

**NIDA-CTN-0044**

**Web-delivery of Evidence-Based, Psychosocial  
Treatment for Substance Use Disorders**

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## 1.0 LIST OF ABBREVIATIONS

AE	Adverse Event
CAI	Computer Assisted Instruction
CCC	Clinical Coordinating Center
CoC	Certificate of Confidentiality
CEA	Cost Effectiveness Analysis
CRA	Community Reinforcement Approach
CRF	Case Report Form
CSS	Coping Strategies Scale
CTN	Clinical Trials Network
CTP	Community Treatment Program
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICER	Incremental Cost Effectiveness Ratio
ICH	International Conference on Harmonization
IOP	Intensive Outpatient Program
IRB	Institutional Review Board
ITT	Intent-to-Treat
LI	Lead Investigator
LN	Lead Node
NIDA	National Institute on Drug Abuse
NMS	Non Study Medical and Other Services
OPT	Outpatient Psychosocial Treatment
PI	Principal Investigator
PV	Protocol Violation
QA	Quality Assurance
QALY	Quality Adjusted Life Year
RA	Research Assistant
RBS	Risk Behavior Survey
SAE	Serious Adverse Event
SUD	Substance Use Disorder
TAU	Treatment-as-Usual
TES	Therapeutic Education System
TLFB	TimeLine Follow Back

## 2.0 STUDY SYNOPSIS

**Objective.** The principal objective of the planned trial is to evaluate the effectiveness of including an interactive, web-based version of the Community Reinforcement Approach (CRA) intervention plus incentives targeting drug abstinence and treatment participation as part of community-based, outpatient substance abuse treatment.

**Population.** Individuals accepted in outpatient treatment for substance use disorders (excluding those receiving opioid pharmacotherapy for opioid dependence) will be eligible to participate.

**Design.** We plan to conduct a multi-site, controlled trial, using NIDA's Clinical Trials Network (CTN) platform, at approximately 10 Community Treatment Programs (CTPs), in which participants (n = approximately 500) are randomized to receive 12 weeks of either: (1) Treatment-as-Usual (TAU), reflecting standard treatment at the collaborating CTPs in which participants are enrolled, or (2) a modification of TAU which includes access to the Therapeutic Education System (TES), a computerized psychosocial intervention which combines skills building modules based on the Community Reinforcement Approach (CRA) with incentives contingent primarily upon abstinence from drugs of abuse and, secondarily, upon completion of TES modules.

**Outcomes.** We will evaluate the relative effectiveness of these interventions on the primary outcome measures of (a) drug abstinence during active treatment (measured as abstinence from all tested drugs of abuse and heavy drinking days during the 12 weeks of treatment via self-report using the TimeLine Follow-Back procedure and urine testing) and (b) treatment retention. We will also evaluate the relative effectiveness of these interventions on several secondary outcome measures, including (a) HIV risk behavior (measured via the Risk Behavior Survey), (b) psychosocial functioning (in areas of criminal activity, health status improvement, psychological status, family/social relationships, and employment, as measured via the SAS-SR, Non-study Medical and Other Services (NMS, and BSI) and (c) treatment acceptability (based on participant feedback). Additionally, we will evaluate outcomes at 3- and 6-month post-intervention follow-ups. As an additional secondary analysis, we will perform a comprehensive economic analysis of including TES with TAU to inform decisions regarding adoption of this new therapeutic tool (assessing incremental costs per increased abstinence time and quality adjusted life year, measured via modified versions of the EuroQol EQ5D, NMS and Program DATCAP). The economic analyses are clinically important, as even if the computerized intervention is shown to be effective, it may have limited adoption within community-based treatment programs unless it is also shown to be cost-effective.

**Potential Importance of Trial.** Overall, the proposed research will contribute new empirical information relevant to increasing the delivery of science-based psychosocial treatment with fidelity in CTPs in a manner that may be cost-effective and which may promote the adoption of effective treatment. TES provides a comprehensive, science-based, psychosocial treatment from an automated web-based platform with high potential for dissemination. TES, and similar interventions, if found effective, could substantially advance the substance abuse treatment system by improving quality of care delivered, increasing availability of treatment slots by extending and leveraging the efforts of clinical staff, and projecting treatment to rural and other underserved areas.



## **3.0 BACKGROUND AND SIGNIFICANCE**

### **3.1 Provision of Evidence-Based Psychosocial Interventions in Outpatient Substance Abuse Treatment Programs**

The provision of evidence-based psychosocial interventions (e.g., prosocial, life skills training, relapse prevention skills training and HIV/AIDS education) as part of treatment for substance use disorders, is often critical for treatment to be maximally effective. A number of efficacious psychosocial treatments for substance use disorders exist, many of which have been manualized in an effort to enhance their dissemination, adoption, and fidelity. The Community Reinforcement Approach (CRA) with voucher reinforcement is one such widely researched and demonstrably efficacious drug abuse treatment (Budney & Higgins, 1998). CRA is grounded in research related to drug self-administration and a behavioral analysis of drug dependence where drugs are viewed as competing with more delayed prosocial reinforcers because of their relatively more immediate reinforcing effects (Higgins et al., 1994). To address this, the skills training component of the CRA plus vouchers approach teaches skills and encourages behaviors that increase non-drug sources of reinforcement and shares many common elements with other evidence-based, cognitive behavioral and relapse prevention behavioral interventions for substance use disorders. Additionally, the voucher reinforcement procedure in the CRA plus vouchers intervention enables immediate, positive reinforcement (e.g., recreational items) for drug abstinence. Both the CRA and voucher components of this intervention have been shown to independently contribute to its efficacy (Higgins et al., 2003).

Despite these findings, patients in community-based, outpatient substance abuse treatment programs (CTPs) are infrequently provided with such evidence-based psychosocial interventions as part of treatment (Bickel & Marsch, 2007; McLellan et al., 2003). Significant barriers to the widespread adoption of science-based psychosocial interventions in substance abuse treatment programs exist. The most significant barrier to providing psychosocial support is arguably that of cost. Evidence-based, psychosocial interventions are expensive to implement and strain available resources, given the limited staffing and high caseloads at the average CTP. Cognitive behavioral interventions in particular, including the CRA intervention, require considerable staff training and ongoing supervision. Even if evidence-based interventions are initiated by staff in CTPs, it may be difficult to ensure their fidelity. Barriers include significant staff turnover at many CTPs, high patient caseloads maintained by program counselors, and counselors' limited contact time with any one patient. Consequently, there is a need to develop innovative approaches to address these challenges and provide evidence-based psychosocial interventions to patients with substance use disorders in CTPs in a manner that is cost-effective and extends beyond traditional approaches.

An interactive, web-delivered cognitive behavioral intervention has the potential to address these challenges. It allows a complex intervention to be delivered with high fidelity and at a low cost, without increasing demands on staff time or training needs. Additionally, costs saved on a computerized psychosocial intervention could be used to offset participant earnings via efficacious contingency management procedures. Also, a computerized program may be less threatening to patients and may provide greater anonymity. This may be particularly relevant when sensitive issues of sexual behavior and drug taking are addressed (e.g., Des Jarlais et al., 1999). Use of this technology with computer-generated speech can also accommodate individuals who have difficulty reading. It may also appeal to individuals who normally resist other forms of learning (Lieberman et al., 1991). Computer-based interventions, when delivered via the web, can also be quickly and centrally updated to accommodate new information as it becomes available. These technologies also permit temporal flexibility, allowing a user to choose to access the intervention at a convenient time. Finally, computerized interventions may

allow individuals to engage in therapeutic activities for a greater period of time than would be possible with a therapist alone, review repetitive but necessary skills training, and complete educational tasks that a therapist may find uninteresting or repetitive (Bickel & Marsch, 2007; Newman et al., 1996). There is, thus, strong potential for widespread dissemination.

### **3.2 Web-delivered, Evidence-based Psychosocial Intervention for Substance Abuse Treatment: The Therapeutic Education System (TES)**

Bickel, Marsch and colleagues (2008) developed an interactive, self-directed version of the evidence-based Community Reinforcement Approach (CRA) psychosocial intervention (Budney & Higgins, 1998), the Therapeutic Education System (TES), which is delivered via effective informational technologies and multimedia learning tools. TES includes over 65 interactive, multimedia modules, beginning with modules on basic cognitive behavioral relapse prevention skills (drug refusal skills, managing thoughts about drug use, conducting functional analyses and self-management planning, etc). TES also includes modules related to the prevention of HIV, Hepatitis and Sexually Transmitted Infections (STIs). Additional modules teach skills that may help improve psychosocial functioning, including employment status, family/social relations, financial management, communication skills, decision-making skills, management of negative moods, time management and recreational activities. The program is self-directed, and a training module is included to teach individuals how to use it. TES is designed to address substance use in general and is inherently flexible, addressing the substance use-related problems with which patients may present. TES includes a "customization program" that is used to establish an individualized treatment plan for patients.

The evidence-based content in TES is provided using evidence-based informational technologies. Specifically, TES uses "fluency-based" Computer-Assisted Instruction (CAI), grounded in the "precision teaching" approach (e.g., Binder, 1993) to continually assess a patient's grasp of the material and adjust the pace and level of repetition of material in order to promote mastery of the skills and information being taught. It also creates experiential learning environments via the use of interactive videos of actors modeling various behaviors in order for the program user to better learn the modeled behavior (e.g., progressive muscle relaxation, drug refusal skills). Additionally, it employs a variety of interactive exercises to better enhance learning (e.g., graphics and animation) and personalize content for participants (e.g., personalized functional analysis). Further, TES includes a flexible system for tracking and reinforcing target behaviors (e.g., abstinence) and monitoring earnings via contingency management procedures. An electronic reporting system allows therapists to view summaries of their patients' TES activity and progress, recommend modules to be covered, and integrate patients' use of TES into their counseling sessions. In this way, TES can function as a clinician-extender, putting a sophisticated intervention tool at the disposal of clinicians with limited experience or expertise, who can simply evaluate progress and guide the focus of the intervention, while the patient and the program do much of the work.

As described in Section 3.3.1 below, a prior NIDA-funded, randomized clinical efficacy trial demonstrated that TES is as efficacious as CRA delivered by therapists and superior to standard treatment with opioid-dependent outpatients maintained on buprenorphine (Bickel, Marsch et al., 2008). Another NIDA-funded controlled trial demonstrated that the modules related to HIV, Hepatitis and STI risk promoted significantly increased HIV/disease prevention knowledge, self-reported risk for HIV, and intentions to increase safer sex practices and was also perceived as more useful relative to a standard intervention (Marsch et al., 2007a). Overall, results from this prior efficacy research are highly promising and clearly support the efficacy of TES. We now propose to extend this research into community-based treatment by testing the effectiveness of TES for use by a wide variety of substance abusing patients in outpatient CTPs.

### **3.3 Overview of Prior Evaluations of TES**

#### **3.3.1 Efficacy Evaluation of TES**

Of particular relevance to the planned project, Bickel, Marsch and colleagues (2008) designed and demonstrated the efficacy of the interactive, web-based Therapeutic Education System described above. Specifically, this randomized, controlled trial was designed to evaluate the efficacy of TES with opioid-dependent patients receiving treatment with the partial mu-opioid agonist medication, buprenorphine, at a university-based, outpatient treatment clinic (n=135). Participants were randomly assigned to one of three study conditions in this 23-week trial. Participants in the TES condition completed computer sessions for 30 minutes thrice weekly for 12 weeks and then 30 minutes once weekly for the next 11 weeks. They had one session with a substance abuse therapist every other week. Participants in the counselor-delivered CRA therapy condition met with their therapist for 30-minute sessions thrice weekly for 12 weeks and 30 minutes once weekly for the next 11 weeks, and the content of these therapy sessions was identical to the content in the computer system. Participants in both CRA conditions received voucher incentives for the provision of opioid- and cocaine-negative urine samples (on an escalating schedule of reinforcement with potential voucher earnings equivalent to \$1,316.75). Participants in standard counseling had 1-therapy session per week with a therapist modeled after the standard drug counseling offered in methadone programs. During the 23 weeks of treatment, the computer-delivered, therapist-delivered and standard treatments resulted in 7.78 (SEM=1.17), 7.98 (SEM=1.09), and 4.69 (SEM=0.88) mean weeks of continuous cocaine and opioid abstinence, respectively (as measured via urine samples collected thrice weekly). The therapist-delivered and computer-assisted therapy did not produce significantly different outcomes on this measure, but both produced significantly better abstinence compared to standard treatment. Importantly, the mean total minutes of therapist contact time was substantially lower with TES (264 minutes), compared to therapist-delivered CRA (1198 minutes) or standard treatment (647 minutes). Participants in the therapist-delivered and computer-assisted interventions achieved comparable results on measures of treatment retention, Addiction Severity Index composite scores and therapeutic alliance with their counselor. The comparable efficacy obtained with computer-assisted and therapist-delivered therapy may enable more widespread dissemination of the evidence-based CRA plus vouchers intervention in a manner that is cost-effective and ensures treatment fidelity. Currently, Dr. Marsch, in collaboration with Dr. Nunes, is evaluating (via a NIDA-funded R01 grant) the effectiveness and cost-effectiveness of TES when used by patients in methadone maintenance treatment.

#### **3.3.2 Efficacy Evaluation of HIV, STI and Hepatitis Prevention Modules**

A separate randomized, controlled trial evaluated the efficacy of including the TES modules focused on prevention of HIV, Hepatitis and STIs as part of an enhanced prevention intervention for youth in substance abuse treatment compared to a standard of care comparison group (n=56). Participants in the enhanced condition completed the computer program and participated in an educational session led by a prevention specialist, while those in the standard condition only participated in the educational group. Results indicate that the computer program promoted significant increases in HIV/disease prevention knowledge, intentions to use condoms during sex, as well as participants' perception of the importance of carefully choosing sex partners and limiting their number of sex partners. Additionally, the computerized intervention promoted significantly greater increases in HIV/disease prevention knowledge at all post-intervention time points (assessed at 1, 2, and 4 months post-intervention) relative to the standard condition. The enhanced condition also promoted significantly greater reductions in self-reported risk for acquiring HIV and was perceived as significantly more useful relative to the standard condition. These data underscore the ability of these computerized modules to provide

an efficacious, engaging intervention, which may increase the adoption of effective HIV/disease prevention science.

### **3.4 Study Rationale**

In the present trial, we plan to extend prior research to primarily evaluate the effectiveness and, secondarily, evaluate the cost-effectiveness of the evidence-based, computer-delivered TES psychosocial intervention for patients in outpatient CTPs. Results from prior research are highly promising and clearly support the efficacy of TES with participants maintained on buprenorphine at a research clinic. Nonetheless, although such carefully controlled efficacy studies are necessary to demonstrate that an intervention may have utility, they are not sufficient to demonstrate that an intervention may be effective in a less controlled and potentially more complicated, real-world setting in which a broader and more diverse sample of patients may be accessed (Dennis et al., 2005; McLellan, 2002). Additionally, the structure (including fiscal, personnel and programmatic issues) of a grant-funded, university-based research clinic markedly differs from the structure of CTPs.

As previously described, the combination of CRA and incentives for abstinence, offered in a computerized form by TES, represents an efficacious treatment package in promoting drug abstinence. Our plan to assess the effectiveness of this package when provided along with incentives for completion of modules within TES represents an important component of the design and will likely increase treatment retention (see Stitzer & Petry, 2006 for a review). Increasing treatment retention is a clinically important goal, in light of the high attrition rates often observed in community-based substance abuse treatment.

We plan to assess the costs and cost-effectiveness (in addition to the effectiveness) of delivering TES in CTPs to provide data relevant to determining how to best maximize resource allocation (when considering whether or not to employ TES) and minimize financial barriers to adoption of effective and cost-effective interventions.

Adoption of evidence-based research innovations permits substance abuse treatment programs to improve patient services and evolve, while, failing to adopt innovation, may render substance abuse treatment a static and less than optimally effective enterprise (Bickel & Marsch, 2007). Indeed, as McLellan and colleagues (2003) convincingly argue in a recent review of the numerous systemic problems that exist within the national addiction treatment infrastructure, "without modernization and investment, the addiction treatment system will fail to meet the public's needs". Adoption of empirically supported technology may play a critical role in improving community-based substance abuse treatment in a manner that enables rapid diffusion and adoption of science-based interventions and is cost-effective (Carise et al., 2005). Although informational technology continues to rapidly expand and bring about profound changes in our society in general, it has been infrequently employed in the substance abuse treatment field.

Overall, the proposed research will contribute new empirical information relevant to increasing the delivery of science-based psychosocial treatment with fidelity in CTPs in a manner that may be cost-effective and which may promote the adoption of effective treatment. TES provides a comprehensive, science-based, psychosocial treatment from an automated web-based platform with high potential for dissemination. A demonstration of its effectiveness could substantially advance the substance abuse treatment system.

## 4.0 TRIAL OBJECTIVES

### 4.1 Principal Objective

The principal objective of the planned trial is to evaluate the effectiveness of including an interactive, web-based version of the Community Reinforcement Approach (CRA) intervention plus incentives targeting drug abstinence and treatment participation as part of community-based, outpatient substance abuse treatment. We plan to conduct a multi-site, controlled trial on NIDA's Clinical Trials Network (CTN) platform in which individuals entering outpatient treatment for substance use disorders are randomized to receive 12 weeks of either: (1) Treatment as Usual (TAU), reflecting standard treatment at the collaborating outpatient programs in which participants are enrolled, or (2) a modification of TAU which includes access to the Therapeutic Education System (TES), a computerized psychosocial intervention which combines skills building modules based on CRA with incentives primarily targeting abstinence from drugs of abuse and, secondarily, targeting completion of TES modules. We will evaluate the relative effectiveness of these interventions on the primary outcome measures of drug and heavy drinking day abstinence (as measured via urine testing and self-report) and treatment retention.

### 4.2 Secondary Objectives

- To evaluate the relative effectiveness of TAU vs. the modified TAU+TES interventions on several secondary outcome measures, including measures of HIV risk behavior (using the Risk Behavior Survey; Booth et al., 1993), psychosocial functioning (in areas of criminal activity, health status improvement, psychological status, family/social relationships, and employment, using the SAS-SR, Weissman, 1999; NMS; and BSI, Derogatis & Melisaratos, 1983) and treatment acceptability (based on participant feedback). (See Section 7 for planned list of assessments).
- To evaluate if improved outcomes are maintained at 3 and 6 months post-intervention.
- To perform a comprehensive economic analysis of including TES in TAU to inform decisions regarding adoption of this new therapeutic tool (assessing incremental costs per increased abstinence time and quality adjusted life year). The economic analyses are clinically important, as even if the computerized intervention is shown to be effective, it may not be adopted in community-based treatment programs unless it is shown to be cost-effective due to the considerable financial constraints in such treatment settings.
- To examine coping skills acquisition as a treatment process factor that may underlie changes observed during treatment. These analyses will allow an assessment of the extent to which TES impacts the development of coping skills, a hypothesized mediating variable that, in turn, impacts substance use behavior.
- To conduct exploratory analyses to assess (a) the effect of dose of TES exposure on drug abstinence and retention outcomes, (b) whether various sub-groups of participants have differential outcomes in drug abstinence and treatment retention across treatment conditions (e.g. stimulant vs. non-stimulant users; gender) and (c) whether various demographic variables, as well as baseline psychological and other history variables predict successful outcomes across treatment conditions in reducing substance use and promoting treatment retention.

## **5.0 STUDY DESIGN**

### **5.1 Overview of Study Design**

In the proposed CTN multi-site effectiveness trial, a diverse set of drug-using participants entering treatment at collaborating CTPs will be randomly assigned to receive 12 weeks of: (1) TAU or (2) a modified version of TAU which includes access to the computerized TES psychosocial intervention and incentives for abstinence from drugs of abuse and completion of TES modules. We will evaluate the effectiveness of including this computerized intervention as part of TAU to determine if patient use of TES enhances patient outcomes.

Due to the comprehensive, science-based, psychosocial treatment offered by TES, and based on prior work with TES and motivational incentives (Bickel, Marsch et al., 2008) and other work with motivational incentives (e.g., CTN trial published by Petry et al., 2005a), we hypothesize that the modified TAU+TES intervention will promote significantly greater drug abstinence and treatment retention relative to TAU.

### **5.2 Duration of Study and Visit Schedule**

All participants will be asked to participate in a 12-week trial in which they attend the treatment study site at least twice weekly (for a total of 24 visits across the trial period). A 12-week period was selected to best reflect the typical treatment episode duration for the target population in outpatient CTPs. Additionally, detailed participant tracking procedures (see Section 9.5) will be employed to locate participants during the trial and particularly at week 12 and at 2 post-intervention follow-up time points (3- and 6-months post-intervention). All participants (in both study conditions) will be asked to provide urine samples and breath alcohol tests at each twice weekly visit (as described in the Section 7.2.1 Assessments below). Participants in the TAU condition will be asked to participate in individual/group therapeutic sessions in accordance with the standard frequency of counseling at their CTP (as noted in Section 6.5 below, collaborating CTPs will offer TAU at least twice weekly), while those in the modified TAU+TES condition will be asked to participate in twice weekly TES sessions and less frequent therapy sessions/group counseling sessions at the treatment site (design details provided in Section 9.4 below). Participants will also be asked to complete scheduled assessments at these visits as needed, in accordance with the assessment timeline (as described in Section 7 Assessments). Participants who are absent on the day of a scheduled urine sample collection can provide a sample the next time they attend the CTP. Participants may be permitted to attend the CTP on a previously unscheduled day in order to provide urine samples and complete assessments. Urine samples must be provided on non-consecutive days within a week for a sample to qualify for incentive procedures (for those who are in the condition that receive incentives) and for contribution to the primary abstinence outcome.

## 6.0 STUDY POPULATION

### 6.1 Inclusion Criteria

- Male and female patients ( $\geq 18$  years) accepted for outpatient, substance abuse treatment at a participating CTP study site.
- Self-report any substance use problem, including alcohol as long as they also report other substance use in addition to alcohol.
- (1) Report use of a drug of abuse within 30 days prior to screening or (2) have exited a controlled environment (e.g., detoxification unit, hospital, or correctional facility) within 30 days of screening and report use of a drug of abuse within 60 days prior to screening. This sample was selected to ensure a CTP-friendly and real-world oriented effectiveness trial.
- Participants must be within the first month of initiating treatment at a collaborating CTP to ensure that scheduled psychosocial interventions can be initiated early on in treatment for all participants.
- Self-report a planned substance abuse treatment episode of at least 3 months (the planned evaluation phase in this trial).

Note that because few community clinics use formal diagnostic procedures in practice, individuals will not be required to meet DSM-IV criteria for abuse or dependence to participate in this study (although this will be assessed at baseline). Participants can also have had any number of prior substance abuse and/or psychiatric treatment episodes prior to their current substance abuse treatment episode.

All participants will provide written, informed consent, approved by local institutional review boards. A wide range of contact information will be obtained at baseline in order to locate subjects and achieve maximum adherence and follow-up rates (as described in detail in Section 9.5 below).

### 6.2 Exclusion Criteria

- Individuals will be excluded if they are participants in Opioid Treatment Programs (OTPs) and/or receiving opioid replacement medication, as TAU differs considerably in OTPs relative to other outpatient programs. If participants in CTPs are receiving some non-opioid pharmacotherapy for their substance use disorder or psychiatric disorder, we will systematically track this and consider these medication data in planned analyses as appropriate.
- Individuals will be excluded if they plan to move out of the area within the next 3 months.
- Individuals will be excluded if they have insufficient ability to provide informed consent to participate.
- Individuals will be excluded if they lack sufficient ability to use English to participate in the consent process, the interventions or assessments.

Ability to provide informed consent and English proficiency will both be confirmed through the informed consent process and the completion of a comprehension quiz. Participants will be asked to answer a number of questions related to study procedures outlined in the consent form. Any questions that the participant answers incorrectly will form the basis of discussion with a staff person. After discussion, the staff person will make a final determination of English

comprehension and ability to provide informed consent. Further, 100% of the informed consent documentation is monitored according to the quality assurance plan.

### **6.3 Subject Recruitment**

Potential participants will be informed about the opportunity to participate in this trial at the time they enter treatment at a collaborating CTP or within the first 30 days of treatment at the CTP. A variety of strategies may be employed to ensure that all new intakes are informed about the opportunity to participate in the trial. For example, CTP intake workers may introduce the patient to a study Research Assistant so they can learn about the opportunity to participate in the study or arrange a follow-up time to do so. Alternatively, all new intakes can be provided with a form, providing a brief description of the trial, which they can sign to indicate they would like to learn more about the trial. They can provide their contact information on this form and a Research Assistant will then contact them (assuming the patient and Research Assistant are unable to speak at the patient's time of intake). Note that by completing this form, patients are not consenting to participate in the trial but are giving permission for research staff to contact them both while they are at the CTP and/or via phone to inform them about more details of the study. Additionally, IRB-approved study flyers and posters may be posted at collaborating CTPs with information about how to contact research staff to learn more about the opportunity to participate in the study. Staff at the CTPs will also be informed about the study so that they can answer questions and consult with potential participants that are interested in the study.

During the initial contact between potential participants and research staff, staff will conduct a brief screen to assess if participants meet eligibility criteria for the study and do not meet exclusionary criteria for the study. Only information necessary to assess individuals' eligibility will be obtained at this initial screening (described in Sections 6.1 & 6.2 above). If a participant is eligible and interested in joining the study, s/he can complete Informed Consent procedures (described in Section 9.1.) with the Research staff at this initial visit (or within one month of their intake date for a new treatment episode at the CTP).

Based on prior CTN trials targeting a similar population (Petry et al., 2005), we expect that approximately 55% of participants will be female and about 50% of participants will be minorities.

### **6.4 Number of CTP Sites**

We plan to sample approximately 10 outpatient CTPs from the CTN platform and recruit approximately 50 participants per site (see justification of sample size in Section 14.4). Sites will be selected for the geographic, ethnic, racial, and gender diversity they offer, as well as their prior history of successful CTN collaborations and ability to demonstrate a sufficient flow of study participants.

### **6.5 CTP Characteristics and Rationale**

CTPs participating in this trial will:

- (a) Offer outpatient, community-based treatment for individuals with a wide variety of substance use disorders. As Treatment as Usual (TAU) differs in Opioid Treatment Programs relative to other outpatient CTPs, Opioid Treatment Programs will not serve as study sites in this trial.
- (b) Require participants in TAU to participate in at least 2-therapeutic sessions onsite per week, approximately 2 hours (group and/or individual sessions) for a minimum of 12 weeks. Note that CTPs that require fewer sessions will be excluded to prevent asking participants in this trial to attend the treatment site more often solely for the purposes of participating in this trial (as this would not then reflect TAU and would



- likely negatively impact participant retention). Additionally, CTPs that offer only intensive outpatient treatment (e.g., daily attendance requirements) will be excluded, as (1) intensive outpatient treatment, when provided, is typically provided only at initial stages of treatment, and (2) intensive outpatient treatment as a treatment modality is being offered with decreasing frequency in light of recent trends within managed care systems to reduce the number of treatment sessions for which reimbursement is provided. Programs that offer intensive outpatient treatment but then provide stepped-down care into less intensive outpatient treatment will not be excluded.
- (c) Project an average treatment intake rate of at least 1 eligible study client per week.
  - (d) Project a minimum of approximately 40 study clients to be enrolled at the site within 1 year.
  - (e) Provide adequate space to accommodate research assistants and study protocol procedures including on-site urinalysis collection and testing and space for computers for participants' access of TES and for site monitoring.
  - (f) Willing to allow participants in the modified TAU+TES condition to reduce their frequency of participation in group and/or individual counseling sessions (and to participate in twice weekly TES sessions).
  - (g) Willing to require all therapists at their CTP to follow study procedures with patients participating in this trial.
  - (h) Able to provide records of all participants' attendance in individual and group counseling sessions. Note that tracking forms for systematically documenting this information will be provided to each CTP so that these data can be summarized and provided in study reports when describing the type and amount of TAU study participants received.
  - (i) Not routinely offer (as part of TAU) contingency management interventions to their patients in which they provide prizes or other tangible incentives to participants contingent on evidence of drug abstinence.

## **7.0 ASSESSMENTS**

Unless otherwise noted, the following assessments will be conducted at baseline, and at Weeks 4, 8, and 12, during the active intervention phase, as well as at 3- and 6-month post-intervention follow-up time points. A timeline of assessment administration is provided at the end of this section. Assessment tools have been selected to measure key constructs that we hypothesize will be impacted by the planned intervention, while ensuring that measures do not assess overlapping constructs.

### **7.1 Assessments conducted at Baseline only.**

#### **7.1.1 Enrollment (ENR-A) (2 min)**

This form tracks the date of informed consent and collects several additional participant demographic variables (education, marital status, living arrangement, and distance from treatment program).

#### **7.1.2 Demographics (DEM) (1 min)**

Participants' basic demographics will be obtained at baseline and include sex, date of birth, and race/ethnicity.

#### **7.1.3 Randomization (ENR-B)**

This form is completed by research staff and documents inclusion/exclusion criteria and randomization information. It should be completed at the end of the baseline assessment.

#### **7.1.4 DSM-IV Checklist (DSM) (5-10 min)**

This is a semi-structured interview that provides current diagnosis for substance use disorders based on DSM-IV diagnostic criteria (Hudziak et al., 1993).

#### **7.1.5 The Patient Health Questionnaire (PHQ) (10 minutes)**

The PHQ will be used to assess co-occurring psychiatric problems, including major depression, social anxiety disorder, generalized anxiety disorder, PTSD, and ADHD (Blanco et al., Spitzer et al., 1999). Participants are asked to respond on a Likert scale the extent to which each of the criteria for a given disorder have been met, and an algorithm is applied to indicate presence/absence of a probable diagnosis.

#### **7.1.6 The MicroCog™ (15 min) (Powell et al., 2004)**

Is a computer-administered battery of tests assessing neurocognitive functioning? Five subtests are selected for use in this study in the following domains: memory, sustained focus attention, inductive reasoning, concept formation and cognitive flexibility, and visuoperceptual analysis. Differential attention, memory, or spatial processing may impact outcomes of the cognitive-behavioral based TES intervention.

### **7.2 Planned Assessment for Effectiveness Analyses**

#### **7.2.1 Substance Use Outcomes based on Urine Toxicology, Breath Alcohol, & Self-Report (10 min)**

Urinalysis and breathalyzer will occur at the baseline visit, twice per week for 12 weeks of the active study phase, and at the 3-month and 6-month follow up visits (procedures will coincide with the timing of planned contingency management procedures designed to reinforce drug abstinence). Each urine sample will be tested for the presence of 10 drugs: cocaine, opiates 2000 ng (includes morphine, codeine, and heroin), amphetamines, cannabinoids (THC), methamphetamines, benzodiazepines, oxycodone, methadone, barbiturates, and MDMA. A

breathalyzer will be used to screen for blood alcohol concentration (BAC), scored as negative versus positive for blood alcohol according to the standard cutoff. Participants whose BAC is above a .08 (standard legal limit) will be asked to wait to complete any additional assessments until their BAC is below .08 to ensure that participants are not intoxicated during the completion of the assessment measures. The intoxication event should be recorded in the progress notes. Research staff will use clinical judgment as whether participants can reasonably complete assessments with BAC levels above .01 but below .08.

Although it is encouraged that urine collections be observed by a same-sex observer to ensure the integrity of samples, it is recognized that this will not be possible in all situations and settings. Two validity checks of urine screens will be employed. First, a valid urine sample must fall within standard temperature ranges (e.g. > 90 and < 100 degrees Fahrenheit) as indicated by temperature strips located on the test cup. A further validity check will be provided by a commercially available adulterant test strip that indicates normal ranges for creatinine, pH (at minimum), nitrate, glutaraldehyde, specific gravity, bleach and pyridinium chloromate in human urine. Participants whose urine does not pass both of the validity checks will be offered the opportunity to provide a second sample. The second sample will need to be validated before urinary drug screen analysis. Urinalysis is never to be performed before a sample is validated and confirmed negative for adulterants. If the participant refuses to offer a sample, then the urinary drug screen will be counted as missing for that day (and positive for purposes of incentive procedures). Missing urine or alcohol samples will override a self-report of no substance use.

The timeline follow-back calendar assessment (TLFB; Sobell & Sobell, 1992) will be completed once per week during the treatment phase to assess self-reported substance use since the time of the last assessment (including time since last assessment during follow-up time points). The TLFB assessment uses calendars to obtain estimates of days of alcohol use, including standardized drink quantities, days of heavy drinking, and other substances (cocaine, opiates, amphetamines, methamphetamines, ecstasy, benzodiazapines, barbiturates, oxycodone/oxycontin, methadone, and marijuana), using memory aids to enhance recall (e.g., patterns of use, key dates). The TLFB has good psychometric properties, including test-retest measurement with multiple populations and content, criterion, and construct validity across multiple related measures (Sobell & Sobell, 2000). A summary of information obtained from the TLFB procedure will be generated from the calendars.

### **7.2.2 Risk Behaviors Scale (RBS) (5 min) (Booth et al., 1993)**

This questionnaire assesses sexual behavior and has been found to be a valid and reliable measure of HIV risk behavior.

### **7.2.3 Social Adjustment Scale – Self Report (SAS-SR) (10 min) (Weissman, 1999)**

This questionnaire consists of 54-items assessing six social role areas (work, social and leisure activities, family relationship, marital relationship, parental role, and role within the family unit). The SAS-SR is completed only at baseline, week 12, and 3- and 6-month follow-up. The SAS-SR has been widely used, with normative data for comparative purposes.

### **7.2.4 Brief Symptom Inventory (BSI) (3 min) (Derogatis & Melisaratos, 1983)**

The Brief Symptom Inventory is a brief, 18-item self-report measure of severity of psychiatric symptoms, derived from the longer SCL-90. It yields a global severity index (GSI), and three clinical subscales, somatization, depression, and anxiety, and has been shown to have good reliability and validity in a broad range of patient populations. This will be assessed at baseline, and weeks 4, 8, 12, and 3- and 6-month follow-up.

### **7.2.5 Fagerstrom Test for Nicotine Dependence (FND) (2 mins)**

The 6-item FND provides an ordinal measure of nicotine dependence related to cigarette smoking, including quantity of cigarette consumption, severity, and compulsion to use. An additional question assesses the use of medication to help stop smoking.

### **7.2.6 Participant Feedback Survey (5 min)**

This scale consists of five questions asking participants to rate how 1) interesting, 2) easy to understand, and 3) useful their psychosocial intervention with counselor and computer (for those in the test arm of the trial) was, and the 4) extent to which the intervention provided them with novel information and asks 5) how satisfied they were with their substance abuse treatment when combined with the psychosocial intervention they experienced (ranging from 0-10, anchored at “not at all” to “very much”). They will also be asked to provide information related to these same issues in Free Response format (e.g., qualitative, prose-like comments). Separate forms will be used for each study condition. This measure will be completed only at weeks 4, 8 and 12.

### **7.2.7 Coping Strategies Scale (CSS) – Brief Version (4 min) (Litt et al., 2003)**

This 23-item questionnaire (originally adapted from the Processes of Change questionnaire, Prochaska et al., 1988) assesses change processes and skills taught in coping-skills treatment, such as problem solving and dealing with urges to use substances of abuse. Participants will rate on a 4-point scale their frequency of using each strategy to help avoid substance use. Total coping is measured by taking the mean across all 23 items (internal reliability from multiple samples  $\alpha=.83$  to  $.87$ ). The CSS yields 4 subscales: active-behavioral, active-cognitive, avoidant-behavioral, and avoidant-cognitive. This scale will be of primary importance to assess the extent to which the Therapeutic Education System (TES) impacts the development of coping skills, a hypothesized mediating variable that, in turn, impacts substance use behavior. This measure will be completed only at baseline, week 12 and at the 3- and 6-month follow-up time points.

### **7.2.8 Treatment as Usual Tracking (TTF) (5 min)**

This form is completed by the research staff on a weekly basis during the 12-week treatment phase to capture services received in TAU, including modality and frequency.

## **7.3 Planned Assessments for Economic Analyses**

The following assessments will be used to obtain data needed for the planned economic analyses:

### **7.3.1 EuroQol EQ5D (QOL) (3 min) (the EuroQol Group, 1990; Dolan, 1997)**

The EuroQol instrument is a standardized general (not disease-specific) system for describing and valuing health-related quality of life. The instrument consists of two components: the EuroQol classification instrument, which describes the respondent's health within 5 domains, and a visual analog scale, with which respondents rate their health. Responses to each component yield a preference weight that can be used to construct Quality-Adjusted Life Year estimates (QALYs).

### **7.3.2 Non-Study Medical and Other Services (NMS) (5-7 min)**

Medical resources that are not part of the treatment intervention are primarily recorded on the NMS form. (As noted in Section 9.4.1.1, any services provided at the treatment site will be recorded on a separate tracking form). The NMS form captures services received outside of the study and CTP to include therapy visits, physician visits, residential program detoxification,

hospital detoxification, hospital visits, and emergency room visits and medication use through patient self-report. The assessment also captures health insurance status, employment, internet use, criminal activities, and contact with the criminal justice system. Validity of self-reported health care utilization has been demonstrated (Wallihan et al., 1999; Roberts et al., 1996; Jay et al., 1994; Harlow & Linet, 1989). The NMS was designed as part of Dr. Daniel Polsky's (our collaborating economist's) NIDA funded RO1 "CEA in CTN: BUP/NAL treatment for opioid addicted youth" because the Treatment Services Review (TSR) is not structured for a comprehensive cost analysis of treatment services (French et al., 2000).

### 7.3.3 Program DATCAP (30 min)

The program DATCAP is to be completed one time only per site by a program and/or fiscal director at each site, with a separate section completed by each active counselor. This will be completed at about the same time at each site during the trial period about mid-way through overall trial recruitment).

Program-specific costs (including salaries of personnel delivering services, facility costs associated with utilizing TES, counselor hours, and work tasks) will be measured via a modified form of the Program DATCAP (French, Dunlap et al., 1996; 1997). The process for administering the program DATCAP and analyzing the economic cost data are explained in detail within the instrument and User's Manual (French, 2001a; 2001b; www.DATCAP.com), as well as related papers (French et al., 1996; French et al., 1997; French & McGeary, 1997; Salomé & French, 2001).

### Assessment Schedule

Measure	Time (min)	Treatment Week														3/6 Mo F/U	
		S	BL	1	2	3	4	5	6	7	8	9	10	11	12		
Brief Screen (BSS)	5	X															
Enrollment (ENR-A)	2																
Demographics (DEM)	1		X														
DSM-IV Checklist (DSM)	10		X														
Patient Health Questionnaire (PHQ)	10		X														
MicroCog	15		X														
Urine Screen (UDS)	5		X	2	2	2	2	2	2	2	2	2	2	2	2	2	X
Alcohol Screen (ABS)	3		X	2	2	2	2	2	2	2	2	2	2	2	2	2	X
TLFB (TLFB Summary Form)	10		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Risk Behavior	5		X				X				X				X		X

### Assessment Schedule

Treatment Week																
Survey (RBS)																
SAS-SR (SAS)	10		X												X	X
Brief Symptom Inventory (BSI)	3		X				X					X			X	X
Coping Strategies Scale (CSS)	4		X												X	X
Randomization (ENR-B)	RA		X													
Participant Feedback (PFB)	5						X					X			X	
EuroQol (QOL)	3		X				X					X			X	X
NMS Non-Study Medical and Other Services (NMS)	7		X				X					X			X	X
TAU Tracking (TTF)	RA			X	X	X	X	X	X	X	X	X	X	X	X	
Program DATCAP (PDC)	30	<b>Single Administration (half way through study recruitment)</b>														

NOTE. S=Screening, BL=Baseline, F/U=Follow Up

## **8.0 OUTCOME MEASURES**

### **8.1 Primary Outcome Measures**

This study will include two primary outcome measures. The first primary outcome will be a measure of abstinence and we hypothesize that the modified TAU+TES intervention will promote significantly greater drug and heavy alcohol use abstinence compared to the TAU arm during the 12 weeks of treatment. Specifically, we will use longitudinal, piecewise, logistic regression to model all 12 weeks, but test for a treatment difference only during the last 4 weeks of the treatment phase. This first primary outcome measure will use half-weeks of abstinence from all tested drugs of abuse and heavy drinking (i.e., 5 or more drinks per day for men and 4 or more for women) during the 12 weeks of treatment, as confirmed via urine toxicology results measured twice weekly and self-reported use assessed via the TimeLine Follow-Back (completed weekly). Thus, the primary outcome measure will depend on urine-confirmed self report of drug use and self report of heavy drinking days. Participants will be considered negative from all drugs and heavy drinking days if both urine and self-report data reflect the absence of drug/alcohol use. Drug use will be evaluated by considering the following stratification variables as covariates: testing drug positive or negative at baseline and primary drug of use as a stimulant or non stimulant. Primary analyses will be conducted to model the effects observed during the intervention period; and separate analyses will be conducted to examine the durability of effects during the post-intervention follow-up period.

The second primary outcome is a measure of retention. We hypothesize that the modified TAU+TES intervention will promote significantly greater treatment retention relative to TAU during the 12-week treatment phase. The measure of treatment retention will be the number of days participants are in treatment (time until last face-to-face contact). As previously discussed, we have included both drug abstinence and retention as primary outcome measures in this trial, as drug abstinence is the primary goal of the planned treatment interventions and retention is typically quite low in the target population and is a clinically significant outcome that is strongly predictive of drug abstinence. Based on prior work with TES (Bickel, Marsch et al., 2008) and the prior CTN trials using non-computerized contingency management interventions with a similar population (MIEDAR CTN protocols # 006 & 007, published in Petry et al., 2005a), we expect that the modified TAU+TES intervention to be evaluated in this trial will positively impact both drug abstinence and treatment retention relative to TAU.

### **8.2 Secondary Outcome Measures**

We will also evaluate secondary outcomes of (a) HIV risk behavior (using the Risk Behaviors Survey; Booth et al., 1993), (b) Psychosocial functioning in areas of criminal activity, health status improvement, psychological status, family/social relationships, and employment (via the SAS-SR, Weissman, 1999; NMS, and BSI, Derogatis & Melisaratos, 1983), and (c) treatment acceptability measured via the Participant Feedback Survey (which we have successfully used in prior trials).

## **9.0 STUDY PROCEDURES**

### **9.1 Informed Consent Procedures**

Informed consent procedures must be conducted within 30 days of the date that participants entered the CTP for a new treatment episode. Every effort will be made to conduct consent procedures as soon as possible after a patient enters a CTP for a new treatment episode; however, a 30-day window allows for a broader array of eligible patients to be considered for study participation. As part of the informed consent procedure, the schedule for earning incentives for drug negative urines and alcohol breath tests and for completion of TES modules will be presented to and discussed with the participant.

### **9.2 Baseline Assessment**

After signing Informed Consent, participants will be asked to complete the baseline assessments (including the urine sample and breath alcohol collection), as described in Section 8 above. We expect that participants will complete Informed Consent and baseline assessments in the same day. If s/he does not finish the Informed Consent and baseline assessments in one day, s/he will be asked to return as soon as possible (and preferably the following day but within the eligibility window of one month post treatment intake) to finish the baseline assessment. In this case, another urine and breath alcohol sample will be collected at the subsequent visit and the day that the intake is completed will be counted as the study intake day.

### **9.3 Randomization**

After providing Informed Consent and completing the baseline assessment, participants will be randomly assigned to either (1) TAU or (2) modified TAU that incorporates the computerized intervention and incentives (TAU+TES). The randomization is used to provide balance with respect to measured and unmeasured patient characteristics across the randomized treatment arms. Randomization will be stratified on (1) site, (2) participants' primary substance of abuse (dichotomized as stimulant vs. non-stimulant) and (3) whether one is drug-positive/negative at baseline (based on urine/breath screens). The randomization procedure will be conducted in a centralized process through the CTN Data and Statistics Center 2 (DSC 2). The randomization sequence will be unknown to staff, but group assignment will not be masked after randomization. The DSC 2 statistician will generate the randomization scheme for the study. The randomization schedules will consist of balanced blocks within strata to ensure relative equality of assignment across treatment groups. The block sizes will be varied and randomly permuted to further prevent the potential for guessing the next assignment, which is heightened when a fixed block-size is used. The block size will not be revealed to participating investigators and will be randomly selected from a small number of different block sizes to help reduce the likelihood of an investigator predicting the next treatment assignment. This scheme will provide chronological balance during patient enrollment with respect to the number of patients allocated to each treatment arm, and will thus balance the treatment groups with respect to possible changes in the mix of patients over time. The DSC 2 statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. The randomization slot will not be re-allocated to a new patient due to the intent-to-treat nature of the study.



## 9.4 Treatment

### 9.4.1 Study Interventions

#### 9.4.1.1 Condition 1: Treatment as Usual (TAU)

Participants in this condition will receive TAU, consisting of standard treatment at each collaborating CTP and will reflect the model of treatment typically provided to most individuals in outpatient, community-based substance abuse treatment settings in the U.S. These sessions will consist of a combination of group and/or some individual counseling. The nature of TAU provided to participants at each collaborating site will be documented using a CTP Services TAU tracking form (e.g., duration and frequency of group vs. individual sessions; inclusion of HIV prevention content; provision of pharmacotherapy for substance use disorders, medical disorders or psychiatric disorders; frequency and type of Internet usage by participants for any purpose). Additionally, program counselors will typically provide crisis management and supportive counseling to help participants deal with personal problems or clinical issues, as needed. As previously described, CTPs that routinely offer at least twice weekly group and/or individual counseling sessions will be included. Individuals in Condition 1, TAU, will not receive contingency management incentives.

#### 9.4.1.2 Condition 2: Modified TAU Plus Computerized Psychosocial Intervention and Contingency Management

Participants in this condition will receive a modified version of TAU (described below) plus the computerized CRA and incentives offered by TES. TES will substitute for an average of 2 hours of therapeutic activity in TAU at each study site per week (or approx. 8 hours per month). Thus, participants in this condition will reduce their time in individual and/or group counseling by an average of 2 hours per week in order to participate in 2 TES sessions per week (approximately 1 hour per session). Participants in this condition will continue to participate in a group and/or individual counseling session at their CTP ideally at least once every other week.

- (a) **Treatment as Usual (TAU)**. Participants in Condition 2 will receive a modified version of TAU such that they will reduce the frequency of their participation in standard treatment (group and/or individual counseling) at the CTP. That is, an average of two hours of standard therapeutic programming at a given site will be replaced by TES. Although participants in this condition will have less time in group and/or individual counseling relative to participants in Condition 1, the nature of their individual sessions will be similar to individuals in Condition 1, except that counselors may also talk with participants in this condition about modules they are completing within TES, how useful they are finding it to be, and what modules they may want to consider doing during their next session. Detailed tracking procedures will be followed to document the frequency and type (e.g., individual or group sessions) of standard treatment for all participants (using the “TTF” tracking form).
- (b) **TES Psychosocial Intervention**. Participants in Condition 2 will be asked to use the self-directed TES intervention twice weekly and will be asked to complete 2 modules during each session (for a total of 4 modules per week) during the 12-week intervention. We expect that each module will take approx. 20-30 minutes to complete, so each session will last approx. 40-60 minutes on average. Thus, for example, if TAU at a given study site typically involves 2 one-hour individual and/or group sessions per week, a participant in this arm of the trial would be asked to participate in only one individual or group session every other week and complete 4 TES modules every week during the trial. If TAU at a given study site typically involves 3 one-hour individual and/or group sessions per week, a participant in this

arm of the trial may be asked to participate in only one individual or group session each week and complete 4 TES modules every week during the trial.

Note that participants in the prior trial completed 3 TES sessions per week, which coincided with their visits to their treatment program for buprenorphine medication. To better mimic participation requirements in routine outpatient treatment that does not involve opioid pharmacotherapy, and not place an undue participation burden on participants, we will ask participants to complete 2 sessions per week in this trial. Participants will be provided with access to TES on computers set-up at the CTP where they are receiving treatment or can choose to complete TES sessions within the privacy of their homes (assuming they have computers and appropriate Internet access). As TES has a back-end system that tracks participant activity using TES, onsite and offsite participant access to TES will be routinely documented (and will be used to assess participant's "dose" of exposure to TES in planned analyses). If participants choose to complete TES modules at home, they will still be asked to come in twice per week for urine testing.

Users of the program need not have any prior experience with computers in order to use TES. The program is self-directed. The first module a participant will access in the program is a training module to teach them how to use it (e.g., provides an overview of the goals of TES, how TES is organized, how to respond to questions on the computer, etc.). After a user completes the training module, they will be asked to complete 32 "core modules" during the first 8 weeks of the intervention (4 modules spread across two sessions per week for 8 weeks) and then can choose to re-visit modules and/or complete "optional modules" (up to 30 optional modules available) during the remaining 4 weeks of the intervention. Core modules will include those focused on basic, cognitive behavioral and relapse prevention skills (e.g., functional analysis of drug use and self-management planning, drug refusal skills) and basic HIV prevention. Optional modules will include those focused on relationships, communication skills, employment status, time management, insomnia and more detailed modules on HIV, hepatitis and STI prevention. (See list below of Core and Optional modules).

TES also includes an electronic reporting system (with appropriate password protection and an encrypted Internet connection via Secure Sockets Layer, the de facto standard for securing communications on the World Wide Web) summarizing patients' activity using TES. This feature allows the research staff to provide therapists reports on participant activity with TES and integrate participants' use of TES into their counseling sessions with the patient. In the planned study, counselors will be trained on how to help participants organize their customized TES plan based on unique needs. Thus, TES is a tool that counselors can use to extend their therapeutic efforts. We will track the extent to which counselors discuss TES with their clients in individual sessions.

### **CORE Modules within Therapeutic Education System (TES)**

A total of 32 Modules will represent CORE modules within TES in this trial, and participants will be asked to complete these modules within weeks 1-8 of the trial (4 modules per week for 8 weeks, approx. 20-30 minutes per module).

1. Training Module
2. What is Functional Analysis?
3. Conducting a Functional Analysis
4. Self-Management Planning
5. Introduction to Problem Solving
6. Effective Problem Solving

7. Drug Refusal Skills Training
8. Seemingly Irrelevant Decisions
9. Coping with Thoughts about Using
10. Awareness of Negative Thinking
11. Managing Negative Thinking
12. Managing Thoughts about Using
13. Managing Negative Moods and Depression
14. Decision-Making Skills
15. Increasing Self-Confidence in Decision-Making
16. Introduction to Assertiveness
17. How to Express Oneself in an Assertive Manner
18. Introduction to Giving Criticism
19. Steps for Giving Constructive Criticism
20. Receiving Criticism
21. Giving and Receiving Compliments
22. Communication Skills
23. Nonverbal Communication
24. Social Recreational Counseling
25. Attentive Listening
26. Sharing Feelings
27. HIV and AIDS
28. Sexually Transmitted Infections (STIs)
29. Sexual Transmission of HIV and STIs
30. Drug Use, HIV and Hepatitis
31. Identifying/Managing Triggers for Risky Sex
32. Identifying/Managing Triggers for Risky Drug Use

### **OPTIONAL Modules within Therapeutic Education System**

A total of 30 Modules will represent OPTIONAL modules within TES in this trial, and participants will be asked to complete these modules within weeks 9-12 of the trial. Participants can also select to re-do any Core modules if they so choose during weeks 9-12 of the trial (4 sessions per week).

1. Vocational Counseling
2. Financial Management
3. Insomnia
4. Time Management
5. Introduction to Relaxation Training
6. Progressive Muscle Relaxation Training
7. Progressive Muscle Relaxation Generalization
8. Introduction to Anger Management

9. How to Become More Aware of the Feeling of Anger
10. Coping with Anger
11. Relationship Counseling – Part 1
12. Relationship Counseling – Part 2
13. Relationship Counseling – Part 3
14. Hepatitis
15. Alcohol Use and risk for HIV, STIs and Hepatitis
16. Getting Tested for HIV, STI and Hepatitis
17. Finding More HIV, STI and Hepatitis Information
18. The Female Condom
19. Negotiating Safer Sex
20. Taking Responsibility for Choices
21. Birth Control Use and HIV and STIs
22. Living with HIV: Communication Skills for Disclosing HIV Status
23. Living with HIV: Drug Use and Immune System
24. Living with HIV: Managing Treatment and Medications
25. Living with HIV: Daily Routines to Promote Health
26. Living with Hepatitis C: Coping Skills
27. Living with Hepatitis C: Managing Treatment, Promoting Health
28. Naltrexone
29. Limited Alcohol Use
30. Alcohol and Disulfiram

**(c) Incentives for Abstinence**

Participants in Condition 2 will earn incentives contingent upon objective evidence of abstinence from their primary substance of abuse in accordance with an intermittent schedule of reinforcement shown to be efficacious in a prior CTN study conducted at CTPs (“fishbowl” prize system; Petry et al., 2005a). Specifically, participants will receive prize incentives for providing urine samples negative for their primary substance of abuse (as assessed on the DSM-IV Checklist), or breath samples negative for alcohol if alcohol is their primary substance of abuse (samples collected twice per week). As various participants in community-based outpatient substance abuse treatment will likely be in treatment for different substances of abuse, these procedures will be used to ensure that contingencies target the various substances of choice among this heterogeneous sample and that results will be generalizable to diverse sub-groups of substance-using individuals. If urine specimen results are ambiguous, inconclusive, or invalid (as described in Section 7.2.1), participants will be offered the opportunity to provide a second sample. If they choose not to do this, their sample will be counted as missing for that day (and positive for purposes of incentive procedures).

Contingency management interventions have been shown to be efficacious in targeting this array of substances in prior research (see Stitzer & Petry, 2006 for a review). In this process, each time a participant provides a urine/breath sample that is negative for their primary substance of choice, s/he will receive a draw from the computerized ‘prize bowl’ included in TES, which allows for automation of all prize calculation & tracking on any desired probability

schedule (and thus does not require these activities to be implemented by CTP staff). Half of the draws in the prize bowl will be non-winning and will read “good job” (or equivalent). The other “winning” half of draws will be structured such that 41.8% of draws will be for ‘small’ prizes worth about \$1 (e.g., make-up, socks, restaurant gift certificates), 8% will be for large prizes worth about \$20 (e.g., watches, clothing), and 0.2% will be for a jumbo prize worth up to \$100 (e.g., TV, Playstation). The number of draws will increase by 1 for each week in which all submitted samples are free of the primary substance (and will reset to 1 after an unexcused absence or submission of a sample positive for one’s primary substance). To offset low rates of reinforcement early in the study, when number of draws is low, a large prize will be awarded when the participant first achieves 2 consecutive weeks of abstinence from their primary substance of abuse. Also, participants can earn 2 bonus draws each time their samples are negative for all tested substances. This procedure will be employed to promote abstinence from all drugs and not just a single substance of abuse. Probabilities of winning will remain constant. Participants can earn a maximum of approximately \$452 if they earn all possible draws; however, based on prior experience with such schedules, we predict that they will likely earn about 45%-65% of possible earnings (approx. \$249).

Note that we chose to use this schedule (as opposed to the fixed, escalating schedule of reinforcement in which monetary voucher reinforcers were given in the prior efficacy trial with TES; Bickel, Marsch et al., 2008) for a number of reasons. Specifically, intermittent prize-based, “fishbowl” schedules of reinforcement (1) have been shown to be of comparable efficacy to fixed, voucher-based escalating reinforcement schedules (Petry et al., 2005b), (2) have repeatedly been demonstrated (including in national, multi-site studies on the CTN platform) to be effective, cost-effective and feasible to implement in a wide variety of outpatient CTPs (e.g., Petry, Martin, Cooney, & Kranzler, 2000; Petry et al., 2004; Stitzer & Petry, 2006; Sindelar et al., 2007), (3) have been shown to create a positive culture within CTPs (Kellogg et al., 2005), (4) may be more acceptable to CTPs because they can provide patients with rewards for abstinence from a fixed range of prizes rather than requiring program staff to purchase virtually any item of the patients’ choice with vouchers earned for abstinence, and (5) can allow for evidence-based contingency management procedures to be implemented in community settings at a lower cost (relative to fixed, voucher schedules of reinforcement), which is important for treatment programs who may have considerable financial constraints. These factors are considered in our economic analyses in the planned trial.

As previously indicated, participants will be asked to provide urine/breath samples twice weekly. Participants who are absent on the day of a scheduled urine/breath sample collection can provide a sample the next time they attend the CTP. Participants may be permitted to attend the CTP on a previously unscheduled day in order to provide urine/breath samples and complete assessments. Two samples must be provided on non-consecutive days in order to qualify for incentive procedures (for those who receive incentives) and the primary outcome measure of abstinence.

As noted above, participants will receive the opportunity to earn prize incentives for being abstinent from all tested substances, as measured twice weekly. We recognize that THC may be detected for longer periods of time relative to other drugs; however, we plan to evaluate THC (based on urine-confirmed self-report) at the same frequency as other drugs for consistency. Thus, the same set of criteria will be used in our evaluation of abstinence for all tested drugs of abuse. A similar procedure was used in a prior CTN study in which incentives were provided for abstinence from various drugs of abuse (Petry et al., 2005).

Tangible incentives will be stored in a locked cabinet at each CTP, on display to participants. Research staff at each site will be responsible for ensuring that the cabinets are well-stocked with incentives. Each site will be required to have available prizes of small (about \$1), large

(about \$20) and jumbo values (about \$100); however, they will have flexibility regarding the types of prizes offered as long as they are not deemed by clinic and research staff to be non-therapeutic. CTPs may also seek patient input into the types of prize incentives that may be most useful/desirable to them. Counselors can be present at the time their clients select prizes from the prize cabinet to provide the client with further reinforcement.

- (d) **Incentives for Module Completion.** Participants in Condition 2 will be provided with a single draw from the computerized ‘prize bowl’ after each module that they complete within TES. As participants will be asked to complete 4 modules per week, they can receive a maximum of 4 draws per week contingent on module completion. Probabilities of winning will be identical to those described above in the section on Incentives for Abstinence. If participants complete all scheduled modules each week during the 12-week intervention, they can earn a maximum of approximately \$106 in incentives (with an expected payout of about \$58).

#### **9.4.2 Therapist Involvement in Study Conditions**

All therapists at each collaborating CTP may work with participants in each study condition. This procedure will reflect how TES might be best integrated into real-world CTPs, such that existing therapists at the CTP integrate TES into TAU they provide to their clients. This procedure will also help ensure that specific therapists do not differentially impact one study condition. Additionally, it is likely that participants may see more than one therapist (e.g., group therapy will likely be a common treatment modality at participating CTPs, and the therapists leading groups will likely change over time), and it would thus be difficult to match participants in specific study conditions to therapists. Therapists at all collaborating CTPs will receive training on the TES and for ensuring the fidelity of the interventions (as described in Sections 10 and 11 below). They will also be required to complete Human Subject’s Protection training.

#### **9.4.3 Subject and Treatment Discontinuation Criteria/Stopping Rules**

Participants will be considered to be active in the study throughout the 12 week period following their baseline assessment, independent of the frequency with which they attend the CTP. If a participant is terminated or discharged from the CTP, then they are no longer eligible to participate in the active treatment portion of this study. A standardized criterion for CTP discharge will be adopted during the conduct of this trial (e.g., no contact with a patient for 30 consecutive days). Participants will still be tracked and asked to complete all assessments, including treatment week 12, 3- and 6-month follow up assessment visits.

### **9.5 Follow-Up**

Successful completion of assessments during the 12-week intervention phase and at follow-up will require active participant tracking procedures. A variety of strategies may be used to ensure the highest possible participant assessment completion rates, particularly at week 12 and at follow-up time points. First, a wide variety of contact information will be obtained from all participants at intake and will include the participant’s current address and phone numbers, including cell phone numbers, names, addresses and phone numbers of persons who may know how to reach the participant, including at least one close family member, if possible. The study Consent Form will ask for permission for the research team to contact these people if unable to locate the participant. When making contact, research staff will explain that they are trying to locate the participant to follow-up on a research study, and no specific information about the participant or the nature of the study will be revealed. Social Security numbers and driver’s license numbers will also be obtained, with participant permission. Taken together, these data can be used in conjunction with standard search engines to help locate participants. Research staff will update participant contact information at least every 4 weeks during the active intervention phase and at the 3 month assessment. Second, research staff will call

participants (repeatedly as needed) and leave messages in order to remind them of appointments and schedule follow-up appointments. Third, a reminder letter will be mailed and/or sent via email to participants within 2 weeks of their scheduled interview. If no contact is made with the participant by the follow-up due date, additional letters/e-mails will be sent to all contact addresses and additional phone calls made to try to reach participants. Fourth, a dedicated follow-up “tracker” at each collaborating CTP whose main responsibility will be to maintain contact with participants and locate them for follow-up assessments will be strongly encouraged. In addition to using the above strategies, this person may also go to participants’ homes, places they frequent, etc. to contact participants, and these procedures will be outlined in the study informed consent. Assessments may also be completed by the participant (and overseen by the follow-up tracker) at a location convenient for the participant (instead of at the CTP) if necessary. An expert follow-up tracker at the Lead Node will be available to assist research staffs at the sites with location of participants.

### **9.5.1 Follow-Up with Participants who Become Prisoners during Study Participation**

In addition to the follow up procedures detailed above, research staff will attempt to conduct assessments with participants who may become incarcerated during the course of the study. Specifically, research staff may attempt the week 12 monthly, 3- or 6-month follow up assessments with prisoner participants.

The study will not recruit individuals with prisoner status (eligibility criteria require that participants be able to attend 12 weeks of treatment in person), but will only attempt to gather follow up assessment data with participants whose status changes to that of prisoner during the course of participation. Research staff will follow procedures set forth by individual jails or prisons to access participant prisoners and will procure institutional approval prior to conducting assessments. Institutional approvals to conduct assessments will be maintained at the local site. Research assessments with prisoner participants will only be administered if they do not interfere with a prisoner receiving visitors or meeting with legal counsel and there is space where confidentiality can be assured (i.e., no one else will be able to hear the participant’s responses). Research staff will ensure confidentiality is protected or the research assessment will not be completed. In addition, research staff will not divulge the exact nature of the research study (i.e., a study related to substance use disorders) to jail/prison authorities.

The consent form has been modified to include the following language: (1) staff may seek out jail / prison records in an attempt to contact individuals should they become incarcerated, (2) participants who are incarcerated will be approached to ask if they would be willing to complete assessments during detainment (under the rules of the institution in which they are detained), and (3) criminal justice personnel (including parole or probation entities) will not have access to research data. Biological screening (urine drug and breath alcohol) will not be collected from prisoner participants. Interviews conducted within prison settings will be administered by research staff on paper forms and take approximately 1 hour to complete. The following assessments will be completed at treatment week 12, 3- and 6-month follow up with prisoner participants: Risk Behavior Survey, Timeline Follow-back, Non-study Medical and Other Services, Brief Symptom Inventory, EuroQOL, Fagerstrom Test for Nicotine Dependence, Coping Strategies, Social Adjustment Scale, and Participant Feedback Survey (week 12 only). A more detailed description of each assessment can be found in section 7.

Prisoner participants will not receive compensation for research assessments completed while in jail/prison.

## **9.6 Blinding**

Study condition will not be blinded in this trial.

## 9.7 Participant Compensation

All participants will receive the following compensation for time and effort related to research activities (although various sites may offer slightly different amounts depending on the appropriateness of compensation rates in their setting): \$50 for assessments at baseline, treatment weeks 4, 8, 12, and 3- and 6-month post treatment follow-up visits (participants will receive an additional \$50 bonus if they complete all of these assessment visits). The maximum compensation for assessments is \$350. In addition, all participants will be compensated \$5 for each urine sample they provide during the 12-week treatment phase (a maximum of 24 urine screens for a total of \$120). To avoid competing with the potential treatment effect of the contingency management component in the modified TAU + TES condition, compensation for providing urine samples will be given to all participants at the monthly treatment phase visits (i.e., weeks 4, 8, and 12). Each CTP can determine whether participant compensation for assessment is made in cash or voucher depending on what is most appropriate for their site. As is typical in many clinical trials, providing compensation to all study participants will help ensure we obtain study data critical for evaluation of our planned interventions. We expect that this aspect of the intervention should not greatly impact the planned economic analyses, as both groups of participants will receive compensation for assessments and we do not expect this to differ across groups. Also, these assessments and the associated compensation for completing them would not be needed in routine clinical practice and thus would not be associated with the cost of implementing such interventions in real-world settings.



## 10.0 TREATMENT FIDELITY & ADHERENCE

As previously discussed, by automating the CRA + incentives psychosocial intervention with TES, the fidelity of the delivery of the intervention is assured. Indeed, the computerized delivery of CRA helps reduce concerns about fidelity in the delivery of the intervention and all incentives earnings will be calculated via pre-established earnings probabilities for the various target behaviors (as described in Section 9.4.1.2). To monitor participant adherence, the electronic progress reporting system within TES will enable automated tracking of participant activity using TES. This tracking system will enable research staff to view information regarding what modules participants have accessed and/or completed and how long they spent in computer sessions. As previously noted, data from this tracking system will be used to assess participant's "dose" of exposure to TES in planned analyses.

TAU will not be manualized to better reflect how TAU is provided within CTPs and thereby increase the generalizability of study results. Note that, in addition to the automated tracking of participant activity with the web-based intervention, our research staff will obtain attendance records of participants in group and/or individual counseling sessions from each CTP, along with information on the duration of each session. The research team will document this information about provider contact with patients in both the TAU and the modified TAU + TES condition (using the TAU Tracking form created for this purpose and described in the assessment section). All CTP counselors will be asked to "check-in" with clients who are randomized to the TES+TAU arm and complete a brief counselor checklist (including approximate number of minutes spent discussing TES). The check-in will include an inquiry about the TES experience, updates on module completion, and discussion of optional module completion, as appropriate. Counselors will receive reports from the research staff documenting which TES modules their individual clients have completed. This is intended to be consistent with the model of TES as "clinician extender" which is being tested in this trial.

Further, a clinical supervisor at each site will receive training from the Lead Node in overseeing counselor interactions with TES clients. Supervisors will be trained in reviewing completion of the counselor checklist and discussing with counselors how the information from TES reports is being used in the counseling sessions. Clinical supervisors will meet with counselors monthly to discuss and monitor interactions with TES clients.

## **11.0 TRAINING PROCEDURES**

All research staff will be thoroughly trained on all study procedures, including Informed Consent, the use of TES, and participant tracking procedures. Additionally, counselors at each collaborating CTP will be thoroughly trained in the study design, human subject's protection, their role in each of the two study conditions, and how to review their clients' activity reports within TES. Research staff will also be trained on all assessment measures, including assessments administered via computer, to be able to answer all participant questions.

## **12.0 CONCOMITANT THERAPY**

### **12.1 General Considerations**

To avoid placing artificial constraints on the study design and reduce the generalizability of study findings, we will not exclude participants who engage in substance abuse treatment or psychiatric treatment outside of the study during the 12-week study phase. Rather, we will track the type, frequency, and duration of such concomitant therapy and consider these data in planned analyses as appropriate (via the NMS).

### **12.2 Medications Allowed During the Trial**

We do not expect that many patients in CTPs will be receiving pharmacotherapy for substance use disorders (especially because individuals with opioid use disorders receiving opioid pharmacotherapy will not be eligible to participate in this trial). However, as previously noted, we will track this information for all participants and consider pharmacotherapy data in planned analyses as appropriate (via the NMS).

## **13.0 REPORTING AND MONITORING**

### **13.1 Statement of Compliance**

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

### **13.2 Regulatory Files**

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

### **13.3 Informed Consent**

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. Each study site must have the study informed consent approved by their IRB(s). A copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the lead node (LN) prior to the site initiation visit. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

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

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

study procedures and have the person re-take the consent quiz prior to signing the informed consent document. The content of the quiz may be modified per local IRB requirements.

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

Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

### **13.4 Health Insurance Portability and Accountability Act (HIPAA)**

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

### **13.5 Investigator Assurances**

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

### **13.6 Financial Disclosure**

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

### **13.7 Clinical monitoring**

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

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

## **13.8 Study documentation**

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

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

## **13.9 Safety Monitoring**

### **13.9.1 Data and Safety Monitoring Board (DSMB)**

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

### **13.9.2 Protocol Violations Reporting and Management**

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

All protocol violations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Violations CRF. Additionally, each site is responsible for tracking and reporting to their IRB as required. Protocol deviations will be noted by participating sites and reported to their IRBs as required. The CCC and the Data and Statistics Center 2 and the Lead Investigator must be contacted immediately if an unqualified/ineligible participant is randomized into the study.

### **13.9.3 Confidentiality**

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The NIH office that

issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary.

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

#### **13.9.4 Adverse Events (AEs)**

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

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

#### **Definitions of Adverse Event and Serious Adverse Event**

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

#### **Reportable Adverse Event and Serious Adverse Event**

##### **Adverse Events**

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

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

This would typically include physical events such as headache, cold, etc that was considered unrelated to study participation.

##### **Serious Adverse Events**

For the purpose of this study, the following SAEs will not be recorded in the data system but will be documented in the source documentation as medically indicated. They would be reported to local IRBs per local IRB guidelines:

- Admission to a hospital or freestanding residential facility for drug detoxification; the event will be captured on the NMS form (described above).
- Admission to a hospital/surgery center for preplanned/elective surgeries;
- Admission to a hospital for scheduled labor and delivery;
- Inpatient hospital admission for a medical event (i.e. gallbladder surgery, pneumonia)

## 14.0 STATISTICAL ANALYSES

### 14.1 Outline of Study Hypotheses

#### 14.1.1 Two Co-Primary Hypotheses

- Due to the comprehensive, science-based, psychosocial treatment offered by TES, we hypothesize that the modified TAU+TES intervention will promote significantly greater drug and heavy alcohol use abstinence compared to the TAU arm during the 12 weeks of treatment. Specifically, we will use longitudinal, piecewise, logistic regression to model all 12 weeks, but test for a treatment difference only during the last 4 weeks of the treatment phase.
- We hypothesize that the modified TAU+TES intervention will promote significantly greater treatment retention relative to TAU during the 12-week treatment phase.

#### 14.1.2 Secondary Hypotheses

- We hypothesize that differential outcomes in drug abstinence observed across groups during treatment will continue to be observed at the 3- and 6- month follow-up time points.
- We expect that psychosocial functioning will improve in the group that received the modified TAU+TES at 3- and 6-month follow-up time points relative to the TAU alone condition.
- We hypothesize that the modified TAU+TES intervention will be cost-effective relative to TAU from both the health care sector and CTP program perspectives at the 3- and 6-month follow-up time points.
- We hypothesize that individuals in modified TAU+TES will show significant increases in coping skills acquisition (as measured via the Coping Strategies Scale) relative to TAU at end of treatment and 3- and 6-month time points, and we expect that coping skills will be shown to serve as a mediator substance use outcomes.

### 14.2 Primary Outcome Measures

This study will include two co-primary outcome measures, a measure of abstinence from all drugs and heavy drinking days and a treatment retention measure, as described below. The primary endpoints will be analyzed according to the intent-to-treat principle. This means that patients will be analyzed according to the randomized treatment regardless of the subsequent sequence of events. In other words, patients will be considered to belong to the randomized group even though they may not be perfectly compliant or may not follow the prescribed treatment.

#### 14.2.1 Primary Abstinence Measure

The first primary outcome measure will be an indicator of abstinence from all drugs of abuse and heavy drinking days in the interval between the two biweekly urine collections. We refer to this interval as a “half-week”, since it will be 3-4 days on average. Thus the primary abstinence measure is actually a set (i.e. vector) of binary indicators over the 24 half-weeks comprising the 12 week treatment phase of the study. Evidence of abstinence from drugs of abuse in a given half-week will be obtained via urine toxicology measured at the end of the half-week and via self-reported use assessed by the TimeLine Follow-Back. Heavy drinking days will be assessed via the TimeLine Follow-Back. Thus, the primary outcome measure will be based on urine-confirmed self report of drug/alcohol use. Participants will be considered negative from all



substances (abstinent) in a given half-week if their urinalysis at the end of the half-week and their self-report data both reflect the absence of drug and heavy alcohol use. If either a urine sample or self-report data indicate drug or alcohol use in a given half-week, the participant will be considered positive for substance use (non-abstinent) for that half-week. Table 1 gives the half-week outcome coding for all possible joint occurrences of urinalysis and self-report, including where either or both are missing. Note that self report for a particular half-week is missing only if one (or more) follow-back day is unobserved and all other days in the half-week are reported negative or all days in the half-week are missing. If the urine sample at the end of a given half-week is missing, and the subject reports no use, then they are considered to be missing the indicator of abstinence for that half-week.

**Table 1.** Half-week outcome coding corresponding to UDS and self-report outcomes.

		<u>Urine Drug Screen</u>		
		Positive	Negative	Missing
<u>Self Report</u>	Positive <sup>a</sup>	+	+	+
	Negative <sup>b</sup>	+	-	Missing
	Missing <sup>c</sup>	+	Missing	Missing

<sup>a</sup> Positive self report indicates  $\geq 1$  reported non-abstinent day in the half-week.

<sup>b</sup> Negative self report indicates all days in the half-week were reported abstinent.

<sup>c</sup> Self report is missing if there is no TLFB data for  $\geq 1$  day in the half-week.

Missing urine sample collections require additional assumptions in order to define the intervals for each half-week. For example, if a subject contributed a urine sample only on day two of the week, then we must specify a rule for deciding when the second urine collection should have been made. Table 2 describes this rule set for setting a date of collection for a missing urine sample when there is one urine specimen obtained in a week. If there are no urine samples collected in a particular week, then the dates of collection are assumed to be days 3 and 6.

**Table 2.** Specifying collection dates for missing urine samples.

<b>Observed Collection Day</b>	<u>Day in a Given Week</u>						
	1	2	3	4	5	6	7
<b>Imputed Collection Day</b>	6	6	6	2	3	3	3

In this way, we can define half-weeks even if the urine screen defining the end of the interval was not collected. Missing data in the primary abstinence measure, as defined in Table 1, will be excluded from the primary analysis. However, secondary analyses of the primary abstinence measure will utilize other methods of handling missing data (see Section 14.13). In the event two urine screens were collected on consecutive days, only the first sample will be considered for the analysis of all abstinence outcomes.

See Sections 14.6 and 14.7 for descriptions of secondary analyses using alternative outcome measures of abstinence: the total number of abstinent weeks and the number of consecutive weeks abstinent.

### 14.2.2 Primary Retention Measure

The second primary outcome measure will be time to drop-out from treatment (including TAU) and will be treated as time-to-event data (time until last face to face contact). Drop-out is considered an event, and for each participant who does not complete all 12 weeks of treatment, time (in weeks) from start of treatment to drop-out from treatment is recorded, with values potentially ranging from 0 through 11. Participants completing all 12 weeks of treatment will have time value recorded as 12 weeks and will be considered censored at that time.

### 14.3 Rationale for Considered Magnitude of Treatment Effects

Effect sizes and variability estimates were obtained from data from prior CTN trials that had some similar design characteristics as the planned trial (CTN MIEDAR study protocols #006 and 007 published in Petry et al., 2005a). Specifically, these prior CTN trials evaluated a similar non-computerized, motivational incentives intervention for a similar duration (12 weeks) as will be evaluated in the present trial. As prior research by our group and others (e.g., Bickel, Marsch et al., 2008; Marsch et al., 2007b) has demonstrated the comparable efficacy of computerized and non-computerized psychosocial interventions, we expect the effect sizes to be observed in the planned trial will be comparable to those observed in this prior CTN trial (details of effect sizes discussed in Section 14.4. below).

### 14.4 Sample Size and Statistical Methods for Primary Outcomes

We propose to recruit a sample size of about 500 participants (about 250 per condition). We plan to collaborate with approximately 10 (range 8-12) CTP sites to recruit participants for this trial, and we plan for each collaborating CTP to recruit approximately 40-60 participants in one year (for a total of about 500 participants enrolled in year 1). As discussed below, these sample size calculations are based on having sufficient power to detect group differences in our primary outcome measures of (1) abstinence during the 24 half-weeks of treatment (calculated as urine confirmed self-report) and (2) treatment retention.

Hence, the overall null hypothesis of the study has two individual null hypotheses, each corresponding to one primary endpoint. The first individual null hypothesis  $H_{0-1}$  states that the TAU+TES therapy does not change abstinence as compared to the TAU arm of the trial. The second individual null hypothesis  $H_{0-2}$  states that the TAU+TES therapy does not change treatment retention as compared to TAU.

The alternative overall hypothesis states that the TAU+TES therapy changes at least one primary endpoint (abstinence or retention) as compared to TAU. It is expected that the TAU+TES therapy, when compared to TAU alone, will increase abstinence and improve retention in treatment.

Since the study considers simultaneously two co-primary endpoints, one needs to account for multiplicity of comparisons to protect type I error. During analysis we propose to use the method proposed by Hochberg (Hochberg, 1988). The method states that the overall null hypothesis can be rejected if either of the following two conditions holds:

- Both endpoints are significant at the  $\alpha = 0.05$  significance level (i.e. both individual null hypotheses  $H_{0-1}$  and  $H_{0-2}$  are rejected at  $\alpha = 0.05$ )
- Either endpoint is significant at the  $\alpha = 0.025$  significance level (i.e. at least one of the two individual null hypotheses  $H_{0-1}$  or  $H_{0-2}$  is rejected at  $\alpha = 0.025$ ).

Sample size estimates for the Hochberg approach require simulations. Hence, the sample size computations below will be based on a more conservative (i.e. requiring somewhat larger sample size) Bonferroni adjustment approach, in which both individual hypotheses  $H_{0-1}$  and  $H_{0-2}$

need to be rejected at the  $\alpha=0.05/2 = 0.025$  level. However, for analysis, as mentioned above, we will use the more powerful Hochberg approach.

#### 14.4.1 Statistical Methods and Sample Size Considerations for Primary Abstinence Measure

Let  $y_{it}$  denote the indicator of abstinence for participant  $i$  ( $i=1, \dots, n$ ) during half-week  $t$  ( $t=1, \dots, 24$ ). The vector of outcomes for a participant,  $\mathbf{y}_i = (y_{i1}, \dots, y_{i24})$ , constitutes the primary outcome measure of abstinence. The precise definition of half-week  $t$  is the time between the  $(t-1)^{\text{th}}$  urine collection and the  $t^{\text{th}}$  urine collection. For example, consider a participant whose third and fourth urine collections fall on days 8 and 11 of the treatment phase of the study. The fourth half-week would then comprise TLFB self report data from days 8 through 10 confirmed by the urinalysis on day 11. To be considered abstinent in the fourth half-week ( $y_{i4} = 1$ ), the participant must report no drug or heavy alcohol use on days 8, 9 and 10 and the urine sample collected on day 11 must be negative. If that urine sample is missing for any reason and no use was reported via TLFB, then the indicator of abstinence for the participant is missing for the fourth half-week. If on days 8-10 there is at least one self-reported day of heavy drinking or drug use (i.e., positive self report) or the urinalysis is positive, then the participant is considered not abstinent ( $y_{i4} = 0$ ).

The primary outcome analysis of abstinence will evaluate whether assignment to TAU+TES is associated with more abstinence in the last four weeks of the treatment phase of the study compared with those assigned to TAU. Previous CTN studies have noted that after a certain period of time (approximately four weeks), the effect of both TAU and contingency management therapies stabilize. To minimize the possibility of a time by treatment interaction affecting the primary comparison between the two treatment groups, we will model all 24 half-weeks, but only test for a treatment difference during the last eight half-weeks of the 12-week treatment phase.

Since the primary outcome of abstinence is binary and measured over the 12 weeks of the treatment phase, a longitudinal logistic regression model will be used for the analysis. The logistic model has two components: a linear association between treatment and the log-odds of abstinence over the first 16 half-weeks, and a constant treatment effect (odds ratio) beginning at half-week 17, and extending through the end of the treatment phase. Figure 1 gives a graphical representation of this “piecewise linear” model. The intercepts  $\alpha_0$  and  $\alpha_1$  are the log-odds of abstinence in the first half-week for the TAU and TAU+TES arms respectively.  $\beta_0$  and  $\beta_1$  are the increase in the log-odds of abstinence across consecutive half-weeks (for  $t=1, \dots, 16$ ). The slope of the log-odds line after half-week 16, that is common to both treatment arms, is captured by  $\Phi$ .

Letting  $TES_i$  be an indicator of whether a participant was randomized to the TAU+TES arm, the piece-wise model for all  $i$  ( $i=1, \dots, n$ ) and  $t$  ( $t=1, \dots, 24$ ) is given by

$$\text{logit } P(y_{it} = 1) = \alpha_0 (1 - TES_i) + \alpha_1 TES_i + \beta_0 (1 - TES_i) [17 + I\{t < 17\}(t - 17)] \\ + \beta_1 TES_i [17 + I\{t < 17\}(t - 17)] + \Phi I\{t \geq 17\}(t - 17)$$

where  $I\{\cdot\}$  is the indicator function. More simply, the logit  $P(y_{it} = 1)$  can be split as follows:

$$t < 17: \alpha_0 (1 - TES_i) + \alpha_1 TES_i + \beta_0 (1 - TES_i) (t) + \beta_1 TES_i (t)$$

$$t \geq 17: \alpha_0 (1 - TES_i) + \alpha_1 TES_i + 17 \beta_0 (1 - TES_i) + 17 \beta_1 TES_i + \Phi (t - 17)$$

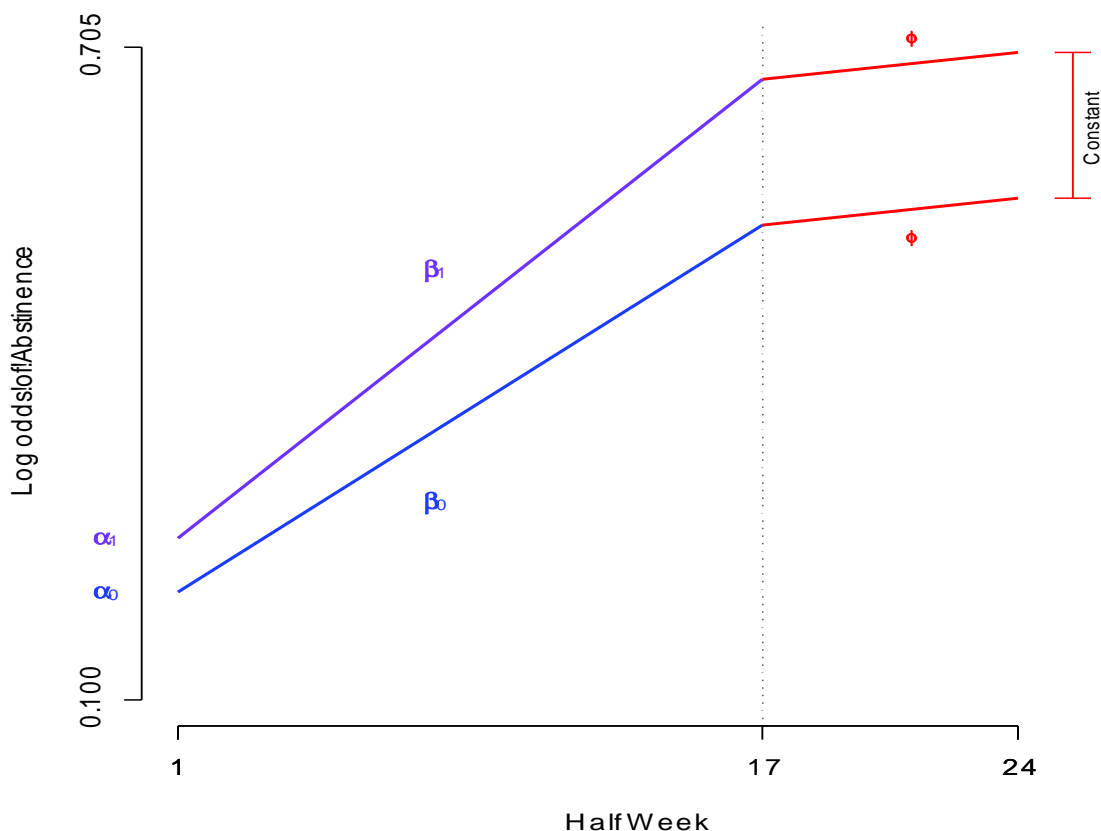
Further, we adjust for the two stratification factors. Let  $z_i$  be an indicator of whether the participant's primary drug of use is a stimulant, and  $x_i$  an indicator of whether the participant's baseline urine screen was positive. In this case the longitudinal logistic regression becomes:

$$t < 17: \gamma z_i + \eta x_i + \alpha_0 (1 - TES_i) + \alpha_1 TES_i + \beta_0 (1 - TES_i) (t) + \beta_1 TES_i (t)$$

$$t \geq 17: \gamma z_i + \eta x_i + \alpha_0 (1 - TES_i) + \alpha_1 TES_i + 17 \beta_0 (1 - TES_i) + 17 \beta_1 TES_i + \Phi (t - 17)$$

In this model the log-OR of abstinence associated with using a stimulant is captured by  $\gamma$ , and the log-OR associated with testing positive at baseline is denoted by  $\eta$ .

**Figure 1.** Longitudinal Logistic Model for Primary Abstinence Outcome Measure.



To adjust for the correlation of half-week abstinence indicators within participants, we will utilize the robust variance estimator from generalized estimating equation (GEE) methodology (Liang & Zeger, 1986). For the 24 binary outcomes within a participant, we will assume an auto-regressive lag-1 covariance matrix. This correlation is then used to compute a robust variance estimator. One advantage of using GEEs is that the correlation of participants within the same CTP can also be incorporated without additional distributional assumptions, such as required by a mixed effects model. Further, the GEE variance estimates are robust to the potential misspecification of the auto-regressive lag-1 covariance matrix. This methodology will be implemented using PROC GENMOD in SAS v9.2.

The test of treatment effect in the last four weeks of the active treatment phase can be captured by testing whether the following contrast is equal to zero:

$$C = (\alpha_1 + 17 \beta_1) - (\alpha_0 + 17 \beta_0)$$

For sample size calculations, we used data from CTN-0006 to get estimates of:  $\alpha_0$ ,  $\alpha_1$ , and  $\eta$ . In that study, both treatment arms had similar rates of abstinence in the first week, so we set  $\alpha_0 = \alpha_1 = \log(0.2/0.8) = -1.39$  since the observed probability of abstinence during the first week of treatment was 20%. The observed log-OR of having a positive UDS at baseline ( $\eta$ ) was

estimated as 2.65 with a 95% confidence interval of 1.97 to 3.34. The power analyses for the current study considered these three values of  $\eta$ . To simulate the data we also used CTN-0006 to estimate the probability of a positive UDS at baseline (20%). From a questionnaire completed by CTPs involved in the current study, on average, 27.5% of substance use patients in the CTPs were primary users of stimulants. There are no available data to suggest an appropriate estimate of the OR associated with being a stimulant user, so we considered ORs of 0.5, 1.0 and 2.0. From analyses of CTN-0006, there is no need to simulate a slope for the log-odds curves after half-week 16 since the slope is zero (i.e.  $\Phi=0$ ). Various values of  $\beta_0$  and  $\beta_1$  were considered that yielded estimates of the treatment odds ratio of 1.3, 1.5 and 1.8.

These parameter estimates were used to generate 24 half-week outcomes for 500 subjects. The correlation between the half-weeks within a participant was generated via a Markov Chain using estimated transition probabilities from CTN-0006. These estimates yielded a correlation between consecutive half-weeks of 0.56. Intermittent missing data indicators were also generated using a Markov Chain with the transition probabilities from CTN-0006, where the consecutive half-week correlation between being missing is 0.4. This yielded an overall probability of being missing at any half-week of 50%, as seen in Petry et al. (2005).

Table 3 provides power estimates for 500 participants and the detectable odds ratio ( $e^c$ ). Regardless of the effect sizes for the two stratification factors, a clinically meaningful OR of 1.5 can be detected with 500 subjects and over 80%. In addition, this analysis may be conservative as the amount of missing data is expected to be much less than CTN-0006 since the proposed study will employ aggressive participant tracking strategies.

**Table 3.** Power analysis for 500 participants (250 participants per treatment arm).

<u>Assumed OR for Each Stratification Variable<sup>†</sup></u>		<u>Power for Specific OR Values Capturing Treatment Effect of TAU+TES</u>		
Primary Use of a Stimulant	Positive Baseline UDS <sup>‡</sup>	OR = 1.3	OR = 1.5	OR = 1.8
0.5	7	43%	86%	99%
1.0	7	43%	88%	100%
2.0	7	44%	89%	100%
0.5	14	40%	84%	99%
1.0	14	41%	86%	99%
2.0	14	43%	87%	99%
0.5	28	37%	81%	99%
1.0	28	39%	84%	99%
2.0	28	41%	86%	99%

<sup>†</sup> Stratification factors used in randomization.

<sup>‡</sup> OR values observed in CTN-0006 (Petry et al, 2005a).

#### **14.4.2 Sample Size Considerations and Statistical Methods for Primary Retention Measure**

If a participant did not complete 12 weeks of treatment, time of drop-out from substance abuse treatment will be recorded. If a participant completes all 12 weeks of substance abuse treatment then time to drop-out will be considered as censored at 12 weeks. Data from the TAU+TES and TAU groups will be displayed with Kaplan-Meier curves estimating the probability of retention in the CTP until time  $t$ , over time. The TAU+TES and TAU groups will be compared with a Log-Rank test stratified by site.

Assuming 50% retention at 12 weeks in TAU+TES group and 35% retention at 12 weeks in the TAU group (hazard ratio  $HR = \log(0.35)/\log(0.50) = 1.515$ ), there is 90% power to reject  $H_{0-2}$ :  $HR=1.0$  with the total sample size of 500 when considering two-sided  $\alpha=0.025$ . Power is based on an unstratified log-rank test. Sample size computations were performed with the Power And Precision 2.1 package.

#### **14.5 Interim Analyses**

A DSMB will monitor the progress of the trial. In coordination with the centralized Data and Statistics Center 2, an interim check of the error variance for the primary abstinence outcome measure will be conducted to assess the adequacy of the projected study sample size. This check will not reveal the treatment effect observed in the trial at the time of this interim analysis. If the error variance is substantially different from the assumed value, there may be a need to adjust the sample size. This analysis will be conducted when approximately half participants have been enrolled and have completed the active treatment phase of the study.

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

#### **14.6 Secondary Analysis of Total Number of Abstinent Half-Weeks**

The secondary outcome measure of abstinence will be the total number of abstinent half-weeks. This approach is analogous to that utilized in CTN protocols #006 and #007, but using half-weeks instead of the full seven-day week. This outcome measure is simply the sum of all 24 abstinence indicators for an individual. For example, a patient could have a string of 24 half-weekly abstinence data values of 1, 1, 1, 1, 0, 0, 1, 1, 1, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 0, 0, 0, 1 where 1 denotes abstinence, and 0 drug use. This patient was abstinent in weeks 1-2, week 4, part of week 5, weeks 7-10, and the end of week 12. In this case, the total number of abstinent half-weeks is 16. Missing data will be handled in the same manner as Petry et al. (2005a). Those authors used three different methods of handling missing outcomes: (i) treat missing outcomes as being non-abstinent, (ii) treat them as abstinent, (iii) and allow them to be missing and implement an analytic method that allows for missing data. The total number of abstinent weeks will likely not be normally-distributed, but if it is then a mixed effects model can be used with fixed effects capturing the two stratification factors and indicator of treatment with TES, and a random effect capturing within site correlation. In the case of a deviation from the normality assumption, quantile regression can be used instead.

## **14.7 Secondary Analysis of Consecutive Half-Weeks of Abstinence**

As an alternative tertiary abstinence outcome measure, at the end of the 12-week treatment we will consider the longest continuous abstinence measured in half-weeks (i.e., the largest number of consecutive half-weeks of abstinence) observed during 12 weeks of treatment. Hence, possible outcome value for a subject can be in the range between 0 and 24 half-weeks. Using these data we will compute the longest continuous abstinence. For example, considering the patient mentioned in Section 14.6, the longest continuous abstinence is 4 weeks (8 half-weeks). Missing data will be handled using the same methodology as Petry et al. (2005a). The analysis will utilize the same approach as the analysis of the total number of abstinent weeks, but with the longest continuous abstinence outcome as the response variable.

## **14.8 Other Secondary Outcome Measures**

We will also evaluate secondary outcomes of (a) HIV risk behavior (using the Risk Behaviors Scale; Booth et al., 1993), (b) psychosocial functioning in areas of criminal activity, health status improvement, psychological status, family/social relationships, and employment (via the SAS-SR, Weissman, 1999, NMS, and BSI, Derogatis & Melisaratos, 1983), (c) Treatment acceptability measured via the Participant Feedback Survey (which we have successfully used in prior trials). These measures will be compared across study groups using repeated measures analyses of covariance using SAS, PROC MIXED or PROC GLIMMIX if other than normal errors are present. This procedure allows for incomplete data and varied covariance structures. We will also consider as a secondary outcome the number of abstinent half-weeks based solely on urine and breathalyzer screening (i.e. no self-report data). This outcome will be analyzed in the same way as the primary abstinence measure outcome.

## **14.9 Factors for Stratification**

Randomization will be stratified by site and within site, by two stratifying factors: urine test positive or negative at baseline, and class of primary drug of use (stimulant vs. non stimulant). The stratification factors will be included in the analyses.

## **14.10 Significance testing**

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

Hence, for the two pre-specified primary outcomes we consider the Hochberg approach as described in detail at the beginning of Section 14.4. In summary, this approach allows detection of treatment effect for both primary outcomes at the 0.05 level if each outcomes is significant at the 0.05 level. If either outcome is not significant at the 0.05 level, then the other will only be significant if its p-value is less than 0.025 ( $=0.05/2$ ).

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

## **14.11 Demographic and Baseline Characteristics**

Baseline demographic and clinical variables will be summarized for each arm of the study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation.

Categorical variables will be summarized in terms of frequencies and percentages. Since randomization is expected to produce balance at baseline between the two arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics should be more informal. In case differences between treatments arms are suspected, statistical testing will be performed. For comparisons of treatment groups with respect to continuous baseline variables we will use the two sample Wilcoxon test. Group comparisons with respect to discrete baseline variables will use the chi-square test or Fisher's Exact Test as appropriate.

#### **14.12 Gender Exploratory Analysis**

We plan to conduct exploratory analyses to examine if differential outcomes are observed on the two primary outcome measures of weeks of abstinence and retention, as well as the outcome measure of intervention acceptability (based on participant feedback data), by gender. We will conclude differential treatment effect if the interaction between treatment and gender is significant at the 0.05 level.

#### **14.13 Other Exploratory Analyses**

Finally, we plan to conduct analyses to determine if differential outcomes are observed across various sub-groups (e.g., individuals whose primary drug of abuse is a stimulant vs. non-stimulant, etc.). We will also examine a variety of demographic variables, as well as baseline psychological and other history variables (e.g., comorbid psychiatric disorders), which may predict successful outcomes in reducing substance use and treatment retention. In this process, repeated measures logistic regression (abstinence) and Cox Regression (retention) will be used to examine this secondary aim of establishing whether specific measured subject characteristics at baseline are predictive of treatment outcome on these measures. Interaction tests will also be conducted to examine differential effects of predictors across each condition for each outcome measure (i.e., exploring for moderators of treatment effect). The resulting data may be important to understanding if specific sub-groups of individuals with substance use disorders may differentially benefit from the web-based intervention.

We will also consider sensitivity analysis to assess impact of the approach to dealing with missingness of abstinence data on estimated treatment effect for the primary abstinence outcome. One method we will use to evaluate our method of handling missing data is to compare it to that of Petry et al. (2005a) where a week with unknown (missing) substance use status is considered positive, i.e. probability of positive substance use is considered to be 1. Multiple imputation methods will also be used if the amount of within-subject missingness is reasonable. It is likely that the missingness mechanism involved in drug use trials is non-ignorable since a subject may not appear at their scheduled visit if they have used drugs. One method of evaluating the sensitivity of the proposed primary analysis of abstinence is to implement pattern mixture models (Hedeker & Gibbons, 1997), which are thought to deal with non-ignorable missingness more appropriately.

Sensitivity analyses will also be performed to evaluate whether the assumed model is reasonable. As previously described, we assume no treatment by time interaction after half-week 17, but we plan to relax this assumption in the planned sensitivity analyses. Another assumption we will relax is that the relationship between time and treatment effect is linear prior to half-week 17. Lastly, it is possible that using a cut-off other than week 8 is more appropriate. Methods for identifying knot locations will be used to identify how sensitive the observed results are to consideration of a different time-point where the time by treatment interaction is minimal.

After conducting all planned primary, secondary and exploratory outcome analyses, we may conduct additional analyses with data obtained in the trial, as appropriate.



## 14.14 Economic Analyses

We estimate and analyze incremental cost-effectiveness ratios (ICER) to inform an adoption decision from a health care sector perspective and the treatment program's perspective. The primary ICER will be the incremental costs per increased abstinence time (the clinical measure of effectiveness) and the secondary ICER will be incremental costs per increased quality adjusted life year (QALY) (the economic measure of effectiveness). We distinguish the health care perspective from the CTP perspective by the costs included in the cost-effectiveness ratio. The health care sector perspective include all medical and treatment costs regardless of the setting in which they are incurred. The CTP perspective only includes those costs that are incurred during the substance abuse treatment received within the CTP. All ICERs are assessed over 3 months and over 6 months. There are also two separate exploratory economic analyses. We assess the benefit of reduced criminal activity and use of the criminal justice system and we assess the fixed costs of program startup.

### 14.14.1 Estimation for Economic Analyses

- (a) **Calculate Medical Costs.** We calculate medical costs using the resource costing method. This method involves determining a price weight for each resource unit consumed (Brown, 1998; Gold, 1996; Glick, 1995; Drummond et al., 1991) and multiplying price weights by units of service. Price weights will be determined from the Program DATCAP described earlier and from published information. Counts of resource units are available from clinical forms within the study site for study delivered services and from the NMS form for services delivered outside the study. CTP costs are based on resources used in the treatment program and medical costs are based on all medical resources used including those used in the treatment program.
- (b) **Estimate Cost of Treatment.** The estimates of costs and cost differences between treatment groups will be expressed by use of the arithmetic mean because this summary measure permits a budgetary assessment of treatment. We will use the parametric t-test, which is the most common univariate statistical test for differences in arithmetic means. Because of the often highly skewed distribution of cost data with a long and sometimes heavy right tail, the normality assumption underlying this test may be called into question. As a result, the non-parametric bootstrap, which has the added advantage of avoiding a parametric assumption about the distribution of costs, will be used as a check on the robustness of standard parametric t-tests (Efron & Tibshirani, 1994; Desgagne et al., 1998; Barber & Thompson 2000). We will use the inverse probability weighting method proposed by Lin (2000b) to account for censored cost data.

### 14.14.2 Estimate Incremental Effectiveness of Treatment

The statistical model used for the primary effectiveness outcome (abstinence weeks) will be the same as described for the clinical study and the statistical model for the secondary effectiveness outcome (QALYs) will be the same as those used for costs in Section 14.14.1(b).

### 14.14.3 Estimate Incremental Cost-Effectiveness Ratio

The primary ICER is estimated as the difference between mean costs of the modified TAU + TES group and the mean costs of the TAU group divided by the mean abstinence weeks of the modified TAU+TES group and the mean abstinence weeks of the TAU group. This ratio represents the additional cost of the experimental arm over TAU necessary to produce an additional drug-free week. We will estimate this ratio for both treatment costs and all medical costs. Similarly, a cost-effectiveness ratio will be estimated using QALYs in the denominator. We will estimate the cost-effectiveness ratios at 12 weeks and at 6 months. In total we will have

8 outcomes with the 4 outcomes using abstinence weeks as the denominator as the primary economic outcomes.

#### **14.14.4 Power for Economic Hypothesis**

We estimate the power for the outcome of cost for increased rate of abstinence at Week 12 given the target sample size of about 500 (about 250 participants per group). The primary effectiveness measure will be abstinent weeks. As above, we assume 2.4 weeks for TAU (SD=3.38) and 3.6 weeks for TAU+TES (SD=3.87). We use a standard deviation of 3.63. The additional costs over 12 weeks are assumed to be \$467 (SD=374) in the TAU group and \$823 (SD=659) in the intervention group. These numbers are derived from the TAU costs of the 12 week CM interventions for (1) cocaine abuse (2) and stimulant abuse. The expected CM payout is \$293 with 55% compliance assumed. The TAU+TES group also includes higher TAU treatment costs due to greater retention of 42% and a 20% reduction in TAU treatment costs from “reduced” TAU. The final parameter for estimating power in cost-effectiveness is the correlation between costs and effects. Because CM costs are highly likely to cost more for the most successful clients (greater payouts and greater treatment duration) there is a strong positive correlation. We assume a correlation coefficient of 0.15.

Using the equation for power for cost-effectiveness ratios (Glick et al., 2001), we find 96% power with a proposed sample size of 500. The study is powered at 90% for a cost effectiveness ratio of costs per abstinence week of \$920 per abstinence week.

Note on power for cost-effectiveness. A cost-effectiveness ratio is powered relative to its maximum acceptable value. The range of maximum acceptable values typically used is \$50,000 to \$100,000 per quality adjusted life year (QALY). However, clinical trials in the substance abuse research field generally have not used QALYs or even life years saved as a measure of effectiveness (as is often done in other areas of medicine). This is true for this project as well where the primary clinical outcome is a continuous drug free week. Recent data from a CTN study using QALYs found that for every 15 percentage point increase in the rate of abstinence (which converts to 1.8 weeks over 12 weeks), QALYs increased by 5 percentage points. We translate the \$50,000 per QALY threshold to \$1,400 per week of abstinence.

#### **14.14.5 Sensitivity Analysis**

Sensitivity analyses will be performed to assess the sensitivity of our estimates of medical costs and cost-effectiveness to the assumptions made regarding some of the values that will be used in the analysis. We will consider how cost-effectiveness may change with: (1) different costs of TES; (2) different methods to handle attrition of cost data; and (2) different ceiling ratios.

#### **14.14.6 Exploratory Economic**

**(a) Costs related to criminal activity and contact with the criminal justice system.** We will value each crime committed that has been reported on the NMS based on the sum of the value of victim costs and the risk of a homicide, and we will value charges and convictions for crimes based on criminal justice system costs (Rajikumar & French, 1997). We will assess differences in these costs using the techniques described 13.14.1(b).

**(b) Assessment of Fixed Costs of Program Start-up.** In an additional economic analysis we will model the fixed costs incurred by the treatment programs as a result of the intervention which are primarily driven by training and other start up expenses. These costs are not part of the primary cost-effectiveness ratio for two critical reasons. First, they are setting dependent in that these costs on a per-patient basis, will depend largely on the skills of the staff and the size of the program. Second, these costs, as they are incurred during the clinical trial, may not reflect the costs

that would be incurred in a more generalized setting. However, because of the considerable cost constraints within CTPs, these fixed costs are critical. We will use this information to develop models which could demonstrate the financial consequences of adoption of a new therapeutic intervention at the program level.

## **15.0 DATA MANAGEMENT**

### **15.1 Design and Development**

This protocol will utilize a centralized Data and Statistics Center (DSC 2). The DSC 2 will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. A web-based distributed data entry model will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

### **15.2 Data Collection Forms**

The data collection process consists of direct data entry at the study sites into the EDC system(s) provided for the protocol. In the event that the EDC system(s) are not available, the DSC 2 will provide the sites with a final set of guided source documents and completion instructions. Data entry into the eCRFs should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant. The DSC 2 is not responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

### **15.3 Data Acquisition and Entry**

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

### **15.4 Site Responsibilities**

The data management responsibilities of each individual CTP will be specified by the DSC 2 and outlined in the DM plan.

### **15.5 Data Center Responsibilities**

The DSC 2 will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating CTPs, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

### **15.6 Data Editing**

Completed data will be entered into the DSC 2 automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the DSC 2 automated data acquisition and management system in accordance with the data management plan.

### **15.7 Data Transfer**

Data will be transmitted by the DSC 2 to the NIDA central data repository as requested by NIDA. The DSC 2 will conduct final data quality assurance checks and "lock" the study

database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

### **15.8 Training**

The training plan for CTP staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of computerized systems, as required.

### **15.9 Data QA**

To address the issue of data entry quality, the DSC 2 will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

## 16.0 SIGNATURES

### SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____
CCTN Designee		

### INVESTIGATOR (S)

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

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

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## APPENDIX A

### Adverse Event Reporting Definitions and Procedures

#### Definitions of Adverse Events and Serious Adverse Events

**Adverse Event:** An adverse event (AE) is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a clinical trial treatment or procedure, regardless of whether it is considered related to the clinical trial treatment or procedure, that occurs during the course of the study. Any new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. In order to avoid reporting pre-existing conditions as new AEs, and to assist in the assessment of a condition that has worsened in intensity or severity, a thorough medical history should be performed during the eligibility assessment phase to record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. The AE case report form (CRF) is used to capture reportable AEs (as defined by the protocol) and may also be used to record follow-up information for unresolved events reported during previous visits. A study investigator is responsible for identifying and characterizing each AE, and is expected to follow appropriate reporting procedures.

**Serious Adverse Event (SAE):** A serious adverse event (SAE) is defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

- Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported.
- Life threatening: Any adverse therapy experience that places the participant or participants, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more serious form, might have caused death).
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- An event that required intervention in order to prevent one of the above outcomes

#### Laboratory Results

Laboratory results will be captured on laboratory collection CRFs. A study investigator is responsible for identifying and characterizing each abnormal lab result as clinically significant or not clinically significant and report any clinically significant lab results as AEs.

**Eliciting and Monitoring Adverse Events:** Qualified research staff will elicit participant reporting of AEs/SAEs at study assessment visits that have been designated to collect AEs and at any other time during the clinical trial that they have contact with or about the participant. Adverse event (medical and/or psychiatric) assessments will initiate once the participant is consented or randomized and will continue to occur through 30 days post last study visit. The research staff will obtain as much information as possible about the reportable AE/SAE to complete the AE/SAE forms and will consult with designated staff as warranted. Reportable SAEs will be reported as indicated below. A study investigator will review reportable AEs for seriousness, severity, and relatedness weekly. Appropriate site staff will review all reportable

AE documentation and verify accuracy of assessments at least once weekly when the participant attends the CTP to ensure that all of these AEs are appropriately reported and to identify any unreported AEs that require reporting. Reportable AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization even beyond the end of the study. Each participating site's Protocol PI is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Protocol monitors from the Clinical Coordinating Center (CCC) and local node staff will review the study sites and study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable SAEs are being followed appropriately by the research staff. The node staff or CCC monitor will ensure that any unreported or unidentified reportable SAEs discovered during visits are promptly reported by the site to the Safety Monitor, NIDA, the Node or Protocol PI or designee, the lead investigator for the study and the IRB per local IRB requirements and will be reported on the monitoring report. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or SAEs are discovered, to ensure future identification and timely reporting by the site. The NIDA CTN DSMB will also review data related to safety monitoring for this trial periodically at regularly scheduled meetings.

**Assessment of Severity and Relatedness**

Qualified research staff will review each reportable AE for seriousness, relatedness, and severity at each study assessment visit designated to collect AEs. The severity of the experience refers to the intensity of the event. The relatedness of the event refers to causality of the event to the study intervention. Relatedness requires an assessment of temporal relationships, underlying diseases or other causative factors and plausibility.

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

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/ therapy intervention required, hospitalization or hospice care probable.
Grade 5	Death	

**Relatedness:** Relationship to therapy is defined as:

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

**Reporting and Management Procedures of AE/SAEs**

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). A participating site must alert the NIDA-assigned Safety Monitor and the Lead Investigator of reportable SAEs within 24 hours of learning of the event. The SAE form and summary and any other relevant documentation should also be submitted with the initial report if adequate information is available at the time of the initial report to evaluate the event and provide a complete report. Local sites are responsible for reporting SAEs to their IRB, per their IRB's guidelines.

Additional information may need to be gathered to evaluate the SAE and to complete the AE and SAE forms. This process may include obtaining hospital discharge reports, physician records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event. Within 14 days of learning of the event, an SAE form and related documents must be completed and entered into the data base. Documentation of the event that cannot be entered into the data base should be sent to the NIDA-assigned Safety Monitor. If the SAE is not resolved or stabilized at this time or if new information becomes available after the SAE form is submitted, follow-up SAE information must be submitted as soon as possible, but at least within 14 days after the site learns the information.

The study investigator at the site must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be removed from study intervention. The study investigator may consult with the Safety Monitor as needed. If necessary, an Investigator may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. Subsequent review by the Medical Monitor, DSMB, ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor and DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is

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

A NIDA-assigned Safety Monitor is responsible for reviewing all serious adverse event reports. The monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. Serious adverse events will be followed until resolved or considered stable, with reporting to the NIDA assigned Safety Monitor through the follow-up period. The site must actively seek information about the SAE as appropriate until the SAE is resolved or stabilized or until the participant is lost to follow-up and terminated from the study. The DSMB or the NIDA- assigned Safety Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, should be summarized by the Investigator in writing upon request for review by the NIDA-assigned Safety Monitor, DSMB, local ethics Committee/IRBs or regulatory authorities.

