etc.) are eligible
3. meet DSM-IV criteria for dependence (either current or lifetime) for any psychoactive substance other than nicotine or for abuse (both current and lifetime) for any psychoactive substance other than nicotine or for alcohol for which a life-time history of abuse is allowed
4. have a positive urine toxicology screen
5. screen positive for Major Depressive Syndrome, other Depressive Syndrome, Panic Syndrome, or other Anxiety Syndrome as assessed by the Patient Health Questionnaire
6. meet criteria for ADHD based on the Wender Utah Rating Scale
7. have HIV/AIDS based on self-report
8. have a history of an injury in which consciousness was lost for more than 30 minutes

6.4 Definition of Treatment Completers – METH/Cocaine Abusers

Several study objectives, including the primary objective, focus on the ability of neurocognitive measures and/or oxidative damage level to predict treatment completion. Previous studies finding that neurocognitive measure performance is predictive of treatment completion were, like the present study, add-on studies to clinical trials (Aharonovich et al., 2006; Streeter et al., 2007). In Aharonovich et al. (2006), participants were enrolled in placebo-controlled pharmacotherapy trials in which all participants received cognitive behavioral therapy (CBT); treatment completion was defined as completing the 12-week treatment phase without missing two or more consecutive weeks of treatment.

In Streeter et al. (2007), participants were enrolled in placebo-controlled pharmacotherapy trials in which all participants received CBT and, for the add-on study, were scheduled to complete neurocognitive testing at baseline and after the final follow-up visit for the clinical trial in which they were enrolled. Completing the follow-up neurocognitive testing required successful completion of the clinical trial, defined as not missing treatment for two or more consecutive weeks. A completer was defined as a participant who completed the follow-up neurocognitive testing session.

The present study is an add-on to the CTN-0031 trial, in which participants are scheduled to complete a 5-8 week intervention period. The CTN-0031-A staff will use clinic records to record each participant's treatment attendance during the first 8 weeks of CTN-0031, which will provide information for each participant's full intervention period. The outcome that will be used to test hypotheses related to treatment attendance is whether or not the participant completed treatment. For the present study, completers are those who attend the first 5 weeks of treatment without missing two or more consecutive weeks; a participant who attends the first 4 weeks of treatment and misses the fifth week will be considered a treatment completer if s/he attends treatment during the sixth week. The treatment attendance data obtained by the CTN-0031-A staff will be used to classify each participant as a completer or non-completer.

6.5 Substance Use Data

Several secondary objectives focus on the ability of neurocognitive measures and/or oxidative damage level to predict stimulant use reduction; the self-report substance use data collected for the CTN-0031 study will be utilized for these analyses. Specifically, the CTN-0031 study assesses stimulant use via the Substance Use Calendar, a self-report assessment of the participant's use of substances for each day of the study, using the Timeline Follow-Back procedure (Sobell and Sobell, 1992; Fals-Stewart, 2000). The outcome of interest will be the percent of days of stimulant use as measured by self-report. In addition, the present trial may include exploratory analyses to evaluate the ability of neurocognitive measures and/or oxidative damage level to predict reductions in the use of non-stimulant drugs of abuse as measured by self-report and reductions in positive urine drug screens for both stimulants and non-stimulant drugs of abuse; all of the substance use data for these analyses will come from the CTN-0031 dataset.

6.6 Predictor Measures

6.6.1 Primary Predictor Measure – Interference reaction time (RT) on the Stroop Color Word Task

The Stroop Color Word Task, considered to be one of the most reliable psychometric tests of cognitive control, has been a standard in neuropsychological assessment since the Stroop effect was reported in 1935.

The task addresses key cognitive processes associated with resistance to interference from outside stimuli, cognitive control, and goal-oriented behavior. It is also a test of executive functioning, requiring the inhibition of an over-learned concept in favor of a novel concept. The Comalli-Kaplan version, described in 1962, utilizes timed trials, in which three stimulus cards are presented in a standard order. Card 1 presents blocks of color and asks the participant to name the color of each block. Card 2 involves asking the participant to read text of color names that are printed in black and white. Card 3 is an interference task in which the color names are printed in incongruently-colored ink, and the participant is asked to name the ink color. There is a maximum time limit for each trial. Errors that are spontaneously self-corrected are counted as correct responses. Study staff will record the time required and the number of errors for each trial, yielding three summary scores and a derived interference score. The derived interference reaction time (RT) will be utilized as the primary predictor measure. Ideally, the Stroop administrations will be audiotaped; this will allow assessors to double-check their work to ensure correct coding.

6.6.2 Secondary Predictor Measures

6.6.2.1 RAVLT

The RAVLT, described by Rey in 1941, is a commonly used neuropsychological measure that assesses verbal learning and memory, including proactive inhibition, retention, encoding versus retrieval, and subjective organization. The measure has evolved over the years, and several variations of the test have emerged. The standard RAVLT format starts with a list of 15 words (list A), which an examiner reads aloud at the rate of one per second. The patient's task is to repeat all the words he or she can remember, in any order. This procedure is carried out a total of five times (i.e., Trials I-V). Then the examiner presents a second list of 15 words (list B), allowing the patient only one attempt at recall, this is referred to as the Interference trial. Immediately following this, the patient is asked to remember as many words as possible from the first list, which is referred to as Trial VI. The results yielded by the RAVLT include learning, which is the total number of words recalled during trials I-V, interference recall, which is the number of words recalled from the Interference Trial, and immediate recall, which is the number of words recalled during Trial VI. Interference recall has been found to be significantly worse in METH dependent patients, compared to normal controls (Hoffman et al., 2006), to be significantly correlated with striatal dopamine transporters in METH dependent patients (Volkow et al., 2001) and to be significantly worse in AD patients who did not improve from a social/cognitive group intervention, compared to AD patients who did improve (Haddad and Nussbaum, 1989). Consequently the interference recall score will be used as the RAVLT secondary predictor measure; the other measures yielded by the RAVLT (i.e., learning and immediate recall) will be evaluated in exploratory analyses. Ideally, the RAVLT administrations will be audiotaped; this will allow assessors to double-check their work to ensure correct coding.

6.6.2.2 Gambling Task

The Iowa Gambling Task is a gambling exercise that simulates real-life decision making. Developed by Bechara and colleagues in 1994 and computerized in 2001, the task probes for deficits in judgment and decision-making. Four decks of cards are displayed, labeled “A”, “B”, “C”, and “D.” Participants are instructed to click the mouse in order to pick a card, and then proceed in a way that will allow them to obtain the highest overall “winnings.” Each card carries an immediate reward, but some cards also carry a penalty. Two decks pay higher amounts, but come with higher penalties, leading to an overall loss (disadvantageous decks). The other two decks pay less, but have lower penalties, leading to an overall gain (advantageous decks). The amount of reward and penalty, along with the net gain or loss, is displayed on the screen for the participant. In all, participants are allowed to select 100 cards, across 5 blocks of 20 trials. Performance will be measured by the number of cards selected from the advantageous vs. the disadvantageous decks (Verdejo-Garcia et al., 2007).

6.6.2.3 Wisconsin Card Sorting Task (WCST)
In the electronic version of this test, participants are positioned in front of a computer and instructed to match 128 response cards, one at a time, to four stimulus cards by clicking a mouse. The cards can be sorted along three dimensions (color, form, and number), and participants must utilize feedback following each selection to modify their responses and successfully sort the cards. The sorting principle changes after ten consecutive correct responses, allowing for assessment of perseverative responding and cognitive flexibility (i.e., the participant's ability to generate alternative strategies). Measures yielded by the WCST include the number of perseverative errors and scores for perseverative responses, failure to maintain set, and categories completed. The number of perseverative errors will be used as the WCST secondary predictor measure; the other measures yielded by the WCST (i.e., perseverative responses, failure to maintain set, and categories completed) will be evaluated in exploratory analyses.

6.6.2.4 BIS-11
The BIS-11 consists of 30 self-report items, with responses in a four-point Likert-type scale ranging from "Rarely/Never" to "Almost Always/Always" and comprises three domains: Attentional impulsiveness (AI), Motor impulsiveness (MI), and Non-planning impulsiveness (NP); these three domains are summed to yield a total score. The total score will be utilized as the BIS-11 secondary predictor measure while the individual scales (i.e., AI, MI, NP) will be evaluated in exploratory analyses.

6.6.2.5 FrSBe
The FrSBe is written at a 6^{th}-grade reading level and consists of 46 self-report items, with responses in a five-point Likert-type scale. The FrSBe assesses three domains: Apathy (14 items), Disinhibition (15 items), and Executive Dysfunction (17 items); these three domains are summed to yield a total score. The total score will be utilized as the FrSBe secondary predictor measure while the individual scales (i.e., Apathy, Disinhibition, and Executive Dysfunction) will be evaluated in exploratory analyses.

6.6.2.6 Oxidative Damage
The comet assay, also called single cell gel electrophoresis (SCGE), is a sensitive and rapid technique for quantifying and analyzing oxidative DNA damage. Oxidized DNA bases are stained using fluorescent dyes and the resulting image resembles a "comet" with a distinct head and tail. The head is composed of intact DNA, while the tail consists of damaged (single-strand or double-strand breaks) or broken pieces of DNA. Individual cells are embedded in a thin agarose gel on a microscope slide. All cellular proteins are then removed from the cells by lysing. The DNA is then allowed to unwind under alkaline conditions. Following the unwinding, the DNA undergoes electrophoresis, allowing the broken DNA fragments or damaged DNA to migrate away from the nucleus. After staining with a DNA-specific fluorescent dye such as ethidium bromide, the gel is read for fluorescence intensity in head and tail as well as length of head and tail. The extent of DNA liberated from the head of the comet is directly proportional to the amount of DNA damage (Singh et al., 1988). Tail length will be used as a secondary predictor measure while tail fluorescence intensity, will be evaluated in exploratory analyses. The content of malondialdehyde will be analyzed after derivatization with thiobarbituric acid. The resulting adduct will be separated by High Performance Liquid Chromatography (HPLC) and detected by fluorescence at excitation and emission wavelengths of 532 nm and 553 nm. Quantification will be carried out by external calibration curves (Somoza et al., 2005). MDA will be used as a secondary predictor measure.

6.6.2.7 Oxidative Stress

Measures of oxidative stress will be obtained by assessing antioxidant parameters, including SOD, GSH-Px, CAT and TAC. These parameters will be analyzed photometrically using standard test kits. These parameters will be utilized in exploratory analyses as outlined in section 9.4.

6.7 Other Measures

6.7.1 Wender Utah Rating Scale

The Wender Utah Rating Scale (WURS) is a 61-item self-report questionnaire that has shown good validity and reliability in identifying adults with ADHD (Rossini and O'Connor 1995; Stein et al, 1995; McCann et al, 2000). Ward et al (1993) found that 25 of the items were the most useful in discriminating between ADHD and normal comparison participants, with the optimal cut-off score for determining ADHD being 46 or more; in the present study, participants will be regarded as positive for ADHD using this cut-off score.

6.7.2 Patient Health Questionnaire

The Patient Health Questionnaire (PHQ), first reported by Spitzer and colleagues in 1999, is a fully self-administered version of the PRIME-MD. The assessment is designed to assist in the screening and diagnosis of some of the most common psychiatric illnesses, including depression, anxiety, somatoform disorders, alcohol problems, and eating disorders. The authors have provided instructions for customizing the instrument to focus on one or more disorders of interest, and a diagnostic algorithm has been provided for several threshold syndromes that correspond to specific DSM-IV disorders and sub-threshold syndromes in which the criteria encompass fewer symptoms than for any specific DSM-IV disorder. In this study, the investigators have chosen to assess for the PHQ diagnoses of Major Depressive Syndrome, other Depressive Syndrome, Panic Syndrome, and other Anxiety Syndrome. Determination of the presence of these syndromes will be based on the coding rules for the PHQ. Studies have found good agreement between PHQ diagnoses and those of independent mental health professionals. Formal diagnoses will not be utilized in the current study.

6.7.3 Traumatic Brain Injury (TBI)

A structured interview will be utilized by research staff to determine if participants may have experienced a moderate or severe TBI by assessing for the presence of any history of traumatic head or neck injury and any resultant loss of consciousness greater than 30 minutes. Information obtained from the interview will result in a dichotomous indicator as to whether or not the participant is likely to have suffered at least a moderate TBI. The questions for this assessment are adapted with permission from the Ohio State University TBI Identification Method (Corrigan et al., 2007).

6.7.4 Self-report of HIV status

Participant HIV status will be assessed via self-report, evaluated using a subset of four questions from the Multicenter Aids Cohort Study (MACS, Munoz, et al, 1993) Screening Form (http://www.statepi.jhsph.edu/macs/forms.html). Participant HIV status will be scored on a 4-point scale, which will indicate HIV testing history as well as status of any HIV/AIDS infection; specifically, participants will be scored as having a negative test (0), not being tested (1), being HIV positive (2), or being positive for AIDS (3).

7.0 STUDY PROCEDURES – METH/Cocaine Abusers

7.1 Overview of study assessments

Table 2 delineates the procedures and assessments for the METH/Cocaine abusing participants.

Table 2: Overview of Study Assessments and Procedures

Procedure/Measure	Time Estimate (in minutes)
Informed Consent/HIPAA/ Release of Information	30
General Health Form *(e.g, Stroop discrimination screen, assessment for a history of stroke and/or seizure disorder, smoking history, TBI, etc.)*	9
Blood Draw	5
Patient Health Questionnaire	5
Wender Utah Rating Scale	7
Impulsivity questionnaire (BIS-11)	5
Frontal Systems Behavior Scale (FrSBe)	10
Urine Drug Screen	5
Stroop task	5
RAVLT	15
Gambling Task	10
WCST	20
Query about complications related to blood draw	2
Total time estimate	**128 minutes**

Note: The CTN-0031-A staff will use clinic records to record the participant's treatment attendance during the eight-week intervention phase of CTN-0031.

7.2 Participant Recruitment and Consent

Recruitment will target participants who are randomized into the CTN-0031 study and who were found to meet DSM-IV criteria for current abuse or dependence for METH and/or cocaine and to endorse METH or cocaine as the primary drug of choice during screening/baseline for CTN-0031. These candidates will ideally be provided with information about the present study and, if interested, will be given an opportunity to review, inquire about, and sign the informed consent form. Any participant who has difficulty understanding the information contained in the consent form is asked to review the misunderstood portion(s) of the consent and discuss them with a research staff member until he or she shows complete understanding of the information and may thus give full consent. Any participant who is unable to demonstrate understanding of the information contained in the informed consent is excluded from study participation.

7.3 Screening/Research Visit

After signing the informed consent form, the study participant will proceed to complete the very minimal screening to determine if he or she has a history of stroke and/or seizure disorder and if s/he is able to correctly distinguish the colored stimuli on the Stoop task. If eligible, the participant will then complete the research visit. Ideally, the research visit, which will take approximately 128 minutes to complete, will be completed in a single visit. The timing of this visit will ideally occur within the first week following the participant's randomization into CTN-0031 but can occur as late as 2 weeks following randomization.

7.4 Treatment Attendance

The CTN-0031-A staff will utilize clinic records to record each participant's treatment attendance, including the dates on which treatment was attended and the number of individual and group treatment hours attended, during the eight-week intervention phase of CTN-0031.

7.5 Participant Reimbursement

Participants will be reimbursed for their transportation, inconvenience, and time. This reimbursement will be in the form of retail scrip, vouchers, or cash, at the discretion of the site. It is recommended that participants receive $50 for completing the entire research visit, including providing a blood sample. It is also recommended that participants who do not complete the entire research visit, either due to being ineligible or to other circumstances, receive $10. However, participant reimbursement might vary across study sites to take into account local IRB guidelines, as well as special circumstances and geographic differences across sites.

8.0 STUDY PROCEDURES – Normal Comparison Participants

8.1 Overview of study assessments

Table 3 provides an overview of the procedures and assessments for the normal comparison participants.

Table 3: Overview of Study Assessments and Procedures

Procedure/Measure	Time Estimate (in minutes)
Informed Consent/HIPAA	20
Demographics	5
General Health Form *(e.g., assessment for a history of stroke and/or seizure disorder, smoking history, TBI, etc.)*	7
Patient Health Questionnaire	5
Wender Utah Rating Scale	7
Urine Drug Screen	5
DSM-IV Checklist	20
Blood Draw	5
Query about complications related to blood draw	2
Total time estimate	**76 minutes**

8.2 Normal Comparison Participant Recruitment and Consent

Advertising (e.g., newspaper, radio) will be the primary recruitment strategy for the normal comparison group. Interested candidates who have been determined by a brief telephone or face-to-face interview as likely to meet study eligibility criteria will be invited to the site to review, inquire about, and sign the consent form. Any participant who has difficulty understanding the information contained in the consent form is asked to review the misunderstood portion(s) of the consent and discuss them with a research staff member until he or she shows complete understanding of the information and may thus give full consent. Any participant who is unable to demonstrate understanding of the information contained in the informed consent is excluded from study participation.

As noted above, the normal comparison group will include both men and women, individuals who smoke and non-smokers, and will be approximately the same age as the METH/Cocaine group. It should be noted that age generally does not have a substantial impact on oxidative damage level until individuals reach the age of 70, which is substantially greater than the age that generally will be seen in the METH/Cocaine group.

Consequently, recruiting a normal comparison group which is roughly in the same age range as the METH/Cocaine group, and including age as a covariate, will be sufficient to account for the effects of age on oxidative damage level. In order to obtain an age estimate for the METH/Cocaine group, after we enroll approximately a third of the METH/Cocaine group (i.e., approximately 54 participants) we will use the ages for these participants as the basis for specifying our age ranges for the normal comparison participants.

8.3 Normal Comparison Participant Screening/Research Visit

After signing the informed consent form, the study participant proceeds to complete screening to determine if he or she is eligible. If eligible, the participant will then provide a blood sample for the oxidative stress/damage analysis.

8.4 Normal Comparison Participant Reimbursement

Normal comparison participants will be reimbursed for their transportation, inconvenience, and time. This reimbursement will be in the form of retail scrip, vouchers, or cash, at the discretion of the site. It is recommended that participants receive $50 for completing the entire research visit, including providing a blood sample. It is also recommended that participants who do not complete the entire research visit, either due to being ineligible or to other circumstances, receive $20; this amount is more than that proposed for METH/Cocaine abusing participants who do not complete the entire visit due to the greater number of screening assessments for the normal comparison participants.

9.0 ANALYTICAL PLAN

9.1 Statistical Hypotheses

9.1.1 Primary Hypothesis

The primary hypothesis is that Reaction Time (RT) on the Comalli-Kaplan version of the Stroop color-word task will be associated with completion of the intervention phase of the CTN-0031 study (see section 6.4 for definition of completion). The working hypothesis is that METH/cocaine abusers with shorter derived interference RT on the Comalli-Kaplan version of the Stroop color-word task will have a higher probability of completion.

9.1.2 Secondary Hypotheses

9.1.2.1 Hypotheses related to treatment completion

It is hypothesized that METH/cocaine abusers who are treatment completers (see section 6.4 for definition), compared to non-completers, will:

1. have significantly better verbal learning and memory as measured by the RAVLT
2. have significantly better delay and risk assessment as assessed by the GT
3. be significantly better at response reversal as assessed by the WCST
4. be significantly less impulsive as measured by the BIS-11
5. have significantly fewer frontal-lobe related behavioral problems as measured by the FrSBe
6. have significantly less oxidative damage as assessed by the comet and malondialdehyde assays

9.1.2.2 Hypotheses related to substance use

It is hypothesized that the degree to which stimulant use is reduced, relative to baseline, will be significantly and positively associated with:

1. ability to suppress prepotent responses as measured by the Stroop

2. verbal learning and memory ability as measured by the RAVLT
3. delay and risk assessment ability as assessed by the GT
4. response reversal ability as assessed by the WCST

In addition, the degree to which stimulant use is reduced, relative to baseline, will be significantly and inversely associated with:

5. impulsivity as measured by the BIS-11
6. frontal-lobe related behavioral problems as measured by the FrSBe
7. oxidative damage as assessed by the comet and malondialdehyde assays

9.1.2.3 Hypotheses related to the association between neurocognitive measures and oxidative damage in METH/Cocaine abusers

It is hypothesized that the level of oxidative damage, as assessed by the comet and malondialdehyde assays will be significantly and positively associated with impulsivity as measured by the BIS-11 and with frontal lobe related behavioral problems as measured by the FrSBe and will be significantly and inversely related to:

1. ability to suppress prepotent responses as measured by the Stroop
2. verbal learning and memory ability as measured by the RAVLT
3. delay and risk assessment ability as assessed by the GT
4. response reversal ability as assessed by the WCST

9.1.2.4 Hypotheses related to oxidative damage in METH/Cocaine abusers vs. normal comparison participants

It is hypothesized that the level of oxidative damage in the METH/Cocaine group will be significantly greater than the normal comparison group, as measured by the comet and malondialdehyde assays.

9.2 Analysis Plan

9.2.1 Overview

Samples: The sample of approximately 164 METH/Cocaine abusers will be employed for all primary and secondary analyses. The normal comparison group will be employed in the analyses involving oxidative damage in which normals are compared to the METH/Cocaine group.

Selection Bias: To assess selection bias among the cases, baseline values for participants consenting and entering the study will be compared to those participants in the parent study who do not enter this ancillary study. To accomplish this, the important baseline variables, including demographic (age, gender, site) and drug use (baseline percent of days of stimulant use) variables, will be extracted from the CTN-0031 trial. The bivariate association of these variables with entry status (yes/no) will be calculated for each variable listed by Wilcoxon Rank-Sum (for interval and ordinal variables), or chi-square goodness-of-fit statistics (for nominal variables).

Primary Analysis: The design is longitudinal and quasi-experimental. At a simple level, the binary response (complete/not complete) is predicted by RT on the Stroop test. Censoring is not an issue, as any early termination will be labeled 'not complete.' The initial, bivariate test will predict completion status given RT using logistic regression. However, since randomization of completion status is not possible, the analysis requires covariate adjustment to control for potential moderation and mediation. Statistical significance of this test of this primary model will be declared under this covariate adjusted model.

To accomplish this, we will develop the covariate model without respect to RT. The variables to be employed are listed fully in section 9.2.2., but include demographics (education, gender, age), psychological and drug use baseline measures (e.g., mood, baseline drug use, type of drug use), and trial specific variables (e.g., site, randomization group). Variables will be included into the logistic regression as a block in a forward stepwise fashion. Since adjustment for confounding rather than statistical significance is the purpose, variables will be entered and retained in the regression using a .10 p-value level for entry and retention. For continuous variables, the linearity assumption will be checked and, if necessary, remedial measures employed (e.g. use of quadratic terms in the modeling). Only after the final model is developed will RT be added. The p-value from this final model will provide the test of significance for the primary analysis.

Several final post-hoc tests will be performed. First, the bivariate effect will be compared to the controlled to assess the impact of the covariates. To assess effect modification, the interaction of covariates with Reaction Time will be assessed. In this latter test, to control for Type-I error, the interaction of each of the K variables with Reaction Time will be entered as a 'chunk'(Kleinbaum 1988), and if the chunk is significant (on K df) follow-up univariate tests will be performed.

Secondary Analyses: For the outcomes completion/non-completion, we will employ logistic regression, using the covariate adjusted model as specified above, replacing Stroop RT with the appropriate neurocognitive or oxidative damage variables. For the other continuous outcomes, we will employ least squares procedures. In this latter analysis, we are aware that the distribution of the data may vary significantly from normality. Estimation in the presence of non-normality does not lead to bias in the derived estimates. However, tests of significance may be impacted (Kleinbaum, 1988). As required, we will assess the deviation from normality of the residuals from our models, and, if possible, transform the outcome to bring about approximate normality. For the outcome, change in drug use, we will have indictors of drug use at several time points: 1. Baseline (Week 0) for the past 90 days; 2. Week 4 for the past 30 days; 3. Week 8/End of treatment for the past 30 days; 4. 3 months post randomization for the past 30 days; and 5. 6 months post randomization for the past 90 days. These variables will be transformed to 'percent days of use' during the window. With replicate measures (and missing data observations), analysis by Mixed Models (Singer and Willet, 2003) is appropriate. Use of mixed models has several advantages - missing values present no particular problems in estimation, the method allows for numerous non-normal distributions in estimation, and, time varying covariates are easily incorporated. We will utilize the so-called 'residualized change score' methodology (Chronbach, 1970), analyzing all post-randomization variables adding the baseline value as a covariate. Use of baseline value has several advantages including: (1) control for an important predictor of change, and (2) reduction of error variance. In addition to baseline, other covariates will be added to the model in the manner listed above. Only as a final step will the particular predictor of interest (e.g. an indicator of cognitive function or oxidative damage) be added to the model as a between subject factor.

The normal control group will only be employed in analyses involving oxidative damage. Here, a case-control design will be employed to assess oxidative damage as assessed by comet and malondialdehyde assays. Since case-control status is not randomized, as possible, given the small size of the control sample, we will control for covariates, including age, gender, and smoking status.

Missing Values: Missing values are ubiquitous in studies of drug abuse, and estimation in the presence of missing values may lead to biased and underpowered estimates and hypothesis testing. In the analysis proposed here, the amount of missingness should be minimal. First, participants ideally will be tested within a single short session and will be consented and will agree to that session. Second, missingness on the

longitudinal outcome, completion, will indicate failure to complete. However, even minimal missingness across many variables may compound in the presence of list-wise deletion procedures. If this listwise deletion is greater than 5%, the covariate model will be developed using bootstrap techniques (Efron 1982) as implemented under SAS Proc MI. Bootstrap imputation procedures will not be employed for the primary independent or dependent variables.

9.2.2 Primary Analysis

The primary hypothesis will be tested by comparing the METH/Cocaine abusers who complete treatment to those who do not complete treatment (see section 6.4 for definition of completer), on derived interference RT on the Stroop. As listed above, predicting completion, using logistic regression, the covariate adjusted model will be developed without respect to RT. As a final step, the Stroop RT will be added to the model.

A number of analyses will evaluate the relationship between treatment completion and neurocognitive test performance. Using the methods listed above, for each of these analyses, the covariates listed in Table 4 need to be assessed for inclusion in the model.

Table 4: Covariates to be assessed for statistical models

Covariate	Type	Categories (if applicable)
Mood	categorical	no syndrome; major depressive syndrome; other depressive syndrome; panic syndrome; other anxiety syndrome; more than one syndrome
ADHD	dichotomous	ADHD vs. not ADHD
HIV status	categorical	negative test; not tested; HIV; AIDS
Diagnostic Status for METH/cocaine	categorical	cocaine abuse; cocaine dependence; methamphetamine abuse; methamphetamine dependence; both a cocaine and methamphetamine diagnosis
Diagnostic Status for other substances	categorical	abuse dx-1 non-stimulant drug/alcohol; dependence dx-1 non-stimulant drug/alcohol; abuse/dependence dx for more than 1 non-stimulant drug/alcohol
Court mandated	dichotomous	Court mandated vs. not court mandated
CTN-0031 treatment	dichotomous	STAGE-12 vs. TAU
Baseline percent of days of stimulant use	continuous	
Age of onset of stimulant use	continuous	
Days since last stimulant use	continuous	Note: this refers to the days since last stimulant use at the time of the neurcognitive testing
Days since last use of non-stimulant drug/alcohol	continuous	Note: this refers to the days since last non-stimulant use at the time of the neurcognitive testing
Urine toxicology – stimulant result	dichotomous	Positive for stimulants vs. negative for stimulants on the day of neurocognitive testing
Urine toxicology – non-stimulant result	dichotomous	Positive for non-stimulants vs. negative for non-stimulants on the day of neurocognitive testing
Education	continuous	
Age	continuous	
Gender	dichotomous	Male vs. female
Smoking	dichotomous	Current smoker vs. non-smoker
TBI	dichotomous	TBI vs. no TBI

Covariate	Type	Categories (if applicable)
Race/ethnicity	categorical	TBD by the sample sizes for various ethnic groups
Site effects	categorical	To be determined by the number of sites participating

Note: Other pertinent variables may be assessed for inclusion in the model. For analyses involving completion/ non-completion outcome, pertinent baseline differences between completers and non-completers will also be assessed for inclusion in the statistical models. For other analyses (e.g., predicting change in drug use, etc.), completion status (i.e., completer vs. non-completer) will be assessed for inclusion in the model.

9.2.3 Secondary Analyses

9.2.3.1 The impact of other neurocognitive measures on completion status

In addition to the Stroop RT (primary predictor), the other neurocognitive measures to be analyzed in the prediction of completion status include:

1. the interference recall score from the RAVLT
2. number of advantageous vs. disadvantageous cards from the GT
3. the number of perseverative errors from the WCST
4. the total score from the BIS-11
5. the total score from the FrSBe

9.2.3.2 Impact of oxidative damage on completion status

Using the linear model outlined above, the specific measures to be analyzed are (1) tail length from the comet assay and (2) MDA from the malondialdehyde assay. The baseline covariate model will include age, smoking status, and gender, while follow-up analyses will assess the impact of the other covariates listed in Table 4.

9.2.3.3 Change in drug use and neurocognitive measures

A number of analyses will predict stimulant use reduction given neurocognitive test performance. The neurocognitive predictors have been listed above although no predictor is viewed as 'primary' for the substance use outcome models. For each of these analyses, using the method to develop a covariate adjusted model, listed above, the covariates listed in Table 4 will be assessed for inclusion into the final model. The specific neurocognitive measures to be utilized as predictors are:

1. derived interference reaction time (RT) from the Stroop
2. the interference recall score from the RAVLT
3. number of advantageous vs. disadvantageous cards from the GT
4. the number of perseverative errors from the WCST
5. the total score from the BIS-11
6. the total score from the FrSBe

As outlined above, the repeated outcome, '% days of use', will be analyzed using a repeated measures mixed model. A covariate adjustment model, including baseline use and time, will be developed and only as a final step will the variable of interest be included. Inclusion of baseline will bring about statistical equality. The impact of any particular variable may manifest itself as a main effect (associated with higher or lower drug

use across all measurement points) or as a time by group interaction (impacting drug use only at certain time points). To control type-I error, the two effects (Variable and Variable X time) will be tested as a 'chunk' using nested models and testing the change in log-likelihood, and this 2 df test will provide a basis for declaration of the statistical significance of the variable of interest. If significant, follow-up tests will be performed to test the functional form of the relationship (i.e., testing whether there was a main effect, an interactive effect, or both).

9.2.3.4 Change in drug use and oxidative damage

Two analyses will predict stimulant use reduction given oxidative damage. Using the linear model outlined above, the specific measures to be analyzed are (1) tail length from the comet assay and (2) MDA from the malondialdehyde assay. The baseline covariate model will include age, smoking status, and gender, while follow-up analyses will assess the impact of the other covariates listed above in Table 4.

9.2.3.5 Secondary Analyses related to the association between neurocognitive measures and oxidative damage in METH/Cocaine abusers

We have 6 indicators of cognitive function (1. derived interference reaction time (RT) from the Stroop; 2. the interference recall score from the RAVLT; 3. number of advantageous vs. disadvantageous cards from the GT; 4. the number of perseverative errors from the WCST; 5.the total score from the BIS-11; 6. the total score from the FrSBe) and two measures of oxidative damage (1. tail length from the comet assay and 2. MDA from the malondialdehyde assay), giving 12 combinations of bivariate correlations. Using only the drug abuser group, the relationship between the multiple indicators of cognitive functioning will be related to the oxidative damage indicators by canonical correlation, partialling out (controlling) age, smoking status, and gender. Use of this multivariate test (Bock, 1973), has the statistical advantage of controlling the overall Type-I error rate and multivariate tests are uniformly more powerful than other techniques like Bonferroni correction. The disadvantage is that if the predictors demonstrate multidimensionality, interpretation of the resulting parameters (canonical relationships) may be difficult. If the omnibus test is rejected, follow-up bivariate correlations will be calculated between each cognitive indicator with each oxidative damage variable. Both the first canonical correlation and any significant lower order correlations will be reported along with the weights. If the omnibus test is significant ($p<0.05$) for the canonical correlation, the 10 bivariate correlations (partialling out the covariates above) will also be reported. Followup exploratory analyses will assess the impact of the other covariates listed in Table 4 on the canonical correlations as well as the partial bivariate correlations.

9.2.3.6 Secondary Analyses related to oxidative damage in METH/Cocaine abusers vs. normal comparison participants

As noted above, this is a case-control analysis comparing the level of oxidative damage in the METH/Cocaine group to that of the normal comparison group, as measured by the comet and malondialdehyde assays. For each of these analyses, age, gender, and smoking status will be included as covariates in the model. In addition, prior to the addition of Case-Control status to the final model, we will assess the additional impact of the set of covariates listed in Table 4. Those entering and remaining in the model at $p<0.10$ will be retained in the final model.

In this model, the covariates are likely to be particularly strong predictors of the outcome and have important moderating and mediating influences, both between the covariates themselves and with case-control status. In addition, assessment of these complicated relationships may be further impacted by the presence of a skewed distribution in the outcome. With 30 controls and over 160 cases, testing the assumption of linearity in the covariates, the assumption of no interaction between the covariates and case-control status, may be non-powerful, particularly in the presence of a heavily skewed outcome. Complicated interactions may exist

which are non-detectable given this design and sample size. To experimentally control for these possibilities, matching is often employed. However, post-hoc one-to-one matching in this design would make inefficient use of the data (not all participants would be employed). In an additional post-hoc analysis, we will define strata based on age group, smoking status, and gender and cases and controls will be allocated to the strata. Within each strata, the non-parametric probability estimate of a distributional difference will be calculated (Dudley et al, 1993) and these probability estimates will be aggregated (using the methodology outlined in Breslow and Day, 1987) to assess the overall probability of a distributional difference in the oxidative outcomes. This summary estimate will thus condition on the stratifying variables.

9.3 Power Analysis

For estimation of power for the logistic regression using the Stroop RT to predict treatment completion, we assumed the following:(1) a 30% non-completion rate among the participants, (2) a sample size of 164 and (3) the Stroop RT test split at the median (giving 82 per arm) then, using the formulas due to Fleiss (Fleiss 2003) this design is powered to detect an odds ratio of 2.45. If we approach the problem in the more familiar standardized effect size, our power is approximately equal to that found by Streeter et al. (2007), who used this RT to differentiate completers from non-completers in a cocaine dependent sample (effect size =.53). Based on these assumptions, a sample size of 164 would yield power of almost 90% (.894) to detect a significant difference between the drop-outs and completers, two-sided test, with an alpha level of .05 and assuming 30% non-completion rate. Each study site will be randomizing between 40 and 50 CTN-0031 participants. It is estimated that, on average, a given study site should be able to enroll 27 of their CTN-0031 participants in CTN-0031. Thus, we will need approximately 6 sites to participate in CTN-0031-A in order to enroll a total sample size of approximately 164.

9.4 Post-hoc Analyses

In addition to the analyses described above, a number of post-hoc analyses will be completed. Some examples of possible analyses include an evaluation of the association between a number of neurocognitive measure results and oxidative stress and oxidative damage assessments, which are not being used as secondary predictor measures, and treatment completion and stimulant outcomes in METH/cocaine abusers. Analyses evaluating treatment retention as a continuous measure (e.g., the number of treatment hours attended) will also be conducted. Analyses to evaluate the ability of neurocognitive measures and/or oxidative stress/damage level to predict reductions in the use non-stimulant drug use and reductions in positive urine drug screens for both stimulants and non-stimulant drugs of abuse may be conducted. In addition, analyses comparing the METH/Cocaine and normal comparison groups on oxidative stress may be conducted.

10.0 REGULATORY AND REPORTING REQUIREMENTS

10.1 IRB approval

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

10.2 Informed consent

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

original signed informed consent for every participant in a locked, secure location that is in compliance with their IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

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

10.3 Clinical monitoring

10.3.1 Study Staff

Each of the CTPs participating in this study has established agency practices for managing medical and psychiatric emergencies, and the study staff will be trained to utilize these procedures. NIDA will appoint a Medical Monitor to this study to independently review the safety data and present it to the DSMB for periodic review. The study staff will be trained to identify, assess, document and report complications related to the blood draw.

10.3.2 NIDA contract monitors

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

10.3.3 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons including the safety of the study participants or inadequate trial performance (e.g., poor recruitment).

10.4 Confidentiality

10.4.1 Confidentiality of data

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

10.4.2 Confidentiality of participant records

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

10.5 Safety Reporting

Given that the present study includes participation in a single research visit and does not entail a treatment intervention, required safety reporting will be limited to reporting any complications directly related to the study blood draw occurring before the participant leaves the research visit. Complications requiring medical attention will be followed for resolution. All safety data should be reported, according to study specific procedures, within 7 business days of the site becoming aware of the event. Events spontaneously reported to study staff after the research visit may be reported in the study database at the discretion of the site investigator. Collaboration with the Lead Investigator and the NIDA-appointed Medical Monitor is available.

11.0 DATA MANAGEMENT AND PROCEDURES

11.1 Design and Development

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

11.1.1 Site Responsibilities

The data management responsibilities of each individual CTP will be specified by the CDMC.

11.1.2 Data Center Responsibilities

The CDMC will 1) develop a data management plan and will conduct data management activities, 2) provide final CRF specifications for the collection of all data required by the study, 3) provide data dictionaries for each CRF that will comprehensively define each data element, 4) conduct ongoing data validation and cleaning activities on study data as outlined in Edit Specifications from all participating CTPs through database lock.

11.2 Data Acquisition and Entry

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

11.3 Data Editing

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

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

11.5 Data Training
The training plan for CTP staff includes provisions for training on assessments, CRF completion guidelines, and computerized systems.

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

12.0 QUALITY ASSURANCE MONITORING

12.1 The Goals of QA Monitoring

The primary goals of quality assurance (QA) monitoring are to protect the rights and safety of participants and to ensure that the study is conducted in compliance with the protocol and applicable regulations and results are credible. All aspects of the study will be carefully monitored with respect to current good clinical practices. The NIDA-CTN Data and Safety Monitoring Board (DSMB), the NIDA appointed medical monitor, NIDA-CTN contracted clinical monitors, representatives from the lead investigator's node, and local site managers from the participating node will be given access to facilities and records to review data pertinent to the study and to verify the conduct of study procedures at the site. These individuals will have access to all records and study documentation as necessary to ensure integrity of the data and periodically will review progress of the study with the principal investigator and research staff. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and inform the sponsor of potential problems at the study sites.

12.2 NIDA-Contracted QA Monitors

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

Qualified node personnel will provide site management for each site during the trial. This will take place as specified by the local protocol team or node PI and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will verify that study procedures are properly followed and that site 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.

13.0 PUBLICATIONS AND OTHER RIGHTS
Protocol development and implementation in the NIDA CTN is a collaborative process. The publication plan for the current study will comply with the CTN Publications Subcommittee's guidance on publications.

Individuals making substantive contributions to the protocol development and implementation will have opportunities to participate in publications. Other contributors will also be acknowledged.

14.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____

INVESTIGATOR (S)

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

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

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