

## **NIDA CTN Protocol 0047**

# **Screening, Motivational Assessment, Referral, and Treatment in Emergency Departments (SMART-ED)**

Lead Investigator: Michael P. Bogenschutz, MD  
Co-Lead Investigator: Dennis M. Donovan, PhD

**Version 7.0**  
January 17, 2012

---

**NATIONAL INSTITUTE ON DRUG ABUSE  
CLINICAL TRIALS NETWORK  
NIDA-CTN-0047 Version 7.0 (17 January 2012)**

---

**Lead Investigator (LI):**                      **Michael P. Bogenschutz, MD**  
Southwest Node  
University of New Mexico  
CASAA/HSC

**Co-Lead Investigator (Co-LI):**            **Dennis M. Donovan, PhD**  
Pacific Northwest Node  
Alcohol and Drug Abuse Institute  
University of Washington

**CCTN Protocol Coordinators:**            **Raul Mandler, MD**  
**Harold Perl, PhD**

**Project Director:**                         **Alyssa Forcehimes, PhD**  
Southwest Node  
University of New Mexico  
CASAA

**CCTN Statistical Consultant:**            **Paul Wakim, PhD**

**EMMES (DSC 2):**                              **Neal Oden, PhD, Statistician**  
**Colleen Allen, Project Director**  
**Lauren Bartlett, Data Manager**

**Executive Committee:**                      **Bryon Adinoff, MD**  
Texas Node  
UT Southwestern Medical Center at Dallas  
VA North Texas Health Care System

**Cameron Crandall, MD**  
University of New Mexico Hospital  
Department of Emergency Medicine

**Bob Lindblad, MD**  
EMMES

**Robrina Walker, PhD**  
Texas Node  
UT Southwestern Medical Center at Dallas

## Table of Contents

<b>1.0</b>	<b>LIST OF ABBREVIATIONS</b> .....	<b>7</b>
<b>2.0</b>	<b>STUDY SYNOPSIS AND SCHEMA</b> .....	<b>9</b>
<b>3.0</b>	<b>STUDY FLOW CHART OR TIME AND EVENT TABLE</b> .....	<b>11</b>
<b>4.0</b>	<b>INTRODUCTION</b> .....	<b>12</b>
4.1	Background.....	12
4.2	Rationale.....	14
<b>5.0</b>	<b>OBJECTIVES</b> .....	<b>16</b>
5.1	Primary Objective.....	16
5.2	Secondary Objectives .....	16
<b>6.0</b>	<b>STUDY DESIGN</b> .....	<b>17</b>
6.1	Overview .....	17
6.2	Rationale for the 3-group design .....	17
6.3	Duration of Study and Visit Schedule .....	18
<b>7.0</b>	<b>STUDY POPULATION</b> .....	<b>19</b>
7.1	Inclusion Criteria .....	19
7.2	Exclusion Criteria .....	19
7.3	Subject Recruitment.....	19
7.4	Special Populations to Consider.....	20
7.5	Number of CTP Sites .....	20
7.6	CTP Characteristics .....	20
7.7	Rationale for CTP Selection .....	20
<b>8.0</b>	<b>OUTCOME MEASURES</b> .....	<b>22</b>
8.1	Primary Outcome Measure.....	22
8.2	Secondary Outcome Measures .....	22
<b>9.0</b>	<b>STUDY PROCEDURES</b> .....	<b>23</b>
9.1	Screening and Informed Consent Procedures .....	23
9.1.1	Pre-Screening .....	23
9.1.2	Screening.....	23
9.1.3	Informed Consent Procedures.....	25
9.1.4	Completion of Screening Visit Prior to Randomization.....	25
9.2	Randomization .....	26

---

9.3	Baseline Assessment (SAR and BI-B groups).....	26
9.4	Treatment.....	27
9.4.1	Study Interventions.....	27
9.4.2	Subject Discontinuation.....	27
9.4.3	Treatment Discontinuation.....	27
9.5	Follow-Up.....	27
9.6	Compensation.....	27
9.7	Blinding.....	28
<b>10.0</b>	<b>STUDY ASSESSMENTS.....</b>	<b>29</b>
10.1	Study Timetable.....	30
10.2	Protocol Specific Assessments.....	33
10.2.1	Laboratory tests.....	33
10.2.2	Clinical Assessments.....	33
10.2.2.1	NIDA-Modified Alcohol, Smoking and Substance Involvement Screening Test (NM-ASSIST).....	33
10.2.3	Efficacy Assessments.....	33
10.2.3.1	Time-Line Follow-Back.....	33
10.2.3.2	Hair analysis.....	34
10.2.4	Safety Assessments.....	35
10.2.4.1	Adverse Events (AD1), including Serious Adverse Events (AD2 and AD3), Protocol Violations Log (PVL), and Study Termination (STT).....	35
10.2.5	Treatment Involvement.....	35
10.2.5.1	Intervention Record Form and Booster Record Form.....	35
10.2.5.2	The Treatment Services Review (TSR).....	35
10.2.5.3	Non Study Treatment Form (NTF).....	35
10.2.6	Process Measures.....	36
10.2.6.1	Working Alliance Inventory – Short Version (WAI).....	36
10.2.6.2	Barriers to Treatment Inventory (BTI).....	36
10.2.7	Projected Timetable.....	36
10.3	Common Assessment Battery.....	36
10.3.1	CTN Demographic Form (DEM) and Additional Demographics (ADM).....	36
10.3.2	Locator Questionnaire.....	36
10.4	Interventionist Assessments.....	37
10.4.1	Short Understanding of Substance Abuse Scale (SUS).....	37
10.4.2	Clinician and Supervisor Survey (CNS).....	37
10.4.3	Confidential Pre-training Questionnaire (CPQ).....	37
<b>11.0</b>	<b>STUDY TREATMENTS.....</b>	<b>38</b>
11.1	Minimal Screening Only (MSO).....	38
11.2	Screening and Referral (SAR).....	38
11.3	Brief Intervention + Booster (BI-B).....	38

---

---

<b>12.0</b>	<b>STATISTICAL ANALYSIS.....</b>	<b>40</b>
12.1	Primary Outcome Measure.....	40
12.2	Rationale for Considered Magnitude of Treatment Effects.....	40
12.3	Statistical Methods for Primary Analysis.....	40
12.4	Sample Size and Statistical Power .....	42
12.5	Interim Analyses.....	43
12.5.1	Re-evaluation of the Sample Size.....	43
12.5.2	Efficacy/Futility Analysis .....	43
12.6	Statistical Methods for Secondary Outcomes .....	43
12.6.1	Days of use of the primary drug of abuse in the past 30 days at 6 and 12 months post intervention .....	43
12.6.2	Days of drug use in the past 30 days at 3, 6 and 12 months post intervention.....	43
12.6.3	Days of heavy drinking in the past 30 days at 3, 6 and 12 months.....	43
12.6.4	Dollar value of drug use for primary problem substance used at 3, 6 and 12 months post-baseline .....	44
12.6.5	Magnitude of Change Compared Between SAR and BI-B .....	44
12.6.6	Hair sample drug screen results for any drug and primary drug of abuse at 3, 6, and 12 months (relative change in hair screen level from baseline) .....	44
12.6.7	Consequences of drug use (from the NM ASSIST) at 3, 6, and 12 months .....	44
12.6.8	Days of participation in treatment since the last visit, at 3, 6, and 12 months post intervention among BI-B and SAR participants with probable dependence who are referred for treatment.....	45
12.6.9	Days of health care utilization (number of ED visit days, number of hospital days, and number of outpatient visit days) since the last visit, at 3, 6, and 12 months (self-report from TSR) .....	45
12.7	Evaluation of Putative Predictors of Outcome.....	46
12.8	Evaluation of dose-response to number of booster sessions received (among participants assigned to BI-B).....	46
12.9	Missing Data and Dropouts .....	46
<b>13.0</b>	<b>TRAINING .....</b>	<b>48</b>
13.1	Training, Supervision, and Fidelity Monitoring Procedures for Study Interventions .....	48
13.1.1	Training Timeline .....	48
13.1.2	Selection of Interventionists.....	48
13.1.2.1	Consenting of Interventionists.....	48
13.1.2.2	Inclusion/Exclusion Criteria .....	48
13.1.3	Selection and Training of BI-B Trainers .....	48
13.1.4	Training and Credentialing of BI and Booster interventionists.....	48
13.1.4.1	Pre-training for Brief Interventionists .....	48
13.1.4.2	2-Day Training for Brief Interventionists .....	49
13.1.5	Pilot Delivery of Interventions .....	49
13.2	Treatment Fidelity.....	49

13.2.1	Selection and Training of BI-B Centralized Clinical Supervisors .....	49
13.2.2	Supervision of Interventionists .....	49
13.2.3	Quality Control of Therapies Administered .....	49
13.2.3.1	Motivational Interviewing Treatment Integrity (MITI 3.0).....	50
13.2.3.2	“Drifting” Interventionists .....	51
<b>14.0</b>	<b>REPORTING AND MONITORING .....</b>	<b>52</b>
14.1	Statement of Compliance .....	52
14.2	Regulatory Files .....	52
14.3	Informed Consent.....	52
14.4	Health Insurance Portability and Accountability Act (HIPAA) .....	53
14.5	Investigator Assurances .....	53
14.6	Financial Disclosure .....	53
14.7	Clinical Monitoring .....	53
14.8	Study Documentation .....	54
14.9	Safety Monitoring .....	54
14.9.1	Data and Safety Monitoring Board (DSMB) .....	54
14.9.2	Protocol Violations Reporting and Management .....	54
14.9.3	Confidentiality.....	54
14.9.4	Adverse Events (AEs) .....	55
14.9.5	Definitions of Adverse Event and Serious Adverse Event.....	55
14.9.6	Reportable Adverse Events and Serious Adverse Events .....	55
14.9.6.1	Adverse Events.....	55
14.9.6.2	Serious Adverse Events.....	55
<b>15.0</b>	<b>DATA MANAGEMENT AND PROCEDURES.....</b>	<b>57</b>
15.1	Design and Development .....	57
15.2	Data Collection Forms.....	57
15.3	Data Acquisition and Entry .....	57
15.3.1	Site Responsibilities .....	57
15.3.2	Data Center Responsibilities .....	57
15.3.3	Data Editing.....	57
15.4	Data Transfer .....	58
15.5	Training .....	58
15.6	Data QA .....	58
<b>16.0</b>	<b>STUDY TIMELINE .....</b>	<b>59</b>
<b>17.0</b>	<b>REFERENCES .....</b>	<b>60</b>
<b>18.0</b>	<b>APPENDIX A.....</b>	<b>66</b>

## 1.0 LIST OF ABBREVIATIONS

ACS	American College of Surgeons
AD1	Adverse Events
AD2	Serious Adverse Events Summary
AD3	Serious Adverse Event Medical Reviewer
ADM	Additional Demographics
AE	Adverse Event
ASSIST	Alcohol, Smoking, Substance Involvement Screening Test
ATS	Amphetamine-Type Stimulants
AUDIT	Alcohol Use Disorders Identification Test
BI	Brief Intervention
BI-B	Brief Intervention plus Booster
BIT	Brief Intervention Tool
BTI	Barriers to Treatment Inventory
CCC	Clinical Coordinating Center
CHAT	Case-finding and Help Assessment Tool
CMS	Center for Medicare and Medicaid
CNS	Clinician and Supervisor Survey
CoC	Certificate of Confidentiality
COT	Committee on Trauma
CPT	Current Procedural Terminology
CPQ	Confidential Pre-Training Questionnaire
CSAT	Center for Substance Abuse Treatment
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DAST	Drug Abuse Screening Test
DEM	Demographics
DHHS	Department of Health and Human Services
DM	Data Monitoring
DSC	Data Statistics Center
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
ERC	Ethics Review Committee
FRAMES	Feedback, Responsibility, Advice-Giving, Menu, Empathy, Self-Efficacy
FWA	Federal Wide Assurance
GC	Gas Chromatography
GCP	Good Clinical Practice
HSF	Hair Sample Form

---

HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HSI	Heavy Smoking Index
ICH	International Conference of Harmonization
IRB	Institutional Review Board
LC	Liquid Chromatography
LI	Lead Investigator
LN	Lead Node
MET	Motivational Enhancement Therapy
MI	Motivational Interviewing
MITI	Motivational Interviewing Treatment Integrity
MS	Mass Spectrometry
MSO	Minimal Screening Only
NIDA	National Institute on Drug Abuse
NM-ASSIST	NIDA Modified Alcohol, Smoking and Substance Involvement Screening Test
NTF	Non-Study Treatment Form
PC	Primary Care
PI	Principal Investigator
PT	Patient/Participant
PVL	Protocol Violation Log
QA	Quality Assurance
RA	Research Assistant
RRTC	Regional Research and Training Center
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SAR	Screening, Assessment, and Referral
SBIRT	Screening, Brief Intervention, Referral and Treatment
SD	Standard Deviation
SMART-ED	Screening, Motivational Assessment, Referral and Treatment-Emergency Department
SOP	Standard Operating Procedure
SFF	Secondary Screening Form
STT	Study Termination
SUS	Short Understanding of Substance Abuse Scale
SUD	Substance Use Disorder
TAD	Tobacco, Alcohol and Drug Questionnaire
TAP	Time-Line Follow-Back Assessment Period Form
TC	Trauma Center
TLFB	Time-Line Follow-Back
TSR	Treatment Services Review
WAI	Working Alliance Inventory
WASBIRT	Washington State Screening, Brief Intervention, Referral and Treatment



## **2.0 STUDY SYNOPSIS AND SCHEMA**

### **STUDY OBJECTIVES:**

The study will contrast substance use and substance-related outcomes among patients endorsing problematic drug use during an emergency department (ED) visit who are randomly assigned to one of three treatment conditions: 1) minimal screening only (MSO); 2) screening, assessment, and referral to treatment (if indicated) (SAR); and 3) screening, assessment, and referral plus a brief intervention (BI) with two telephone follow-up booster sessions (BI-B).

### **STUDY DESIGN:**

The proposed project is a 3-group randomized, prospective trial with blinded assessments. Individuals presenting in the ED endorsing problematic drug use on screening will be randomized in 1:1:1 ratio to MSO vs. SAR vs. BI-B. Randomization will occur after screening, and those randomized to MSO will not receive further assessment until follow-up. The other two groups will receive baseline assessment, and assignment to SAR vs. BI-B will not be revealed until after the baseline assessment is complete. Those in the SAR group will then receive referral if indicated or requested, and those assigned to the BI-B group will be receive a brief intervention consisting of motivational enhancement therapy (MET) adapted for use in the ED, followed by referral if indicated or requested. The BI-B group will also receive two booster telephone calls, ideally within one week of the ED visit. Follow-up assessments of all three groups will be conducted face-to-face at 3 months, 6 months, and 12 months post-enrollment.

### **STUDY POPULATION:**

A total of 1285 patients with probable drug abuse or dependence (approximately 429 per group) seeking medical treatment in the ED, recruited from 6 EDs, will be randomized to MSO, SAR, or BI-B. Participating EDs will recruit an average of approximately 215 participants each.

### **ELIGIBILITY CRITERIA:**

Participants will be men and women 18 years of age or older who are seeking medical treatment at the ED, have adequate English proficiency, are able to provide informed consent, endorse current (past 30 days) problematic use of one or more drugs, are willing to participate in the protocol (e.g., be randomized to treatment, participate in follow-up assessment), and have access to a telephone. Individuals will be excluded if they are incapable of informed consent, are prisoners or in police custody, are currently engaged in addiction treatment, reside more than 50 miles from the site where follow-ups are conducted, are unable to provide sufficient contact information, or have already participated in the study.

### **TREATMENTS:**

The MSO group will not receive further assessment or treatment following randomization, but will be given an informational pamphlet about drug use and its potential consequences.

The SAR group will be provided with the same information pamphlet as the MSO group. In addition, following assessment, SAR participants with “probable dependence” on one or more substances (based on ASSIST score  $\geq 27$ ) will also be provided a referral to treatment, consisting of a positive recommendation to seek treatment and a standardized list of available treatment options. Participants who request a referral will also receive one, regardless of ASSIST score. Referrals will be made to CTN-affiliated CTPs as well as other community programs in the normal clinical referral networks of the participating EDs.

Individuals randomized to the BI+Booster (BI-B) condition will receive the same information and referral as those in SAR. In addition, while in the ED the BI-B group will receive a manual-guided brief intervention based on motivational interviewing principles, including feedback based on screening information, the FRAMES heuristic, and development of a change plan if indicated. The brief intervention will focus primarily on the most problematic drug of abuse identified by the participant. The BI will be provided in person in the ED while the participant is still there. In addition, participants in the BI-B group will receive up to 2 phone “booster” sessions that will check to see whether they have engaged in treatment, review change plans, and seek a commitment from them (Mello, Longabaugh et al. 2008). The content of these boosters is patterned after sessions in Motivational Enhancement Therapy (MET). The initial phone booster call will occur within 3 days of discharge from the ED if possible, and the second within 7 days. Booster calls will be made using a centralized, study-wide intervention booster call center.

**SAFETY ASSESSMENT:**

Adverse Events (AEs) including Serious Adverse Events (SAEs) will be monitored and reported throughout the study. These events will be subject to ongoing monitoring by the study executive committee (including representatives of the lead nodes, NIDA, and the Clinical Coordinating Center), and will be presented for DSMB review.

**OUTCOME ASSESSMENTS:**

The primary outcome is days of use of the patient-defined primary problem drug, assessed by the Time-Line Follow-Back for the 30-day period preceding the 3-month follow-up. Secondary outcomes include change from baseline in days of use of the primary substance, the number days abstinent from all drugs, days of heavy drinking, total quantity of drug use, objective change in drug use based on analysis of hair samples, self-reported consequences of drug and alcohol use, percent entering treatment among those classified as having probable dependence, and ED and other health care utilization.

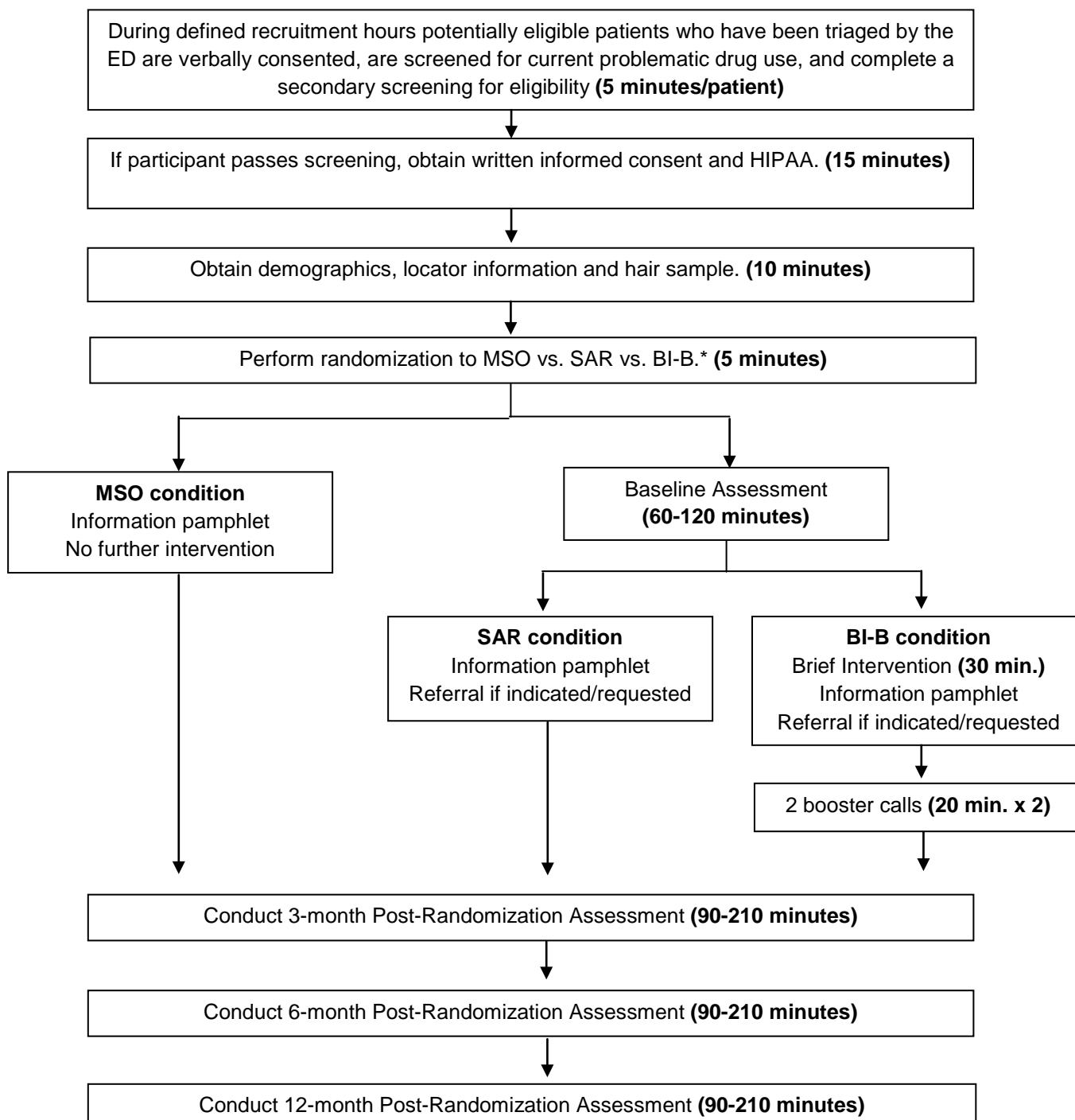
**PRIMARY OUTCOME ANALYSIS:**

The primary analysis will contrast MSO, SAR and BI-B groups with respect to the primary outcome variable (days of use of the primary drug of abuse in the 30 days preceding 3-month follow-up) using a linear mixed model with a random site effect and fixed treatment effect and intercept. Three pairwise contrasts will be made with an overall type 1 error rate of  $\alpha = 0.05$ .

**REGULATORY ISSUES:**

The trial will be conducted in compliance with protocol, ICH Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

### 3.0 STUDY FLOW CHART OR TIME AND EVENT TABLE



\*Allocation to SAR vs. BI-B is concealed until after completion of assessment.

## 4.0 INTRODUCTION

### 4.1 Background

Substance abuse and dependence and other harmful or hazardous use of drugs and alcohol have a tremendous impact on individual health status, contributing to a variety of medical conditions having high levels of associated mortality and morbidity (Mokdad, Marks et al. 2004), thus making medical settings such as primary care clinics (PCs) (U.S. Preventive Services Task Force 2004), emergency departments (EDs) (Calle, Damen et al. 2006; Academic ED SBIRT Research Collaborative 2007; Cherpitel and Ye 2008; Nilsen, Baird et al. 2008), and trauma centers (TCs) (Gentilello, Donovan et al. 1995; Dunn, Donovan et al. 1997; Gentilello, Rivara et al. 1999; Sise, Sise et al. 2005; Gentilello 2007) potential sites for opportunistic case finding and intervention (Babor and Kadden 2005; Madras, Compton et al. 2009). The resources required to attend to these conditions also places increased burden on the medical system, including considerable costs that are often not recovered (Gentilello, Ebel et al. 2005). As an example, individuals seen in EDs in Tennessee who were judged to have a substance use disorder (SUD) and for whom some form of treatment would be appropriate were much more likely to require hospitalization and had higher rates of previous ED utilization than those not having a SUD; the utilization patterns of those with a SUD accounted for an estimated US \$777.2 million in extra hospital charges for Tennessee in 2000 dollars (Rockett, Putnam et al. 2005). Given these large, potentially avoidable health care costs, the future burden of substance-associated ED visits and hospitalizations may be reduced through programs that screen and, as appropriate, provide brief interventions or treatment to these patients (Gentilello, Ebel et al. 2005; Barrett, Byford et al. 2006; Babor, McRee et al. 2007; Madras, Compton et al. 2009).

In response to the impact and cost, both to individuals and health care delivery systems, there has been an increased focus on developing, implementing, and evaluating methods to identify and provide appropriate services to individuals having problematic alcohol use patterns or use of illicit drugs who are seen in health care settings. This work is considerably more advanced in the area of alcohol use. A number of efficacy and effectiveness trials have demonstrated that screening, brief interventions, and/or referral to specialized substance abuse treatment for those with more severe dependence contribute to both subsequent reductions in alcohol consumption and alcohol-related problems and to reduced medical service utilization and costs (Dunn 2003; Babor and Kadden 2005; Academic ED SBIRT Research Collaborative 2007; Saitz 2007). Considerably less is known about the prevalence, effect, and best methods of identifying and intervening with individuals using illicit drugs or abusing prescription medications. While some studies suggest that brief motivationally focused interventions are somewhat effective in reducing the amount of substance use among non-treatment-seeking individuals, these researchers are quick to acknowledge that more conclusive support is needed (McCambridge and Strang 2005; Zahradnik, Otto et al. 2009). The prevalence of hazardous or harmful alcohol use appears greater than illicit drug use in PCs, EDs, and TCs, and the prevalence of illicit drug use is greater in EDs and TCs than in PCs (Calle, Damen et al. 2006; Cherpitel and Ye 2008). Relatively high rates of psychoactive substance use disorders have been found in EDs (Rockett, Putnam et al. 2005; Rockett, Putnam et al. 2006). Among a group of 1,933 patients admitted into a hospital emergency department (Calle, Damen et al. 2006), 198 (10%) were identified with substance abuse leading to the emergency department admission. Among those patients with illicit drug use (with or without co-occurring alcohol abuse), the most frequently reported drugs were cannabis (54%), cocaine (41%), amphetamines (39%) and opiates (39%). Methamphetamine is also increasing markedly in some areas, with meth patients having more serious medical complications and high levels of uncompensated cost of care (Swanson, Sise et al. 2007). Illicit drug use significantly complicates the initial diagnosis and medical management of the substance abusing

patient (Lucas 2005). Despite this, a relatively large percentage of such substance abusing patients are not referred to appropriate psychosocial services (Rockett, Putnam et al. 2005; Calle, Damen et al. 2006). This has led many clinicians and researchers to argue for the development of more effective methods of screening and case finding, brief interventions and referral to appropriate specialty treatment, as well as linkage between substance abuse services and general medical care (Dunn and Ries 1997), for individuals using illicit drugs (Rockett, Putnam et al. 2005; Babor and Kadden 2005 ; Lucas 2005; Babor, McRee et al. 2007; Saitz 2007). Prevention efforts, such as interventions in EDs, should be considered as the most efficient and feasible way to prevent injury recidivism in this patient population (Lucas 2005).

Until recently there had been few data that dealt with screening and brief interventions for drug users in emergency department settings. As opposed to dealing with hazardous or harmful drinking in ED settings, the evidence of the effectiveness of such interventions was considered only suggestive for drug use disorders (Babor and Kadden 2005 ) and there has been a call for further research on the efficacy of screening and brief interventions for drug use, as well as the need to test the effectiveness of such interventions in real world settings (Saitz 2007). However, a recent study, based on the CSAT-funded SBIRT demonstration program, has begun to provide information that such interventions, delivered across a range of different health care settings, can lead to significant reductions in drug use (Madras, Compton et al. 2009). A secondary analysis was conducted on data derived from this large scale multisite trial that employed a variety of different screening procedures and methods of intervening with alcohol and drug users; 6-month follow-up data were collected on a random 10% subsample of participants who had screened positive at baseline. Of 459,599 patients screened, 22.7% screened positive for a spectrum of risky/problematic use or abuse/addiction. The majority were recommended for a brief intervention (15.9%), with a smaller percentage recommended for brief treatment (3.2%) or referral to specialty treatment (3.7%). Among those reporting baseline illicit drug use, rates of drug use at 6-month follow-up were 67.7% lower and heavy alcohol use was 38.6% lower, with comparable findings across sites, gender, race/ethnic, and age subgroups. Additionally, among persons recommended for brief treatment or referral to specialty treatment, this reduction in drug and/or alcohol use was also accompanied by a significant improvement in a number of areas of psychosocial functioning and health. The findings suggest that implementing SBIRT activities is feasible in a variety of health care settings and that they contribute to reduced substance use and improved psychosocial function and quality of life.

Washington State was one of the CSAT-funded SBIRT sites (WASBIRT) included in the report by Madras (Madras, Compton et al. 2009). From its inception in 2003 through July 3, 2008, a total of 89,901 patients had received services through the 9 emergency departments participating in the WASBIRT project. Of these, 23.4% (21,074) screened positive and received an intervention and/or additional services for substance use. Four of the Pacific Northwest Node CTPs (Providence Behavioral Health Services [its ED also participated as a site], Evergreen Manor, Triumph Treatment Services, and Recovery Centers of King County) were involved as agencies receiving referrals for more intensive treatment. Over 2,000 patients, identified as either high or moderate drug use risk based on their screening scores, received either brief intervention or brief intervention followed by brief therapy or chemical dependency treatment and were followed at 6-months (Estee and He 2007). Average days of drug use declined from 13.7 in the 30 days prior to the baseline assessment in the ED to 6.5 days in the 30 days prior to the 6-month follow-up. While a significant reduction in drug use was found in both high and moderate risk groups, the greatest reduction was seen in the high risk group, with more intensive treatment among the high-risk users associated with greater change. In addition to changes in substance use, there were also substantial cost savings for Medicaid patients who were involved in the study. The average reduction in Medicaid costs per member per month was \$366. This was for all Medicaid patients involved in the study, including those who in addition to receiving a brief intervention also received a referral for chemical dependency (CD) treatment. An even greater savings was achieved with a more restrictive subsample. For patients who received a BI

only and had no CD treatment in the year before or the year after the ED visit, the estimated reduction in Medicaid per member per month costs was \$542 (Estee and He 2007).

Another subset of the CSAT SBIRT program was conducted by the InSight Project Research Group in Houston, Texas, including EDs, hospital inpatient and outpatient services, and community health centers (The InSight Project Research Group 2009). This project focused on a period of 3 years beginning one year after SBIRT programs were instituted and integrated into medical facilities. The rationale for this delay was to allow for a period of time where the project intervention was fully matured, staff was fully trained, and fidelity monitoring had been fully implemented. Instead of focusing outcomes on a dichotomous measure of change, use versus nonuse, this study provided analyses in terms of average days of use of both alcohol and drugs. The study found that for three levels of drinkers, the mean days of heavy drinking was reduced. For low level drinkers, the average number days of heavy drinking fell from 5.0 at intake to 2.2 at follow-up. For medium level drinkers, this number fell from 7.8 to 3.8 and for high level drinkers, the mean number of days of heavy drinking fell from 13.2 to 6.6 days.

The results for drug use were similar to those for alcohol use. Low level drug users had their mean number of days of drug use decrease from 4.8 days at intake to 2.3 days at follow-up. For medium level drug users, the mean fell from 8.7 at intake to 4.2 at follow-up. High level users had a reduction fall from an average of 14.0 days of drug use at intake to 7.4 days at follow-up. Consistent with the findings in Washington State, while positive effects were found across all levels of alcohol and drug use, decreases in substance use were most pronounced among individuals with the highest overall use.

Brief motivational interventions appear to have somewhat more limited effectiveness with drug abusers than with alcohol-involved individuals with respect to engaging them into treatment (Donovan, Rosengren et al. 2001; Tait, Hulse et al. 2004) or modifying their drug use (Miller, Yahne et al. 2003; Marsden, Stillwell et al. 2006; Stein, Herman et al. 2009); what positive effects are obtained deteriorate over time (McCambridge and Strang 2005). Findings such as these, suggesting that the “teachable moment” associated with care in an ED fades rapidly as the time between identification of a substance use disorder and intervention increases, have led to the recommendation that “booster sessions” be provided, either in person or via phone (Longabaugh, Woolard et al. 2001; Bernstein and Bernstein 2008; Bernstein, Edwards et al. 2009). While the initial brief intervention may get individuals to focus on changing risk-related behaviors, it might not be sufficient to motivate them to develop and implement a change plan; the booster can focus on and reinforce their putting their plan into action (Longabaugh, Woolard et al. 2001). As Bernstein and Bernstein (2008) state, “A booster session or referral for follow-up sessions outside the confines of a busy ED may be needed in addition to a 10-minute intervention in the course of clinical care” (p. 752). Findings from a sample of adolescent and young adult marijuana users in a pediatric ED (Bernstein, Edwards et al. 2009) indicate that the brief intervention plus booster session was significantly better at promoting marijuana abstinence and reducing consumption compared to the assessment control condition.

## **4.2 Rationale**

The present proposal builds on the extensive experience in developing and implementing screening and brief interventions for harmful and hazardous alcohol use delivered in emergency departments and trauma centers, transferring and evaluating these procedures when applied to drug use. The situation with SBIRT for drug users in ED settings is unusual in that effectiveness studies were conducted prior to definitive efficacy studies. Although the results from the CSAT-funded studies are quite promising with respect to the effects of SBIRT interventions on drug use, controlled trials are required to support causal inference. To justify large-scale change in practice, clear demonstration of benefit associated with the higher level of assessment and intervention is required.

## **Sustainability**

An important consideration in evaluating the present protocol is the extent to which the screening and intervention procedures are likely to be sustained in practice following the completion of research funding. Two factors contribute to the likelihood of this occurring. First is the cost savings associated with SBIRT services (Gentilello, Ebel et al. 2005; Estee and He 2007; Kraemer 2007). There are significant potential savings to health care systems. As an example, Barrett and colleagues (Barrett, Byford et al. 2006) found that referral to an alcohol health worker in an ED was more cost-effective than an information only control condition in reducing alcohol consumption and service utilization among individuals with hazardous drinking patterns. Such cost offsets have been used by many medical centers to hire SBIRT specialists to permanent staff position. The second factor has to do with the recent introduction of reimbursement procedures that cover screening and brief interventions for both alcohol and drug use (Fornili and Alemi 2007). This includes Healthcare Common Procedure Coding System (HCPCS) codes from the Centers for Medicare and Medicaid (CMS) and the American Medical Association CPT Codes, with differing levels of reimbursement based on the length of the session (e.g., 15-30 minutes, more than 30 minutes). Thus, it is likely that the ability to be reimbursed for screening and intervention services that will also lead to cost savings and cost offsets provides incentives for health care systems to incorporate these services. An additional factor, at least in the case of Level I and II trauma centers, is that the American College of Surgeons (ACS) Committee on Trauma (COT) is likely to require the implementation of screening and intervention targeting drug use in a manner similar to their mandate around alcohol use as a condition for recertification (Gentilello 2007).

## 5.0 OBJECTIVES

### 5.1 Primary Objective

The study will contrast substance use and substance-related outcomes among patients endorsing problematic substance use during an emergency department (ED) visit who are randomly assigned to one of three treatment conditions: 1) minimal screening only (MSO); 2) screening, assessment, and referral to treatment (if indicated or requested) (SAR); and 3) screening, assessment, and referral plus a brief intervention (BI) with two telephone follow-up booster sessions (BI-B).

**Primary Hypotheses:** We expect to observe significant differences among the three groups with respect to the primary outcome variable, days of use of the patient-defined primary problem substance during the 30 days prior to the 3-month assessment, as measured by the Time-Line Follow-Back.

**Hypothesis 1.** Participants randomized to BI-B will have fewer days of use relative to participants randomized to MSO.

**Hypothesis 2.** Participants randomized to BI-B will have fewer days of use relative to participants randomized to SAR.

**Hypothesis 3.** Participants randomized to SAR will have fewer days of use relative to participants randomized to MSO.

### 5.2 Secondary Objectives

1. To evaluate the effect of BI-B relative to SAR on substance abuse treatment engagement among those participants who are referred to treatment.
2. To evaluate the effect of the experimental interventions on self-reported health care utilization.
3. To evaluate several putative predictors of outcome (patient demographics, substance use severity at baseline, primary substance of abuse, motivation, therapeutic alliance, and perceived substance-relatedness of ED visit, and psychiatric comorbidity) in terms of both main effect and interaction with treatment assignment.
4. Among participants assigned to BI-B, to evaluate dose-response to number of booster sessions received.



## **6.0 STUDY DESIGN**

### **6.1 Overview**

The proposed project is a 3-group randomized, prospective trial with blinded assessments. Individuals presenting in the ED who endorse problematic substance use on screening will be randomized in 1:1:1 ratio to MSO vs. SAR vs. BI-B. Randomization will occur after screening, and those randomized to MSO will not receive further assessment until follow-up. To preserve the blind (SAR vs. BI-B) for the baseline assessment, allocation to the remaining two groups will not be revealed until after the baseline assessment is complete. Those in the SAR group will then receive referral to addiction treatment if indicated or requested, while those assigned to the BI-B group will receive a brief intervention (BI) consisting of motivational enhancement therapy (MET) adapted for use in the ED, followed by referral if indicated or requested. The BI-B group will also receive two booster telephone calls which will occur within 1 week of enrollment if possible, and no later than 1 month following enrollment. Follow-up assessments will be conducted face-to-face at 3 months, 6 months, and 12 months post-enrollment.

### **6.2 Rationale for the 3-group design**

The contrast between the BI-B and the SAR groups provides a measure of the effect of adding the brief intervention plus booster calls to assessment and referral. However, this contrast does not provide any information about the effect of assessment and referral on outcomes. The issue of assessment reactivity has plagued brief intervention research. It is known that the effects of assessment on outcome can be equal to or greater than the effects of therapeutic interventions (Clifford and Maisto 2000; Clifford, Maisto et al. 2007). This is particularly problematic when the intensity of assessment (in terms of time spent by the participant) is large in relation to the intervention. Without a “no assessment” or “minimal assessment” control, it is not possible to determine how much the assessment may have contributed to outcome, or, in the case of a null finding, whether it masked the effects of the therapeutic intervention.

The inclusion of the MSO group, which receives as little interaction as possible at baseline, provides a control by which to measure the assessment effect. The SAR and the BI-B groups will each be compared to MSO. The comparison of BI-B to MSO provides a measure of the total effect of the intervention (including any therapeutic effects of assessment and referral). The MSO condition offers a better approximation of the true “treatment as usual” than SAR. Since the SAR condition represents a significantly greater intensity of intervention than MSO, the potential difference in outcome between SAR and MSO is of considerable interest. SAR may be considered a minimal intensity active intervention (in relation to MSO) as well as a control (in relation to BI-B).

In sum, all three comparisons are of considerable practical and theoretical interest, and each significant difference between groups, if found, would provide meaningful evidence of treatment effect, but with different implications for practice. The main disadvantage to the three group design is the increase in complexity and cost. Although the increase in complexity is relatively small due to the simplicity of the MSO condition, the cost of recruiting and completing follow-up for a third group is significant, and larger groups are required in order to maintain statistical power to test the three between-group contrasts without the inflating type 1 error rate. The protocol development team believes that the increased potential for knowledge gained with the three-group design more than compensates for the increase in complexity and cost.

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

Screening, assessment, and the initial brief intervention and/or referral will occur during the participant's index ED visit. The target date for the first telephone booster session will be within 3 days of the ED visit, and the target date for the second booster session will be within 7 days of discharge from the ED. If initial attempts to conduct the booster sessions are unsuccessful, attempts to complete these calls will continue for up to one month post-enrollment. Follow-up assessments will occur at 3, 6, and 12 months. Therefore, the total duration of individual participation in the study is 12 months. The estimated duration of each visit and study component is listed in the table in Section 10.1.

## **7.0 STUDY POPULATION**

### **7.1 Inclusion Criteria**

1. Registration as patient in the ED during study screening hours
2. Positive screen (≥3) for problematic use of a non-alcohol, non-nicotine drug based on the Drug Abuse Screening Test (DAST)
3. At least one day of problematic drug use (excluding alcohol and nicotine) in the past 30 days
4. Age 18 years or older
5. Adequate English proficiency
6. Ability to provide informed consent
7. Access to phone (for booster sessions)

### **7.2 Exclusion Criteria**

1. Inability to participate due to emergency treatment
2. Significant impairment of cognition or judgment rendering the person incapable of informed consent. (e.g., traumatic brain injury, delirium, intoxication)
3. Status as a prisoner or in police custody at the time of treatment.
4. Current engagement in addiction treatment
5. Residence more than 50 miles from the location of follow-up visits
6. Inability to provide sufficient contact information (must provide at least 2 reliable locators).
7. Prior participation in the current study.

### **7.3 Subject Recruitment**

It is necessary to have an estimate of the number of participants who will need to be screened in order to yield the required number of randomized participants. In primary care settings, Bernstein et al. found a 5% rate of patients having a DAST score of 3 or greater, and 95% of these patients consented to participate in a randomized brief intervention trial (Bernstein and Bernstein 2008). The rate of patients screening positive in the ED will likely be somewhat higher. In the SAMHSA SBIRT implementation, 11.6% of those screened had used illicit drugs in the past 30 days, a less stringent criterion than ours (Madras, Compton et al. 2009). However, the rate of consent for the current study will likely be lower than 95%. In the Academic ED SBIRT study (which focused on alcohol), only 55% of those who qualified for the study consented to participate (Academic ED SBIRT Research Collaborative 2007). Estimating conservatively that 5% of screened patients will meet inclusion criteria, and that 75% of these will consent to participate in the study, it will be necessary to screen 34,267 patients (5711 per site) to achieve a sample of 1285 randomized participants. Among the 17 EDs responding to our initial site survey, the average patient volume was 6,912 patients per month, indicating that an adequate volume of participants is available for screening in these EDs. We propose to screen approximately 160 individuals per week per site to achieve the targeted enrollment rate of 6 participants per week per site. This will allow recruitment at each site to be accomplished within 9 months.

## **7.4 Special Populations to Consider**

ED patients who are subsequently hospitalized may differ from other ED patients in ways that affect outcome and response to treatment. For example, they would likely have more severe medical conditions which could affect motivation to change, and may have greater exposure to treatment and referral while in the hospital. Since there is no reliable way to know which patients will be hospitalized at the time of randomization, hospitalized patients will be kept in the study. RAs will review the ED log to identify all participants who are ultimately hospitalized as a result of their ED visit. Secondary analyses will explore whether such patients differ from non-hospitalized participants in substance use outcome or treatment response.

## **7.5 Number of CTP Sites**

Approximately six EDs will participate as sites for the study. Each ED may use multiple addiction treatment programs as referral options for participants seen in the ED.

## **7.6 CTP Characteristics**

Participating EDs should have the following characteristics:

- Large volume of patients who use drugs
- Research experience
- No current routine use of the SBIRT model for drug users
- Population representative of US population (in aggregate)
- Ability to present a convincing plan for patient flow and space utilization
- Have or are able to hire appropriate staff to conduct the study (in conjunction with the RRTC)
- Have sufficient referral network for patients needing specialty addiction treatment
- Have an ED physician who can serve as protocol PI or otherwise be actively involved in the protocol

## **7.7 Rationale for CTP Selection**

The volume of patients seen in the ED must be adequate to ensure a steady stream of eligible patients for recruitment. Research experience and successful participation in prior studies is desirable as it provides evidence of the feasibility of study implementation. The ED must not be using an SBIRT model for drug users during the study recruitment period so that there will be sufficient contrast between SAR and the BI + Booster condition. A diverse, representative sample of participants is desirable to enhance the external validity of the study. However, we will strive for relative homogeneity among participating EDs in order to minimize differences in implementation that might affect the magnitude of the treatment effect. Uniform high-quality implementation is critical to the success of an efficacy trial. Patient flow and space utilization promise to be particularly challenging in the ED setting and need to be worked out concretely and in detail prior to site selection to ensure success. Although different sites may have different solutions to meeting the staffing needs of the study (e.g., the roles played by staff of the ED, the RRTC, and potentially local CTPs), it is important that the team of individuals conducting recruitment, screening, assessment, and intervention collectively have a clear understanding of how the ED works, and have good working relationships with the ED staff.

### **Characteristics of EDs nominated by the Nodes**

In response to our initial site survey request, we received 17 responses from 14 nodes. The majority of respondents were large EDs with academic affiliation and significant research experience. The EDs averaged 6,912 patients per month, of whom an estimated 18%, on average, meet criteria for a drug use disorder. Based on proposed inclusion and exclusion criteria, the prospective sites estimated an average of 447 patients eligible per month (we need to recruit 24 per month per site). Only two of these EDs were currently using SBIRT. One of these targeted alcohol use, and the other was limited to trauma service patients admitted to the hospital. Except for these sites, screening and referral for substance use disorders is not being done systematically. These findings make us confident that we will be able to recruit a relatively homogenous group of experienced, high-volume sites that have an ample patient base for recruitment. Site visits are proposed prior to final site selection.

## **8.0 OUTCOME MEASURES**

### **8.1 Primary Outcome Measure**

The primary outcome is days of use of the patient-defined primary problem drug, assessed for the 30-day period preceding the 3-month follow-up using Time-Line Follow-Back (TLFB).

### **8.2 Secondary Outcome Measures**

1. Number of days the primary problem substance was used use during the past 30 days at 6 and 12 months post intervention (TLFB)
2. Days of abstinence from all drug use during the past 30 days at 3, 6, and 12 months post intervention (TLFB)
3. Days of heavy drinking in the past 30 days at 3, 6, and 12 months (TLFB)
4. Quantity of use (dollar value, number of times used) for the primary drug at 3, 6, and 12 months post-baseline (TLFB)
5. Change in days of use of the primary drug between baseline and follow up at 3, 6, and 12 months (TLFB; this outcome is available only for the groups that completed the TLFB at baseline, i.e., SAR and BI-B)
- 6a. Hair sample drug screen results for the primary drug at 3, 6, and 12 months post-intervention (relative change in hair screen level from baseline)
- 6b. Hair sample drug screen results for any drug of abuse at 3, 6, and 12 months (relative change in hair screen level from baseline)
7. Consequences of drug use (from the NM ASSIST)
8. Participation in addiction treatment in the past 30 days at 3, 6, and 12 months post intervention among participants (SAR and BI-B groups only) with probable dependence who are referred for treatment (from the Treatment Services Review: TSR)
9. Health care utilization (number of ED visits, number of hospital days, and number of outpatient visits) in the past 30 days at 3, 6, and 12 months (TSR)

## **9.0 STUDY PROCEDURES**

### **9.1 Screening and Informed Consent Procedures**

#### **9.1.1 Pre-Screening**

During defined recruitment hours, RAs assigned to the study will screen ED patients who are possibly eligible for the study. Each site will develop a sampling procedure to ensure that the patients screened are broadly representative of the ED population. The RA will identify patients seen in the ED within recruitment hours, and will collect anonymous information about screened patients using the Brief Information Tool (BIT) in order to determine representativeness of the study sample. This form includes age, gender, and reason for ED visit. The RA will screen ED patients according to the Operations Manual procedures and local standard operating procedures. Screening will continue until recruitment hours have ended or the recruitment target for the week is achieved (6-12 participants randomized per week per site). The RA will approach ED patients and ask them if they are willing to participate in anonymous screening. Participants will provide verbal (not signed) consent for the anonymous collection of screening data, using a brief IRB-approved script. Refusals and inability to participate (e.g., unavailable due to emergency medical treatment, left without being seen) will be recorded on the BIT.

#### **9.1.2 Screening**

Study staff will time their intervention to minimize interference with medical treatment. Depending on level of acuity, some patients will be approached prior to the initial evaluation by a physician, and some after. For example, patients with high medical acuity will likely receive initial evaluation before being approached about the study. Patients who show signs of intoxication (e.g., somnolence, slurring of speech) will not be screened unless and until these signs resolve. The Research Assistants should use their judgment to assess intoxication and ask the staff clinician if they are unsure. Local procedures will vary from site to site and will be described in a local SOP. The screening data will be collected by research personnel and by participant self-report using direct entry into tablet computers to facilitate rapid screening, electronic data capture, and mobility within the busy ED setting.

The purpose of screening in this study is to define a population of patients who are likely to have problematic drug use, abuse, or dependence for inclusion in the study. In other words, the procedure needs to have a high positive predictive value (probability of the disorder given a positive test), whereas clinical screening instruments are designed to have high sensitivity (probability of a positive test given the disorder).

The logistics of conducting screening in the ED require that the screening process be relatively brief. Further, in order to minimize assessment reactivity in the MSO group, we wish to keep the substance-related screening questions to an absolute minimum. Some instruments commonly used to screen for substance use disorders in medical settings are too long for our purposes, such as the World Health Organization Alcohol Smoking, Substance Involvement Screening Test (ASSIST) (Humeniuk, Ali et al. 2008), which we are using as part of the assessment battery in this trial. A two-item screen for both alcohol and drug use disorders (Brown, Leonard et al. 2001) was found to have a positive predictive value of 51.8% in a primary care population, but this instrument does not distinguish between alcohol and drugs. Other short instruments, such as the Case finding and Help Assessment Tool (CHAT) (Goodyear-Smith, Coupe et al. 2008) have only partial validation, and it was not possible to say where

its cut-off point would lie in relation to well-known instruments such as the DAST. For this reason, we decided to use the 10-item Drug Abuse Screening Test (DAST-10) (Gavin, Ross et al. 1989) to assess degree of drug involvement.

In addition to assessing degree of drug use in this pre-screening questionnaire, we also want the screening questionnaire to do the following:

- 1) assess the degree of alcohol involvement and drug problem severity, which will be used as a stratification variables and thus needs to be determined prior to randomization;
- 2) determine the primary drug of abuse, the number of days it was used in the past 30 days, and the substance-relatedness of the ED visit;
- 3) minimize participant discomfort with answering sensitive questions about drug use by introducing the questionnaire with tobacco-related questions which form a brief screen for nicotine dependence.

Therefore, the pre-screening instrument will consist of 4 sections: The 4-item Heavy Smoking Index, the 3-question Alcohol Use Disorders Identification Test, the 10-item DAST, and 3 questions to determine primary substance of abuse, days of use of the primary substance, and substance-relatedness of the ED visit. The four parts of the pre-screening questionnaire are detailed below. We have named this four-section screening instrument the Tobacco, Alcohol, Drug (TAD) questionnaire to capture the substances assessed:

**Part 1:** Participant discomfort with answering sensitive questions about drug use will be accomplished by introducing the questionnaire with tobacco-related questions which form a brief screen for nicotine dependence, the Heavy Smoking Index (HSI). The Fagerström Test for Nicotine Dependence (FTND) is a widely used six-item questionnaire (Heatherton, Kozlowski et al. 1991). The 4-item Heavy Smoking Index (HSI), is a briefer measure including only two FTND items (time to first cigarette of day and number of daily cigarettes) in addition to two binary questions of “Do you smoke cigarettes or use any other form of tobacco” and “Do you smoke or use tobacco every day” to offer a skip pattern if the patient does not use tobacco. In a prior study comparing HSI with FTND, a high HSI (score  $\geq 4$ ) was an adequate briefer alternative for detecting high nicotine dependence (Diaz, Jané et al. 2005).

**Part 2:** The AUDIT-C is made up of three questions about alcohol consumption (Bush, Kivlahan et al. 1998). The AUDIT-C is a practical, valid primary care screening test for heavy drinking and/or active alcohol abuse or dependence (Bush, Kivlahan et al. 1998; Bradley, DeBenedetti et al. 2007). The AUDIT-C performs about as well as the full AUDIT in identifying alcohol use disorders.

**Part 3:** The DAST-10 (Skinner 1982) is designed to identify drug-use related problems in the previous year. The DAST-10 It has demonstrated good internal consistency ( $\alpha = .94$ ) and temporal stability (test-retest intraclass correlation coefficient = .71) in psychiatric samples. The DAST-10 discriminates between psychiatric outpatients with or without drug use disorders (Cocco and Carey 1998). The DAST-10 was found to have moderate to high levels of validity, sensitivity, and specificity (Yudko, Lozhkina et al. 2007). Scores  $\geq 3$  are indicative of probable abuse or dependence.

**Part 4:** If the DAST score is  $\geq 3$ , follow-up questions will identify the primary drug of abuse and the number of days of use of this substance in the past 30 days. The primary drug of abuse will be identified by patient report. The screen will be considered positive only if the participant

- has a score  $\geq 3$  on the DAST and
- reports past 30-day use of the primary substance.



The requirement for past 30-day use is an inclusion criterion for the study, and should increase the stringency of the screen above that of the DAST drug use questions alone.

The questionnaire will also include a single question about substance-relatedness of the ED visit: “Do you think that this emergency room visit is related to any of the substances you use?” (4 point scale, 1 = “Visit is not at all related to substance use,” 2 = “Substance use played a minor role”, 3 = “Substance use played a major role”, 4 = “Visit happened because of substance use.”) A secondary analysis will explore the role of substance-relatedness of the ED visit as a moderator of outcome and treatment effect.

To maximize confidentiality, the TAD will be completed by the participants, who will enter the data directly using the tablet PC unless the participant is not comfortable with this technology, in which case the data may be entered by the RA. Participants who meet screening criteria based on the TAD will be further screened for eligibility by the RA using the Secondary Screening Form (SSF). The RA will ask participants about (1) current engagement in addiction treatment, (2) whether they reside more than 50 miles from the follow up location, (3) ability to provide at least two locators, and (4) access to a phone, (5) status as a prisoner as well as inquiring whether they are currently on probation, parole, house arrest, and/or electronic monitoring (e.g. ankle bracelet), and the RA will indicate (6) if the informed consent was signed. Specifics on locators, residence, etc. will not be gathered at this time.

These two screening forms will not include identifying information. Those who are interested and eligible will then undergo the informed consent process described below. Patients who screen out of the study will receive no further intervention, but the anonymous screening data will be kept to allow comparison to those who do qualify.

### **9.1.3 Informed Consent Procedures**

Patients will be provided with an IRB-approved informed consent form that will include a description of all significant elements of the study: the assessment interview and questionnaires; the follow-up interviews; description of experimental treatment; risks and benefits of study procedures; alternatives to participation in the study; confidentiality; emergency treatment and compensation for injury; payment for participation; a statement that patients will be informed of any new findings affecting the risks or benefits of the study; a statement that participation is voluntary and that the patient may withdraw at any time; and information about whom to contact with questions or in case of emergency. The consent form will also include assurances of confidentiality and a statement that participation is entirely voluntary, that the decision to participate will in no way influence other aspects of the patient’s treatment, and that the participant is free to withdraw participation at any time. Patients will read the first paragraph of informed consent document (or have it read to them, if they are unable) and express verbally their understanding of the key elements of the study (e.g., random assignment, possible interventions received, duration of follow-up). They then indicate their consent to participate in the study by signing and returning the informed consent form. A HIPAA disclosure form will also be required to allow the study to access protected health information in the patient’s medical record in the ED. Because of the time constraints of completing the assessment and intervention in the ED, and because of the relatively low risks associated with the study, the consent form will be as brief as possible within the constraints of adequate human subjects’ protections.

### **9.1.4 Completion of Screening Visit Prior to Randomization**

Once a participant has consented, the 0047 Screening Form will be completed. Date of assessment, date the informed consent was signed, and the presenting complaint, which will be derived from the Emergency Department records, will be entered on this form. Prior to randomization, all consenting participants will complete a demographic questionnaire, provide locator information, and provide a

hair sample which will provide an objective measure of substance use. The RA will use the 0047 Randomization Form to document inclusion and exclusion criteria, randomization information including the AUDIT and DAST scores, and the reason an eligible participant was not randomized (See Section 10).

## **9.2 Randomization**

After providing informed consent, all eligible participants will be randomly assigned in 1:1:1 ratio to (1) Minimal Screening Only (MSO), (2) screening plus assessment and referral (if indicated or requested) (SAR), or (3) Brief Intervention with two telephone boosters in addition to screening, assessment, and referral (if indicated or requested) (BI-B). Randomization will be stratified on site and presence of alcohol use disorder (AUDIT-C score  $\geq$  4), and drug problem severity (operationalized as a DAST-10 score of  $\geq$  8, based on the score distribution observed in Bernstein et al. (2005)). The randomization procedure will be conducted through a centralized, web-based process set up by the CTN Data and Statistics Center (DSC). The randomization sequence will be unknown to staff, and allocation will be revealed in two stages. Initially, the RA performing the randomization will be informed whether the participant is in the MSO group or not. Those in the MSO group will not receive further assessment until the 3-month follow-up visit. The rest of the participants will receive the baseline assessment. After completion of the baseline assessment, RAs will be informed whether participants are in the SAR or BI-B group. RAs conducting the follow-up assessments will be blinded to treatment condition.

The DSC statistician will generate the randomization scheme for the study. The randomization schedules will consist of balanced varied size blocks within strata to ensure relative equality of assignment across treatment groups. The block sizes 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 statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new patient due to the intent-to-treat nature of the study.

## **9.3 Baseline Assessment (SAR and BI-B groups)**

The baseline assessment for this trial will be kept considerably briefer than those traditionally used in addiction treatment trials. There are both methodological and practical reasons for this. It is important to keep the assessment battery brief in order to minimize assessment reactivity that can obscure treatment effects (Clifford, Maisto et al. 2007). This is of particular concern in brief intervention trials in which the dose of treatment is relatively small, and the putative active ingredients of the treatment include assessment and feedback. The practical issue is that extensive assessments are likely to interfere with the rapid pace of clinical treatment in the ED setting. A cumbersome assessment process is also likely to impede the successful completion of the study through an adverse effect on recruitment and on the quality of the relationship between study staff and clinical ED staff. Even if successfully implemented in the study, an extensive assessment process is unlikely to survive translation into clinical practice.

The baseline assessment will include the NM-ASSIST and a 30-day Time-line Follow-Back (TLFB) interview as the primary baseline measure of substance use. The total time burden for the baseline assessment is approximately 30 minutes.

## **9.4 Treatment**

### **9.4.1 Study Interventions**

The three treatment conditions are Minimal Screening Only (MSO) Screening and Referral (SAR) and Brief Intervention plus Boosters (BI-B), described in Section 11.

### **9.4.2 Subject Discontinuation**

All participants will be followed for the full 12 months unless they withdraw consent, threaten or assault staff, or there is evidence that continuing in the study would be harmful to the participant. Participants could also be discontinued in the unlikely event that technical difficulties (e.g., internet connectivity issues) preclude the timely completion of the baseline visit at some point after consent.

### **9.4.3 Treatment Discontinuation**

Treatment will be discontinued if a participant withdraws consent, threatens or assaults staff, or if there is evidence that continuing in the study would be harmful to the participant.

## **9.5 Follow-Up**

Follow-up assessments will be conducted at 3, 6, and 12 months. Different RAs will be used to complete baseline and follow-up assessments, in order to maintain blinded follow-up assessment. If in-person follow-up is not possible, follow-up visits may be conducted by phone, but this should be avoided if possible as hair samples would be missing in such cases. In addition to measures of substance use, for purposes of tracking substance abuse treatment entry and utilization and medical treatment service utilization, the Treatment Services Review (TSR) will be administered at these follow-up points as well. If a participant comes in for his or her 6-month follow-up and he or she has missed the 3-month follow-up, the RA will reconstruct the Time Line Follow Back form for the 3-month period and complete all 6-month follow-up assessment items.

### **9.5.1 Follow-up with Prisoners (as defined by OHRP)**

Prisoners will not be enrolled in this study. If a participant later meets the OHRP definition of a prisoner as stated in 46 Subpart C after baseline enrollment, sites may keep such individuals in the study and collect follow-up data only if they have local IRB and OHRP approval to do so. Sites intending to collect follow-up data on individuals who become prisoners must submit proposed site-specific procedures to their local IRB, which will in turn submit them to OHRP. These procedures must be compliant with 45 CFR 46 Subpart C. Data may be collected either in person or by electronic means, provided that data collection follows the procedures approved by OHRP and the local IRB.

## **9.6 Compensation**

Because of the expected difficulty of maintaining high follow-up rates in the study population, adequate compensation for time and inconvenience is critical. We propose compensation of \$50 for the screening/baseline visit and \$75 for the 3-month visit (primary outcome) and subsequent visits. Follow up will be conducted in person at a central location, preferably at the RRTC if sufficiently close to the ED. Additionally, if participants are unable to provide for their own transportation to and/or from follow-up visits, sites may provide transportation including bus or taxi fare if they have local IRB approval to do so. If a participant is found to be a prisoner at time of follow-up, as defined above, participant will be compensated the agreed upon amount as approved by local IRB and/or collaborating prison facilities.

Pilot/training patients will be compensated \$30.00 for the brief intervention session. If the pilot/training patient additionally participates in the booster interventions, they will be compensated \$30.00 per booster call session for up to a total of \$90.00 for participating in the brief ED intervention and two booster interventions.

### **9.7 Blinding**

As in almost all psychosocial treatment protocols, study participants will not be blinded. However, RAs conducting baseline assessments will be partially blinded until the assessment has been completed, and RAs conducting follow-up assessments will be blinded to treatment condition. At the beginning of the follow-up interview, the RAs should read a brief script that informs the participant that they should not reveal their treatment assignment. This script is available on all follow-up progress notes to ensure consistency in delivery of this instruction. If the blind is accidentally broken by the participant, the RA should document this on the progress note; this is not a protocol violation.

## **10.0 STUDY ASSESSMENTS**

The selected assessment battery attempts to balance the value of comprehensive data against the costs of data collection in terms of staff time, feasibility of completion in the ED, financial cost, and assessment reactivity. Lengthy assessments are likely to be difficult to implement consistently in ED settings due to the pace of emergency care and the variable, often short time period during which the assessment can be completed. The study is testing the efficacy of a relatively low-intensity intervention that could have a relatively small effect and still be cost-effective and have a significant public health impact. Thus, a relatively large sample size is required, and the size of the assessment battery must be minimized to contain the cost of the study. The issue of assessment reactivity (i.e., therapeutic effects of assessment) is also particularly acute due to the short duration and low intensity of the study interventions. Therefore, assessments have been limited to those that contribute directly to the objectives of the study or are necessary for reasons of safety or regulatory compliance.

## 10.1 Study Timetable

### General Forms

CRF	Est. Time (Minutes)	Done By	Screen MSO	Screen SAR	Screen BI-B	Booster 1 BI-B	Booster 2 BI-B	3 Month	6 Month	12 Month
Brief Information Tool	3	RA	X	X	X					
Tobacco, Alcohol, & Drug Questionnaire	5	***PT/RA	X	X	X					
Secondary Screening Form	2	RA	X	X	X					
Informed Consent	10	RA/PT	X	X	X					
HIPAA	5	RA/PT	X	X	X					
0047 Screening	1	RA	X	X	X					
Demographics	2	RA	X	X	X					
Additional Demographics	2	RA	X	X	X					
Additional Demographics Follow-Up	2	RA						X	X	X
Locator Information Form	5	RA/PT	X	X	X					
Update Baseline Locator Information Form	5	RA						X	X	X
Hair Sample Form	2	RA	X	X	X			X	X	X
0047 Randomization	5	RA	X	X	X					
Pamphlet	1	RA	X	X	X					

**General Forms**

CRF	Est. Time (Minutes)	Done By	Screen MSO	Screen SAR	Screen BI-B	Booster 1 BI-B	Booster 2 BI-B	3 Month	6 Month	12 Month
NIDA-Modified ASSIST	10	RA		X	X			X	X	X
Time-Line Follow-Back Assessment Period	3	RA		X	X			X	X	X
Time-Line Follow-Back	60-180	RA		X	X			X	X	X
Referral List	1	RA		*	*					
Referral Form	1	RA		*	*					
Intervention Record Form	5	INT			X					
Personal Feedback Form	5	INT			X					
Working Alliance Inventory - Short Form - Revised	5	****PT/RA			X					
Booster Record Form	5	TBSI				X	X			
Non-study Treatment Form **	5	RA								
Treatment Services Review	10	RA						X	X	X
Barriers to Treatment Inventory	5	****PT/RA						X		

### Administrative Forms

CRF	Est. Time (Minutes)	Done By	Screen MSO	Screen SAR	Screen BI-B	Booster 1 BI-B	Booster 2 BI-B	3 Month	6 Month	12 Month
Adverse Events	1-15	RA/ INT/ TBSI	*	*	*	*	*	*	*	*
Serious Adverse Event Summary	0-30	RA/ INT/ TBSI	*	*	*	*	*	*	*	*
Serious Adverse Event Medical Reviewer	0-30	RA/ INT/ TBSI	*	*	*	*	*	*	*	*
Protocol Violation Log	0-15	RA/ INT/ TBSI	*	*	*	*	*	*	*	*
Study Termination	0-5	RA/ INT/ TBSI	*	*	*	*	*	*	*	*

\* Administer when indicated

\*\*Administer at 1 month post baseline by RA at ED

\*\*\* It is preferable that the RA administer the TAD, unless there is a lack of privacy which may compromise confidentiality or cause discomfort, in which case the patient should complete the TAD

\*\*\*\* RA should only administer if participant is uncomfortable with using the Tablet PC or computer

### Pre-Training Interventionist Forms

CRF	Est. Time (Minutes)	Done By	Completed prior to BI-B Training
Short Understanding of Substance Abuse Scale	15	INT/ TBSI	x
Clinician & Supervisor Survey	15	INT/ TBSI	x

RA=Research Assistant; INT=Interventionist; TBSI=Telephone Booster Session Interventionists; PT=Participant



## **10.2 Protocol Specific Assessments**

### **10.2.1 Laboratory tests**

No blood or urine samples will be used in the study. For hair analysis, see item 10.2.3.2 below.

### **10.2.2 Clinical Assessments**

#### **10.2.2.1 NIDA-Modified Alcohol, Smoking and Substance Involvement Screening Test (NM-ASSIST)**

The World Health Organization ASSIST (Humeniuk, Ali et al. 2008) is a screening instrument used to assess use of 10 substances: tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants (ATS), inhalants, sedatives, hallucinogens, opioids, and other drugs. The ASSIST investigates frequency of use and associated problems for each substance. Following Q1 concerning lifetime use of substances, Q2 asks about frequency of use during the prior 3 months. Responses for this question (and Q3, Q4 and Q5) are rated on a five-point Likert scale ranging from 'never' (in the past 3 months) to 'daily or almost daily. This question provides critical information about the substances most relevant to the respondent's current health status. If there has been no substance use in the past 3 months, the interviewer can skip to the last three questions about problems and prior usage patterns in their lifetime. If any substance has been used during the past 3 months Q3, Q4 and Q5 are asked for the substances that have been used, before concluding with Q6, Q7 and Q8. Q3 asks about compulsion to use substances in the previous 3 months. This is a measure of psychological dependence. Q4 asks about health, social, financial or legal problems, associated with substance use, that have occurred within the previous 3 months. This is a measure of harmful use. Q5 asks whether participants have failed to meet usual role obligations; Q6–Q8 ask about life-time and recent problems, including whether concern has been expressed by friends or relatives, prior failed attempts at controlling drug use, and current or lifetime injection of drugs. The ASSIST has been found to be reliable and valid in numerous studies (Allen, Litten et al. 1997; Babor and Higgins-Biddle 2000; Humeniuk, Ali et al. 2008) and is used widely throughout the world in primary and other health care settings as part of screening and brief intervention programs. Unlike the DAST, the ASSIST provides substance-specific information and provides scores for each substance that correspond to abuse and dependence diagnoses.

We will use the modified version of the ASSIST developed by NIDA as part of its NIDAMED package for screening for substance use disorders in medical settings (NM-ASSIST, (<http://www.nida.nih.gov/nidamed/>), which includes separate assessment of prescription stimulants and methamphetamine, and of prescription opioids and heroin. However, because of the relevance of smoking and drinking behaviors we will also include the alcohol and smoking questions that are included in the WHO ASSIST but omitted in the NM-ASSIST.

### **10.2.3 Efficacy Assessments**

#### **10.2.3.1 Time-Line Follow-Back**

The Time-Line Follow-Back (TLFB) procedure will be used to assess drug use behavior at baseline and follow-up visits ((Sobell and Sobell 1992; Sobell and Sobell 1996).The Time-Line Follow-Back Assessment Period Form (TAP) will be used to assess the date, assessment period, and inquires if substances were used during the assessment period. The TLFB is a semi-structured interview that provides estimates of the daily quantity, frequency, and pattern of drug use during a specified time period. It uses a calendar prompt and number of other memory aids (e.g., holidays, payday, and other personally relevant dates) to facilitate accurate recall of drug use during the target period. The

procedure has been used in numerous clinical and research contexts. It has demonstrated adequate levels of reliability and validity when administered as an in-person interview, over the telephone, and when administered by computer (Sobell, Sobell et al. 1988; Sobell, Brown et al. 1996; Sobell and Sobell 1996). It is estimated that the TLFB assessment will take approximately 15 minutes to complete. Daily use data will be collected for cannabis, cocaine, methamphetamine and prescription stimulants, street opioids and prescription opioids, inhalants, sedatives, hallucinogens, alcohol, and other drugs. For each day of use, the RA will record amount of the substance that was used, the route of administration of the substance, and the dollar value of the amount of substance consumed.

### 10.2.3.2 Hair analysis

Hair testing will be used at baseline and at 3-, 6-, and 12-month follow-up as an objective secondary measure of drugs and their respective metabolites. The Psychedics Corporation will perform the hair analysis for the study and will use the standard DHHS/SAMSHA drug panel that consists of cocaine (benzoylecgonine, cocaethylene, norcaine), opiates (codeine, morphine, 6-MAM, oxycodone), PCP, Amphetamines (methamphetamine, MDMA, MDEA) and marijuana (nTHC). Compared to body fluids such as urine or saliva, hair testing enables the detection of substance use over a significantly longer window of time (Caplan 2001; Gallardo 2008) and is increasingly being used as an objective approach complementary to self-reported substance use outcomes in clinical trials. In a study comparing self-reported drug use and hair drug testing, the two estimates were modestly but not highly correlated, and results from hair analyses suggested more widespread use, supporting its use as a secondary outcome measure (Tassiopoulos 2004; Ledgerwood 2008). A significant benefit of this testing approach is the non-intrusive nature of collecting a hair sample from the scalp (Kintz 2006)..

Currently, the method with the most empirical support for detecting drugs in hair is a two step process: If a sample has tested positive during the preliminary screening radioimmunoassay then those samples are confirmed using gas chromatography tandem mass spectrometry (GC/MS/MS) for marijuana or liquid chromatography tandem mass spectrometry (LC/MS/MS) for opiates, cocaine, and amphetamines or gas chromatography-mass spectrometry for PCP (Hegstad 2008). This technology appears to offer significantly greater detection ability than other methods of analyzing hair or body fluids. When comparing hair analysis to other matrices, Pelander (2008) reported that in 72% of the cases examined, sample compounds that were not present in other matrices were detected in hair, suggesting the increased sensitivity of this approach relative to other biomarkers.

**Methodology:** A standard test of one hundred milligrams head hair cut close to the scalp can provide a several-month window to detect drug ingestion. The first 3.9 cm of hair corresponds to an average three-month hair growth. Hair samples are preferably snipped from the vertex posterior, located at the back of the head, just below the crown. According to Kintz (2006) "Compared with other areas of the head, this area has less variability in the hair growth rate, the number of hairs in the growing phase is more constant and the hair is less subject to age-and sex-related influences" (p. 442). Approximately 90-120 strands of hair are required (in general, the amount needed is the diameter of a number 2 pencil lead). If necessary, hair can be collected from several locations on the head and combined to obtain the required amount of hair. Facial hair such as beard and mustache can be used as a sample of head hair. Head hair and facial hair can be mixed in one sample for analysis. Only if head hair is not available, can body hair from the leg, chest or underarm be used as an alternative. Since body hair exhibits longer periods of dormancy than head hair, the timeframe of substance use derived from body hair testing is difficult to establish because it spans several months. Head hair and body hair cannot be mixed in a sample for analysis. Only head and body hair cut from the study participant by research personnel is permitted for the study. Samples brought in by study participants from combs, brushes, pillows and other sources are not permitted since there is no way to guarantee that the sample is from the participant. Prior research has found high correlations in drug concentrations between head, axillary and pubic hair (Han 2005). Common hair treatments (perming, dyeing) and

products (e.g., shampoos, conditioners, sprays, mousses and gels) have no significant effect on results. Analyses from a review of eight data sets conducted by Mieczkowski and Newel (2000) did not discern a significant color effect and reported that normal hair treatments such as bleaching, perming and dyeing did not significantly lower the quantitative results. The authors did note that if the protein matrix of the hair has been damaged to the point of breaking (cortex damage) the level of drug can be significantly affected. This would be an indication to use hair from another source such as body hair or facial hair if possible. If a hair sample is inadequate to process and test for the full panel of substances, Psychomedics will test for single drugs, starting with the substance identified as the primary drug of use.

Once hair samples are cut from the participant it is secured in aluminum foil with root ends marked and protruding from the edge of the foil. Do not tamper with the root ends of the sample by cutting them to make them even as this will impair analysis results. Information on whether the individual has a history of hair treatments (dyeing, perming, etc.) and hair location are documented on the Hair Sample Form (HSF). Hair samples do not need to be washed after before packaging the sample for analysis. An extensive wash procedure on test samples is employed by Psychomedics to ensure that any potential contamination has been removed or taken into account. The wash procedure minimizes the potential effect of environmental contamination (Gallardo 2008). Psychomedics uses a digestion method to liquefy the hair, thereby effectively releasing essentially all the drugs present for analysis, and increasing detection capabilities..

#### **10.2.4 Safety Assessments**

##### **10.2.4.1 Adverse Events (AD1), including Serious Adverse Events (AD2 and AD3), Protocol Violations Log (PVL), and Study Termination (STT)**

Adverse Events, Serious Adverse Events, Protocol Violations, and Study Terminations will be assessed and documented as described in Section 14 of the protocol.

#### **10.2.5 Treatment Involvement**

##### **10.2.5.1 Intervention Record Form and Booster Record Form**

The Intervention Record Form and Booster Record Form will be used to document session date, time and whether the session was interrupted. The forms will also include a brief space to type key details of the session. Interventionists will also mark scores on importance, confidence, and readiness if these rulers were used during the intervention as well as give details on a change plan, if one was created during the session.

##### **10.2.5.2 The Treatment Services Review (TSR)**

The TSR (McLellan, Alterman et al. 1992) is a measure of the type and extent of the treatment services that a client reports receiving over a given time period. A modified TSR will be used to capture all substance abuse, emergency, medical, and psychiatric treatment that participants have received at follow-up visits. Information will be captured for both “in” treatment, defined as the health care system where the patient sought care in the ED and “out” treatment, defined as other health care systems.

##### **10.2.5.3 Non Study Treatment Form (NTF)**

The NTF will be completed by RAs approximately 1 month after the patient’s admission to the ED using chart review. This form will track ED discharge diagnoses, whether the patient was admitted to the hospital and length of stay, whether the patient received any additional substance related

interventions during their ED visit, and whether the patient was discharged with any substance use medications (e.g., withdrawal medications).

## **10.2.6 Process Measures**

### **10.2.6.1 Working Alliance Inventory – Short Version (WAI)**

The 12-item Working Alliance Inventory (WAI-SR) (Hatcher and Gillaspay 2006) is a self-report measure based Bordin's (1994) formulation of working alliance. The WAI-SR comprises 12 items that the client scores using a Likert-type scale ranging from 1 to 7. Therefore, the total scoring of the WAI-S ranges from 12 to 84. This instrument assesses the extent to which the individual experiences the therapist and therapy as helpful. Similar to the original 36-item Working Alliance Inventory, the WAI-SR consists of three subscales, each comprising four items: the Goal subscale addresses the extent to which therapy goals are important, mutual, and capable of being accomplished; the Task subscale focuses on the participant's agreement about the steps taken to help improve the client's situation; and the Bond subscale measures mutual liking and attachment by focusing on tone of voice, empathy, and comfort in exploring intimate issues. A psychometric evaluation of the WAI-SR (Hatcher and Gillaspay 2006) indicated that the instrument demonstrated adequate factor structure, differentiated between Goal, Task, and Bond alliance dimensions, and correlated well with other alliance measures. Tracey and Kokotovic (1989) reported strong internal consistency (Cronbach's alpha = .98) of the WAI-SR. For patients uncomfortable with using the tablet PC, this form may be completed as an interview by an RA who did not serve as interventionist for the participant.

### **10.2.6.2 Barriers to Treatment Inventory (BTI)**

Participants will complete the 25-item Barriers to Treatment Inventory (Rapp, Xu et al. 2006) at 3-month follow-up. This Likert-scaled questionnaire has seven internally consistent subscales relating to Absence of Problem, Negative Social Support, Fear of Treatment, Privacy Concerns, Time Conflict, Poor Treatment Availability, and Admission Difficulty. We will add three items to this scale related to child-care, child custody, and child protective services involvement. It may be used to identify perceived barriers to treatment regardless of whether the individual has sought or engaged in treatment. To maximize confidentiality, the BTI will be completed by the participants, who will enter the data directly using the computer unless the participant is not comfortable with this technology, in which case the data may be entered by the RA.

## **10.2.7 Projected Timetable**

Estimated times for the instruments are shown in the table in Section 10.1.

## **10.3 Common Assessment Battery**

### **10.3.1 CTN Demographic Form (DEM) and Additional Demographics (ADM)**

The CTN Demographic Form collects information about date of birth, sex, ethnicity, and race. Additional demographic information will be gathered on the Additional Demographics form and will include education, marital status, employment, and income. This will be completed for all participants at baseline, with an abbreviated version collected at 3, 6 and 12 months.

### **10.3.2 Locator Questionnaire**

An electronic locator form, including home address, will be completed at baseline and updated at the 3 and 6 month follow-up visits and in-between visits, if new locator information is obtained. Data collected on the Basic Data and Locator Questionnaire will be used to facilitate contact with the

participants during the research and follow-up. Participants will be asked to provide locator information including their contact information and the contact information of friends or relatives who can reach the participant if the participant cannot be reached directly.

#### **10.4 Interventionist Assessments**

Interventionists will complete an assessment battery made up of the following instruments prior to attending the 2-day empathy/reflective listening training and 2-day BI-B training. Questionnaires will be filled out using a web-based form and submitted electronically to the DSC.

##### **10.4.1 Short Understanding of Substance Abuse Scale (SUS)**

Humphreys and colleagues (Humphreys, Greenbaum et al. 1996) developed the Short Understanding of Substance Abuse Scale (SUS) as a modified version of the Understanding of Alcoholism Scale. The latter scale was developed originally by Moyers and Miller (1993) to assess alcoholics' beliefs about the etiology and treatment of alcoholism. Two changes were made. First, the scale was shortened from 50 items to 20 items. Second, the wording of the items, as well as the inclusion of some new items, has been broadened to focus on both alcohol and drug use. Three factor analytically derived subscales have been identified: disease model, psychosocial model, and eclectic orientation. These subscales had Cronbach's alpha coefficients of internal consistency of .78, .85 and .61, respectively. A difference between the original and modified short SUS is that Humphreys et al. (1996) had the measure filled out by treatment staff members, while Moyers and Miller (1993) had the original completed by clients in treatment.

##### **10.4.2 Clinician and Supervisor Survey (CNS)**

This self-report survey (Ball, Bachrach et al. 2002) obtains information on: a) interventionist demographics; b) levels of experience, education, and credentials; c) personal recovery; d) counseling orientation; e) and beliefs about treatment, clients, and the recovery process.

##### **10.4.3 Confidential Pre-training Questionnaire (CPQ)**

This instrument (unpublished) is a 17-item self-report questionnaire that assesses practitioner's perceived skill level in practicing MI. Questions include yes/no questions on whether providers have read books or articles on MI as well as 11 Likert-scale questions regarding perceived understanding of the basic ideas and principles of MI and listening skills.

## **11.0 STUDY TREATMENTS**

Interventions used in the study are described below. Training, supervision, and fidelity monitoring procedures for the interventions are described in Section 13.1, and in more detail in the CTN 0047 Training Plan.

### **11.1 Minimal Screening Only (MSO)**

Following randomization, participants in the MSO group will receive an informational pamphlet about drug use and its consequences, addiction, and treatment, and will receive no further intervention. This pamphlet will consist of the information collected from materials produced by NIDA for the general public.

### **11.2 Screening and Referral (SAR)**

Participants in the SAR group will receive the same informational pamphlet as the MSO group. Those with “probable dependence” ( $ASSIST \geq 27$  for any drug or alcohol) will also be provided with minimal scripted feedback to let them know that their score is in the high-risk range, and a recommendation to consider seeking treatment. Any patient requesting referral information, regardless of ASSIST score, will also be provided with referral information. The RA will provide these participants with an information sheet listing treatment and self-help resources in their community. The latter will be standardized in format but with site-specific local information, i.e. names, addresses, and phone numbers of local addiction treatment agencies in the normal clinical referral network of the participating EDs, including but not limited to CTN-affiliated CTPs that are affiliated with the participating EDs. Based on our initial site survey, the majority of responding EDs are not currently screening or referring systematically, so the SAR condition represents a level of care significantly higher than “treatment as usual.”

### **11.3 Brief Intervention + Booster (BI-B)**

Individuals randomized to the BI-B condition will receive the same information and referral, if indicated or requested as those in SAR. However, in addition to these materials, while in the ED the BI-B group will receive a manual-guided brief intervention based on motivational interviewing principles, including feedback based on screening information, the FRAMES heuristic, and development of a change plan, as delivered in previous trauma center trials and the WASBIRT projects (Dunn, Donovan et al. 1997; Dunn, Deroo et al. 2001; Dunn 2003; Dunn and Ostafin 2005; Field, Hungerford et al. 2005). As Sise indicated (Sise, Sise et al. 2005), SBIR services such as these can be integrated effectively into all components of a busy, urban ED service by adding specially trained interventionists to the ED service staff and/or training existing staff. Detailed descriptions of the BI and Booster session contents are described in the BI-B Treatment Manual. The brief intervention will be performed by study RAs who have received training and receive supervision as specified in the training plan for the study, summarized in Section 13 below. For a given study participant, the brief intervention will be performed by an RA who has not conducted assessments with that individual. The BI will be provided in person in the ED while the participant is still there, and will be approximately 30 minutes long. BI-B participants will receive the informational pamphlet and referral for treatment (if indicated/requested) from the BI interventionist.

In addition, participants will receive up to 2 phone “booster” sessions that will check to see whether they have engaged in treatment, review change plans, and seek a commitment from them (Mello, Longabaugh et al. 2008). This number of booster sessions (2) was chosen to replicate the structure of the standard Motivational Enhancement Therapy (MET) with the goal of maximizing the magnitude of

the therapeutic effect while keeping the intervention short enough to be practical. The goal of the first session will be to re-engage and reinforce the change plan and support continuing efforts. The second session will be a check-in session and will address barriers to treatment engagement. Each of these booster calls will be approximately 20 minutes long. The content of these boosters is patterned after sessions in MET (Miller, Zweben et al. 1992; Longabaugh, Woolard et al. 2001). The phone booster process is similar to those previously used to deal with problem drinkers in EDs, either as part of stepped-care interventions initiated in the ED and continued following discharge (Bischof, Grothues et al. 2008) or as stand-alone phone-delivered brief interventions conducted without an initial intervention in the ED (Mello, Longabaugh et al. 2008), and to the procedure used by Donovan and colleagues in a primary care setting (Curry, Ludman et al. 2003). The target window for the initial phone booster call will be within 3 days of discharge from the ED. The second call will be made within 7 days of discharge from the ED. While these are ideal windows, if initial attempts to complete the booster sessions are unsuccessful, further attempts to engage participants will be made for up to one month post-discharge from the ED. Booster calls will be made from a centralized, study-wide intervention booster call center, by interventionists who have received standardized training and supervision.

## 12.0 STATISTICAL ANALYSIS

### 12.1 Primary Outcome Measure

The primary outcome measure is the number of days of use of the primary drug of abuse (defined by the participant at screening) assessed for the 30-day period preceding the 3-month follow-up visit. The primary outcome value will be the number of times the primary problem substance was used will be measured as one of 31 values: 0, 1,.....30.

### 12.2 Rationale for Considered Magnitude of Treatment Effects

There is no straightforward way to estimate the effect size of the proposed MSO vs. BI-B vs. SAR contrasts. Past studies have all differed in some critical aspect, e.g., primary care setting rather than ED, alcohol rather than drug use primary outcome, lack of control group, and/or different primary outcome (e.g., categorical abstinence). We therefore have used the published studies to guide our estimates of treatment effect, but have based the power analysis and sample size calculations on 1) the minimum clinically significant non-standardized effect that we wish to be able to detect between SAR and BI-B, and 2) estimates of error variance based on the data collected in the WASBIRT implementation of an SBIRT model in ED settings.

### 12.3 Statistical Methods for Primary Analysis

The primary analyses will make all three pair-wise comparisons between MSO, SAR and BI-B with respect to the primary outcome variable using a simple closed testing procedure described below to control family-wide type I error at no more than 0.05. The primary outcome will be analyzed according to the intent-to-treat principle in the sense 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. Patients who refuse treatment will still be followed for outcome in their assigned group, but no attempt will be made to impute outcomes for patients who refuse follow-up.

The primary analysis will compare the primary outcome between each pair of treatments taking into account possible variability in the overall level of abstinence between the sites, possible site-by-treatment interaction, the two stratification variables (DAST and AUDIT-C scores) and the level of a baseline covariate. The covariate is the answer to the single baseline question for the primary substance: "In the past 30 days, how many days have you used X?", where X is the primary drug of abuse, as defined at screening by the DAST. DAST and AUDIT-C scores will be included as the fixed effects; site and site-by-treatment interaction will be included as random effects.

In mathematical terms, denote  $Y(ijk)$  as the value of the primary outcome measure (number of days of use of primary drug of abuse within the prior 30 days as evaluated at 3 months post intervention) for the  $i^{th}$  subject at the  $j^{th}$  site and in the  $k^{th}$  treatment group, and consider the following linear mixed model for the primary analysis:

$$Y(ijk) = \beta_0 + \beta_1 * DAST + \beta_2 * AUDIT-C + b(j) + \gamma * x(ijk) + \mu(k) + c(jk) + \epsilon(ijk)$$

where

- $i$  indexes the patient
- $j$  indexes the site;



- $k$  indexes the treatment
- $\beta_0$  is the intercept
- $\beta_1$  is the DAST score effect
- $\beta_2$  is the AUDIT-C score effect
- $b(j)$  is the random site effect reflecting the site's overall level of use
- $x(ijk)$  is the patient-level baseline covariate
- $\gamma$  is the covariate effect
- $\epsilon(ijk)$  is measurement error
- $\mu(k)$  is the mean effect of treatment  $k$  (MSO, SAR, BI-B)
- $c(jk)$  is a random site-by-treatment interaction term

The random site effect is assumed to have a  $N[0, V(b)]$  distribution, the random site-by-treatment interaction term has a  $N[0, V(c)]$  distribution, and the error term has a  $N[0, V(\epsilon)]$  distribution.

As a preliminary to the primary analysis, we will test the significance of the site-by-treatment interaction. If this exists, it means that treatment success varies across sites. Because this can happen in an infinite number of ways, it will not be possible to simply claim a significant treatment effect, even if the  $p$ -value for the treatment effect is nominally significant. Instead, exploratory analyses will concentrate on why and how such sites differ. Even here, it may be that we would want to claim that the treatment is successful, for example, if all sites were successful, but to different degrees (quantitative interaction).

If site-by-treatment interaction is not significant, we will re-estimate the model excluding the  $c$ -term, and then test the three pair-wise treatment differences by means of contrasts in the  $\mu$ -terms. The primary null hypotheses are (1)  $\mu(\text{MSO}) = \mu(\text{SAR})$ , (2)  $\mu(\text{MSO}) = \mu(\text{BI-B})$ , and (3)  $\mu(\text{SAR}) = \mu(\text{BI-B})$ . Each null, if true, would indicate no treatment difference between the respective two groups.

Family-wide type I error will be controlled at no more than 0.05 through a closed procedure that compares an adjusted  $p$ -value to 0.05 for each of the three contrasts. The adjusted  $p$ -value for treatment groups  $i$  and  $j$  will be calculated as follows:  $p^*(ij) = \max[p(ij), p(123)]$ , where  $p^*(ij)$  is the adjusted  $p$ -value,  $p(ij)$  is the unadjusted  $p$ -value, and  $p(123)$  is the unadjusted  $p$ -value for the contrast comparing the means of all three groups.

The preliminary model can be fit and tested with the SAS MIXED procedure as follows:

```
proc mixed data = file covtest;
  class site arm;
  model y = x arm DAST AUDITC / solution;
  random intercept arm / subject = site;
  contrast "1v2" arm -1 1 0;
  contrast "1v3" arm -1 0 1;
  contrast "2v3" arm 0 -1 1;
  contrast "1v2v3" arm -1 1 0, arm -1 0 1;
run;
```

For analysis without the c-term, the SAS commands are:

```
proc mixed data = file;
  class site arm;
  model y = x arm DAST AUDITC / solution;
  random intercept / subject = site;
  contrast "1v2" arm -1 1 0;
  contrast "1v3" arm -1 0 1;
  contrast "2v3" arm 0 -1 1;
  contrast "1v2v3" arm -1 1 0, arm -1 0 1;
run;
```

### 12.4 Sample Size and Statistical Power

From preliminary data we estimate the mean number of use days within prior 30 days (as evaluated at 3 months post intervention) in the SAR group to be  $\mu(\text{SAR}) = 14$  days with standard deviation (SD) equal to 11 days. Considering a decrease in the number of abstinent days by 3 days as a clinically meaningful effect provides an anticipated mean number of use days in the BI-B group  $\mu(\text{BI-B}) = 14 - 3 = 11$  days. Power calculations will concentrate on this difference as the treatment effect of interest.

Sample size computations will consider treatment effect in the range of 2 through 4 days and error standard deviation  $\text{std}(\text{eps})$  in the range 9 - 13 days. Even though the overall level of outcome may differ across sites [i.e.  $V(b) > 0$ ], the primary analysis removes this variation by adjusting for site in the model. We also assume in the power calculation that the site-by-treatment interaction is 0 [i.e.  $V(c) = 0$ ], and that there is no relation between outcome and baseline covariate. We thus calculate the total number of subjects per needed to achieve 90% power to reject  $H_0: \mu(\text{BI-B}) = \mu(\text{SAR})$  via Student's t-test using  $\alpha = 0.05/3 = 0.017$ . Increasing this sample size by 50% to account for the third arm, and dividing it by 0.85 to account for 15% attrition results in the total sample sizes depicted in Table 1. We expect the baseline covariate to improve power by an unknown amount, and the closed test to be better than the Bonferroni correction, so this approach to power will be conservative. Sample size computations were performed in the SAS statistical package.

Table 1 displays total number of subjects needed to achieve 90% power to reject  $H_0: \mu(\text{BI-B}) = \mu(\text{SAR})$  for several possible treatment effects, considering type I error  $\alpha = 0.05/3$  (two-tailed), equal BI-B and SAR group sizes, and several choices of error standard deviation assumed to be the same in both groups.

**Table 1.**

Error standard deviation $\sigma$ (days)	Treatment effect $ \mu(\text{BI-B}) - \mu(\text{SRA}) $ in days		
	2.0	3.0	4.0
9	Total N= 1931	Total N= 862	Total N= 488
11	Total N= 2880	Total N= 1285	Total N= 724
13	Total N= 4020	Total N= 1790	Total N= 1010

For example, if the interest is to detect absolute difference of 3 days between the two groups, then with standard deviation equal to 11 days, one needs 1285 subjects (429 in each arm) to have 90% power (i.e. 90% chance to detect this effect if it indeed exists).

## **12.5 Interim Analyses**

### **12.5.1 Re-evaluation of the Sample Size**

A DSMB will monitor the progress of the trial. In coordination with the centralized Data and Statistics Center (DSC), interim checks of attrition rates and the assumed error standard deviation  $\sigma$  for the primary outcome measure will be conducted to assess the adequacy of the projected study sample size. This check will be performed by an unblinded statistician, who will estimate the primary model, and report back on error variance and drop-out rates. This analysis will be conducted when approximately half participants have the primary outcome available.

### **12.5.2 Efficacy/Futility Analysis**

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 and Fleming 1979) type boundaries generated using the flexible Lan-DeMets approach to group sequential testing (Lan and DeMets 1983). If requested, the monitoring guidance for early stopping for futility will be based upon an approach of conditional power (Jennison and Turnbull 2000).

## **12.6 Statistical Methods for Secondary Outcomes**

A number of secondary substance use outcomes will be examined in analyses parallel to those used for the primary outcome analyses. Comparisons involving the baseline TLFB or ASSIST, will involve only the SAR and BI-B groups.

### **12.6.1 Days of use of the primary drug of abuse in the past 30 days at 6 and 12 months post intervention**

The outcome variable will be TLFB data for the primary substance of abuse as determined at baseline. This analysis will parallel the primary analysis, except it will be performed at 6 and 12 months instead of 3 months. The 6- and 12-month analyses will be performed separately. We hypothesize BI-B < SAR, BIB < MSO, and SAR < MSO.

### **12.6.2 Days of drug use in the past 30 days at 3, 6 and 12 months post intervention**

The outcome variable will be TLFB data collected at 3, 6 and 12 month follow-up, with sample sizes necessarily modified by the follow-up rates at those time points. The analysis will exactly parallel the primary analysis, except it will be performed using days of use of any drug (excluding alcohol and nicotine) instead of the primary drug of abuse. The analysis will be performed separately at 3, 6, and 12 months. We hypothesize BI-B < SAR, BIB < MSO, and SAR < MSO.

### **12.6.3 Days of heavy drinking in the past 30 days at 3, 6 and 12 months**

Again, TLFB data will be used, with analyses based on the field "5+ drinks in one sitting" (number of days out of past 30 days). The three analyses (first for 3 months, second for 6 months, and the third for 12 months) are parallel to those described for the primary analysis except with outcome being number of days of heavy drinking rather than days of substance abuse. We hypothesize BI-B < SAR, BIB < MSO, and SAR < MSO.

#### **12.6.4 Dollar value of drug use for primary problem substance used at 3, 6 and 12 months post-baseline**

Using TLFB data collected at 3, 6 and 12 months, participants will provide the cost per day of the primary substance of use for each of the prior 30 days. The primary outcome value will be sum of the dollar costs for each of the 30 days, and will therefore be a non-negative number. The analysis will parallel the primary analysis, except that the dependent variable will be as described above, and the analysis will be carried out separately at 3, 6, and 12 months. We hypothesize BI-B < SAR, BIB < MSO, and SAR < MSO.

#### **12.6.5 Magnitude of Change Compared Between SAR and BI-B**

Because a complete baseline assessment is completed in the SAR and BI-B groups, the magnitude of the change in each of these substance-use measures (as opposed to the magnitude of the measure itself) will also be compared at each at each follow-up time point. More specifically, this analysis will be carried out for the outcome variables of: the primary analysis, and secondary analyses 1-4. The contrasts based on change should yield larger standardized effect sizes than contrasts based on the follow-up values if there is a high correlation ( $r > .5$ ) between baseline and follow-up values of the outcome measure at an individual level. The analysis will parallel the primary analysis, except that there will be no covariate and only two arms will participate. Considering decreases in substance use as positive change, we hypothesize BI-B > SAR, BIB > MSO, and SAR > MSO.

#### **12.6.6 Hair sample drug screen results for any drug and primary drug of abuse at 3, 6, and 12 months (relative change in hair screen level from baseline)**

This analysis uses relative change from baseline, objective outcome data. The outcome at 3 months is defined as follows: hair screen level at 3 months minus hair screen level at baseline divided by hair screen level at baseline (individuals with baseline values of 0 will be excluded from this analysis, but these should be few since entry criteria require current use). Outcomes for 6 and 12 months are defined in the same way by replacing 3 months measure with 6 or 12 months measures, respectively. When percent changes are calculated in this way, there is the possibility of the data being very non-normal. If so, we will attempt transformations to normality. If that is unsuccessful, the analysis will be rank-based, using Wilcoxon's method. If the transformed data seem acceptably normal, the analysis will be parallel to the primary analysis, except with outcome being relative change in hair screen level rather than days of substance abuse. The three analyses (first for 3 months, second for 6 months, and the third for 12 months) will be performed separately. We hypothesize an effect of treatment on drug screen results. Considering decreases in drug levels as positive change, we hypothesize BI-B > SAR, BIB > MSO, and SAR > MSO.

#### **12.6.7 Consequences of drug use (from the NM ASSIST) at 3, 6, and 12 months**

The NM ASSIST produces a score with values 0-39 for each substance, with higher values indicating higher risk level. Using the patient-defined primary problem drug for questions 2 (how often have you had a strong desire or urge to use) question 3 (how often has your use led to health, social, legal or financial problems) question 4 (how often have you failed to do what was normally expected of you because of your use) and question 5 (has someone expressed concern about your use). For items 4 and 5, which query both lifetime and 3 month time frames, scores will be based on the prior 3 month period only. The analysis will be similar to the primary analysis, except that there will be no covariate. Analyses will be done separately at months 3, 6, and 12. We hypothesize MSO > SAR > BI-B.

### 12.6.8 Days of participation in treatment since the last visit, at 3, 6, and 12 months post intervention among BI-B and SAR participants with probable dependence who are referred for treatment

Involvement in substance use disorder treatment is an explicit goal of the intervention only for participants who meet criteria for probable dependence and are therefore referred for treatment. Therefore, these analyses will be limited to the sub-sample of participants who meet probable dependence criteria at baseline (based on ASSIST score). Since the MSO arm does not complete the ASSIST, this analysis is necessarily restricted to the BI-B and SAR arms. Based on prior SBIRT studies (e.g., Madras et al. 2009) we estimate that 30% of participants will meet probable dependence criteria, yielding a projected total sample size of 210 for these analyses. These analyses are based on self-report from the TSR. We hypothesize a greater chance of treatment engagement in the BI-B group relative to SAR.

The number of days of participation in substance use disorder treatment will be analysed via a generalized linear mixed model (GLMM) using a negative binomial distribution with a log link (one analysis for 3 months, second for 6 months, and the third for 12 months) with site included as a random effect, and log (time since last visit) included as an offset. In mathematical terms, denote  $Y_{ijt}$  as the number of participation days for the  $i^{\text{th}}$  subject in the  $j^{\text{th}}$  site at time (month)  $t$  ( $t = 3, 6, 12$ ), and consider the following generalized linear mixed model:

$$\log[E(Y_{ijt})] = \beta_0 + \beta_1 \text{trt}_{ij} + \log(t_{ij})$$

with  $\text{trt}_{ij}$  indicating randomized group (1=BI-B, 0=SAR); fixed effects  $\beta_0, \beta_1$ ; random effect  $b_j \sim N(0, \sigma_{\text{site}}^2)$  reflecting site's overall participation in substance use disorder treatment level, and  $t_{ij}$  being the time since the participant's last visit. The time offset adjusts for the fact that different participants have different follow-up times. The Negative Binomial distribution allows for possible over-dispersion not handled in Poisson regression, but a Poisson model will also be investigated, and accepted in place of the Negative Binomial if the generalized chi-squared goodness-of-fit fit statistic is close to its degrees of freedom. The model considers randomized group effect to be the same in each site. The primary hypothesis is  $H_0 : \beta_1 = 0$  and it indicates no difference in rate of treatment participation between BI-B and SAR groups. We hope to reject  $H_0 : \beta_1 = 0$  in favor of  $H_1 : \beta_1 \neq 0$ , and rejection of  $H_0 : \beta_1 = 0$  will provide evidence for difference in chance of treatment engagement between BI-B and SAR groups.

The generalized mixed model analysis can be performed with SAS 9.2 GLIMMIX procedure as follows:

```
PROC GLIMMIX method = MMPL; class site; model y = trt / dist=negbin link=log offset = logtime  
solution; RANDOM int / subject=site; run;
```

### 12.6.9 Days of health care utilization (number of ED visit days, number of hospital days, and number of outpatient visit days) since the last visit, at 3, 6, and 12 months (self-report from TSR)

The three analyses (first for 3 months, second for 6 months, and the third for 12 months) are parallel to those described above for participation in treatment except with outcome being number of ED visits or number of hospital days or number of outpatient visits rather than days of substance abuse, and with all three arms partaking in the analysis. As in the primary analysis, all pair-wise comparisons will be carried out as contrasts, with experiment-wise error controlled by the closed procedure discussed in the primary analysis section. The 3, 6, and 12-month analyses will be performed separately. We

hypothesize fewer ED visits, hospital days, and outpatient visits in the BI-B group relative to the SAR group, the BI-B group relative to the MSO group, and the SAR group relative to the MSO group.

### **12.7 Evaluation of Putative Predictors of Outcome**

Exploratory analyses will evaluate the effects of several putative predictors of substance use outcome (patient demographics, substance use severity at baseline, identity of primary substance of abuse, motivation (from readiness rulers), therapeutic alliance, perceived substance-relatedness of ED visit, and psychiatric comorbidity (from TSR)) in terms of both main effect and interaction with treatment assignment. These analyses will be done among those groups for whom the relevant measures were obtained at baseline. We hypothesize main effects of substance use severity (worse outcome with greater severity), motivation (within the BI-B group, better outcome with higher scores on importance, confidence, and readiness rulers completed as part of the brief intervention, as described in Brief Intervention Manual), and perceived substance relatedness of ED visit (better outcome with greater substance relatedness). No specific treatment by patient characteristic interaction is hypothesized. The model will be the same as for the primary analysis and the predictors will be added as additional covariates. Linearity of effect for continuous covariates will be investigated and, if needed, transformations (polynomials or splines) will be considered.

In a parallel second analysis restricted to patients assigned to BI-B, we hypothesize a positive correlation between patient ratings of therapeutic alliance and treatment outcome. The analysis will utilize the same model as for the primary analysis but with ratings of therapeutic alliance entered as a covariate and no treatment variable included.

### **12.8 Evaluation of dose-response to number of booster sessions received (among participants assigned to BI-B)**

Among participants who receive BI-B, we hypothesize a dose response relationship such that there will be a positive correlation between number of booster sessions received (0, 1, or 2) and the number of days abstinent from primary problem drug in the past 30 days at follow-up (3, 6, and 12 months). This hypothesis will be tested separately for each follow-up time using a model parallel to the primary model, except that the covariates will be TLFB-determined baseline abstinent days (in the past 30 days) and number of booster sessions received. Number of booster sessions will be first considered as a categorical variable (set of three indicator variables) and, if linearity of effect is present, as an ordinal variable.

### **12.9 Missing Data and Dropouts**

Baseline characteristics of participants whose data are missing for the primary analysis will be compared to those whose data are available in order to determine whether differential dropout could have systematically biased results. However, no attempt will be made to impute missing data. Participants with missing 3-month data will be excluded from the primary outcome analysis.

It may be that individuals who drop out or refuse follow-up use more drugs than others. We performed a simulation to test the effect of these possibilities upon the primary analysis. Accordingly, we modeled the probability of dropout for a patient with outcome variable Y as:

$$P(Y) = A + (B-A) * [\text{rank}(Y)/N]**k$$

where

N is the number of patients

$$k = (B-E)/(E-A)$$

$$E = 0.15$$

E in (A, B)

The probability of dropout thus has a mean of 0.15. We set (A,B) to (0,1), which means that the probability of dropout is close to zero except for very large values of Y, where it rises very rapidly to 1. We generated data according to the no-interaction model described above, with  $\text{std}(\text{eps}) = 11$ , total sample size = 1285,  $\text{std}(B) = 11$ , the covariate X with mean 0 and variance 1, and gamma chosen so that  $\text{corr}(X, Y|\text{treatment, site}) = 0.1$ . There were 6 sites, and family-wide type I error was controlled at 0.05 using the closed testing method described above. We explored the effect upon power of varying the following parameters:

1. Null versus alternative treatment effects:  $(\mu(\text{MSO})=\mu(\text{SAR})=\mu(\text{BI-B})=0)$  versus  $(\mu(\text{MSO})=\mu(\text{SAR})=0, \mu(\text{BI-B})=-3)$ .
2. Dropout independent of Y (A=B=0.15) versus dropout strongly dependent on Y (A=0, B=1).

Each scenario involved 10,000 iterations. The power of the three tests of pairwise differences between the arms, and the overall probability of rejecting at least one of the arms, are given in Table 2 below.

**Table 2:** Power when dropout depends on the dependent variable

		Null case				Alternative case			
		Arms compared				Arms compared			
Missingness depends on Y?	Std(b)	Any	MSO v SAR	MSO v BI-B	SAR v BI-B	Any	MSO v SAR	MSO v BI-B	SAR v BI-B
Yes	0	0.05	0.03	0.03	0.02	0.93	0.05	0.87	0.87
	11	0.05	0.02	0.03	0.03	0.95	0.05	0.90	0.90
No	0	0.05	0.02	0.03	0.02	0.97	0.05	0.95	0.95
	11	0.05	0.03	0.03	0.03	0.97	0.05	0.94	0.94

As expected, test size is unaffected by missingness because, in the null case, missingness affects all groups equally. As expected in the alternative case, Y-dependent missingness decreases power somewhat (2-8 percentage points over the parameters simulated). This is because there were more high-drug-use dropouts in ineffective groups, which thus lowered their mean use days, moving them closer to the effective group (BI-B). In the worst case, power is 87% instead of the desired 90 %.) We do not consider this a strong effect on power, and it is largely offset by the slightly better-than-expected power under the alternative. This is likely due to the superiority of the closed testing approach to the Bonferroni method, which is notoriously conservative. Site effect does not much affect the analysis.

## **13.0 TRAINING**

Training in study-specific assessments will be provided as specified in a comprehensive training plan that will be developed by EMMES, the Lead and Co-Lead Nodes, and other participating nodes. The trainings will include modules targeting therapists and research staff, conducted via web based, and in-person training sessions. Research assistants (and all other study personnel) will receive GCP training through the web-based system currently in use. The CTN 0047 Training Plan provides a detailed description of training, supervision, and fidelity monitoring procedures.

### **13.1 Training, Supervision, and Fidelity Monitoring Procedures for Study Interventions**

#### **13.1.1 Training Timeline**

Interventionist selection, training and certification is expected to take place within 4 months of completion of site selection, and prior to site endorsement.

#### **13.1.2 Selection of Interventionists**

##### **13.1.2.1 Consenting of Interventionists**

Although interventionists will not be randomly assigned, their written informed consent is required as data will be collected concerning interventionist characteristics, interventionist empathy, and interventionist ratings of sessions.

##### **13.1.2.2 Inclusion/Exclusion Criteria**

It is anticipated that the education, credentials, experience, and background of interventionists will vary by site. Potential BI interventionists for the study will be identified by the site PI in conjunction with CTP supervisors. Booster interventionists will be recruited and selected by the Co-Lead Node.

#### **13.1.3 Selection and Training of BI-B Trainers**

A team of two trainers with expertise in motivational interviewing and brief interventions selected from members of the Co-lead and Lead Nodes. These individuals will be required to be highly proficient at motivational interviewing and to have received training in the training and/or supervision of motivational interviewing.

#### **13.1.4 Training and Credentialing of BI and Booster interventionists**

##### **13.1.4.1 Pre-training for Brief Interventionists**

The content of the 2-day pre-training will be an introduction to the person-centered therapeutic approach. The training will be focused on enhancing skills in reflective listening/accurate empathy. This training will cover basic motivational interviewing skills (open questions, affirmations, reflections, summaries). MI trainers (MINTies) affiliated with local sites will complete webinar training from the Lead Node on training content to ensure consistency across sites. Local trainers will then be responsible for delivering this training to local brief interventionists.



### **13.1.4.2 2-Day Training for Brief Interventionists**

The BI-B trainers will be responsible for providing this protocol-specific training. The content of the training will be based on existing 2-day training formats, modified as needed for the specific content of the Brief Intervention and Booster sessions described in the BI-B manual. The necessary adaptations will be made by the training team under the direction of the Co-lead investigator. All brief interventionists and booster call interventionists will attend a 2-day training in the intervention which will consist of a basic introduction to Motivational Interviewing and Motivational Enhancement Therapy, role-play exercises, complete review of the study treatment manual, and practice sessions of the study interventions. This primary training will be videotaped. The BI will be provided on site, while the booster sessions will be conducted from a central call center. Therefore, these sessions will be conducted by different sets of interventionists. However, all study interventionists will complete the basic training for both intervention components.

### **13.1.5 Pilot Delivery of Interventions**

Upon completion of the basic training, interventionists conducting the brief interventions in the ED will be required to complete at least 2 practice sessions with consenting pilot/training patients, and receive satisfactory fidelity ratings in order to be certified by the central monitoring center. The booster call therapists will be required to submit 4 training sessions, of which two must be pilot/training patients and the other two may be role plays with pseudo-patients.

## **13.2 Treatment Fidelity**

### **13.2.1 Selection and Training of BI-B Centralized Clinical Supervisors**

A team of two clinical supervisors with expertise in motivational interviewing and brief interventions will also be selected from members of the Co-Lead and Lead Nodes. These individuals will be required to be highly proficient in motivational interviewing and must have received training in the training and supervision of motivational interviewing. They will also receive training in the MITI, as a way to understand the motivational interviewing dimensions that will be monitored by the centralized monitoring center. These individuals will serve as ongoing clinical centralized supervisors throughout the duration of the study.

### **13.2.2 Supervision of Interventionists**

All intervention sessions (face-to-face and telephone boosters) will be digitally audio taped. One tape per interventionist per week will be reviewed and scored by the centralized clinical supervisor (using the same checklists used by the interventionists-see intervention manual) and reviewed in a biweekly telephone supervision session. Brief interventionists will also have clinical supervision available through the existing hierarchy where they are employed.

### **13.2.3 Quality Control of Therapies Administered**

5% of both face-to-face and telephone sessions will be monitored on an ongoing basis by coders at the centralized monitoring center. Coders will be trained to a criterion of reliability on the session checklists and the MITI (described below). These ratings will be used to monitor and prevent therapist drift. The initial sessions, in particular, will be monitored as closely as possible to the session itself in order to address areas in need of improvement. Interventionists who receive unsatisfactory fidelity ratings on two consecutive sessions reviewed by the centralized monitoring center will be "Red-lined," meaning that they will not be allowed to see participants in the trial until they have submitted tapes of and received satisfactory ratings for two consecutive sessions with consenting training patients.

### 13.2.3.1 Motivational Interviewing Treatment Integrity (MITI 3.0)

The centralized monitoring center will code 5% of therapist sessions during the trial for quality control. Additionally, following completion of the trial, twenty percent of sessions completed during the trial will be coded using the Motivational Interviewing Treatment Integrity (MITI 3.0) coding system (Moyers, Martin et al. 2005). Coders will listen to a random 20-minute segment of the session and will be instructed to begin at “3” on the five-point Likert scale for the global scores and move up or down based on the coder’s evaluation of the counselor’s level of expertise.

**Global Scores:** A global score requires the coder to assign a single number from a five-point scale to characterize the entire interaction. These scores are meant to capture the rater’s global impression or overall judgment about the dimension, sometimes called the “gestalt”. Five global dimensions are rated: Evocation, Collaboration, Autonomy/Support, Direction, and Empathy. Evocation, Collaboration and Autonomy/Support are averaged together to yield a “Spirit” global score. The Evocation scale is intended to measure the extent to which the therapist conveys an understanding that motivation for change and the ability to move toward that change resides mostly within the client, and therefore focuses efforts to elicit and expand it within the therapeutic interaction. The Collaboration scale measures the extent to which the therapist behaves as if the interview is occurring between two equal partners, both of whom have knowledge that might be useful in the problem under consideration. The Autonomy/Support scale measures the extent to which the therapist supports and actively fosters the client’s perception of choice as opposed to attempts to control the client’s behavior or choices. The Empathy scale is intended to capture the extent to which the therapist understands and/or makes an effort to grasp the client’s perspective and convey that understanding to the client. The Direction scale measures to which degree therapists maintain appropriate focus on a specific target behavior. High scores on the Direction scale do not necessarily reflect better use of MI.

**Behavior Counts:** A behavior count requires the coder to tally instances of particular interviewer behaviors. These running tallies occur from the beginning of the segment being reviewed until the end. The coder is not required to judge the quality or overall adequacy of the event, as with global scores, but simply to count it. The Giving Information category is used when the interviewer gives information, educates, provides feedback or discloses personal information (e.g., providing feedback from assessment instruments, personal feedback about the client that is not already available or educating about a topic). The MI Adherent category is used to capture particular interviewer behaviors that are consistent with a motivational interviewing approach (e.g., asking permission before giving advice, affirmations, emphasizing the client’s control, supporting the client). MI Non-adherent behaviors capture those interviewer behaviors that are inconsistent with a motivational interviewing approach (e.g., advising without permission, confronting, directing). The questions category is divided into open and closed questions. Closed questions are counted when the interviewer asks the client a question that can be answered with a “yes” or “no” response. An open question is coded when the interviewer asks a question that allows a wide range of possible answers. The reflections category is meant to capture reflective listening statements made by the therapist in response to client statements. This category is divided into simple and complex reflections. Simple reflections typically convey understanding or facilitate client/therapist exchanges. These reflections add little or no meaning (or emphasis) to what clients have said. Complex reflections typically add substantial meaning or emphasis to what the client has said.

**Summary Scores:** Summary scores will be calculated using the following formulas and will be compared to normative data:

% Complex Reflections (% CR) = Rc / Total reflections

% Open Questions (% OC) = OQ / (OQ + Closed Questions)

Reflection : Question Ratio (R:Q) = Total reflections/(Closed Questions + OQ)

% MI Adherent (% MiA) = MiA / (MiA + MI Non-adherent)

### **13.2.3.2 “Drifting” Interventionists**

Interventionists who do not meet predefined fidelity standards based on substandard ratings by the centralized monitoring center will receive increased coaching by the centralized clinical supervisor and will not be allowed to see patients until adequate performance is documented by two consecutive adequate ratings on sessions conducted with consenting training patients.

## **14.0 REPORTING AND MONITORING**

### **14.1 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.

### **14.2 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.

### **14.3 Informed Consent**

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. Because this study is very low-risk and due to the scientific need to minimize assessment reactivity, the informed consent form for this study will be shorter than those used in many clinical trials. However, the form will include all of the required elements of informed consent. 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 who are knowledgeable about the study will explain the study to the potential participant and provide the participant with a copy of the consent to read. If the participant is interested in participating in the study, a researcher who is authorized to obtain informed consent by the PI and if applicable by the IRB, will review each section of the informed consent form in detail and answer any questions the participant may have. 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.

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 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.

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

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

#### **14.5 Investigator Assurances**

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

#### **14.6 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.

#### **14.7 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. Node QA staff will audit source documentation, including informed consent forms and HIPAA forms. 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 QA 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 QA staff will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

## **14.8 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.

## **14.9 Safety Monitoring**

### **14.9.1 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).

### **14.9.2 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 Violation Log. Additionally, each site is responsible for tracking and reporting to their IRB as required. Protocol deviations will be noted by participating sites and reported to their IRBs as required. The CCC and the Data and Statistics Center and the Lead Investigator must be contacted immediately if an unqualified/ ineligible participant is randomized into the study.

### **14.9.3 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.

#### **14.9.4 Adverse Events (AEs)**

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

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

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

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

#### **14.9.6 Reportable Adverse Events and Serious Adverse Events**

##### **14.9.6.1 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 were considered unrelated to study participation.

- Substance Use Events, including
  - Worsening of drug use
  - Need for higher level of care
  - Signs and symptoms of withdrawal
  - Drug craving
  - Admission for detoxification and/or residential treatment
  - Medical events that are directly related to substance use

##### **14.9.6.2 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.
- 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, substance related).



## **15.0 DATA MANAGEMENT AND PROCEDURES**

### **15.1 Design and Development**

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

### **15.2 Data Collection Forms**

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

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

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

#### **15.3.1 Site Responsibilities**

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

#### **15.3.2 Data Center Responsibilities**

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

#### **15.3.3 Data Editing**

Completed data will be entered into the DSC 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 automated data acquisition and management system in accordance with the data management plan.

#### **15.4 Data Transfer**

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

#### **15.5 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.

#### **15.6 Data QA**

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

## **16.0 STUDY TIMELINE**

Upon approval of the final version of the protocol, 8 months will be allowed for preparations including IRB approval, obtaining a Certificate of Confidentiality, data system development, CTP selection and preparation, initial investigator meeting and training, and completion of the operations manual. We propose to implement the study sites in two groups of three sites. The first three sites will begin recruitment after 8 months, and the second three sites will begin 4 months later. For all sites, target recruitment is expected to take 6 months, with follow-up continuing for 12 months after the end of recruitment. Two months will be allowed for data lock after the end of the follow-up period. Thus data lock is projected to occur  $8 + 4 + 6 + 12 + 2 = 32$  months after protocol approval.

## 17.0 REFERENCES

- Academic ED SBIRT Research Collaborative (2007). "The impact of screening, brief intervention, and referral for treatment on Emergency Department patients' alcohol use." *Annals of Emergency Medicine* 50(6): 699-710.e696.
- Allen JP, Litten RZ, et al. (1997). "A review of research on the Alcohol Use Disorders Identification Test (AUDIT)." *Alcoholism: Clinical and Experimental Research* 21(4): 613-619.
- Babor TF and Higgins-Biddle JC. (2000). "Alcohol screening and brief intervention: Dissemination strategies for medical practice and public health." *Addiction* 95(5): 677-686.
- Babor TF and Kadden RM. (2005). "Screening and interventions for alcohol and drug problems in medical settings: what works?" *Journal of Trauma* 59(3 Suppl): S80-87.
- Babor TF, McRee BG, et al. (2007). "Screening, Brief Intervention, and Referral to Treatment (SBIRT): Toward a public health approach to the management of substance abuse." *Substance Abuse* 28(3): 7-30.
- Ball S, Bachrach K, et al. (2002). "Characteristics, beliefs and practices of community clinicians trained to provide manual-guided therapy for substance abusers." *Journal of Substance Abuse Treatment* 23(4): 309-318.
- Barrett B, Byford S, et al. (2006). "Cost-effectiveness of screening and referral to an alcohol health worker in alcohol misusing patients attending an accident and emergency department: A decision-making approach." *Drug and Alcohol Dependence* 81(1): 47-54.
- Bernstein E. and Bernstein J. (2008). "Effectiveness of alcohol screening and brief motivational intervention in the Emergency Department setting." *Annals of Emergency Medicine* 51(6): 751-754.
- Bernstein E and Bernstein J. (2008). "Effectiveness of alcohol screening and brief motivational intervention in the emergency department setting." *Ann Emerg Med* 51(6): 751-754.
- Bernstein E, Edwards E, et al. (2009). "Screening and brief intervention to reduce marijuana use among youth and young adults in a pediatric emergency department." *Academic Emergency Medicine* 16(11): 1174-1185.
- Bischof G, Grothues JM, et al. (2008). "Evaluation of a telephone-based stepped care intervention for alcohol-related disorders: A randomized controlled trial." *Drug and Alcohol Dependence* 93(3): 244-251.
- Bordin ES. (1994). *Theory and research on the therapeutic working alliance: New directions. The working alliance: Theory, research, and practice.* A. O. Horvath and L. S. Greenberg. Oxford England, John Wiley & Sons: 13-37.
- Bradley KA, DeBenedetti AF, et al. (2007). "AUDIT-C as a brief screen for alcohol misuse in primary care." *Alcoholism: Clinical and Experimental Research* 31(7): 1208-1217.

- Brown RL, Leonard T, et al. (2001). "A two-item conjoint screen for alcohol and other drug problems." *J Am Board Fam Pract* 14(2): 95-106.
- Bush K, Kivlahan DR, et al. (1998). "The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test." *Arch Intern Med* 158(16): 1789-1795.
- Calle PA, Damen J, et al. (2006). "A survey on alcohol and illicit drug abuse among emergency department patients." *Acta Clinica Belgica* 61(4): 188-195.
- Caplan YH, & Goldberger BA. (2001). "Alternative Specimens for workplace drug testing." *Journal of Analytical Toxicology* 25: 396-399.
- Cherpitel CJ and Ye Y. (2008). "Drug use and problem drinking associated with primary care and emergency room utilization in the US general population: Data from the 2005 national alcohol survey." *Drug and Alcohol Dependence* 97(3): 226-230.
- Clifford PR and Maisto SA. (2000). "Subject reactivity effects and alcohol treatment outcome research." *J Stud Alcohol* 61(6): 787-793.
- Clifford PR, Maisto SA, et al. (2007). "Alcohol treatment research assessment exposure subject reactivity effects: part I. Alcohol use and related consequences." *J Stud Alcohol Drugs* 68(4): 519-528.
- Cocco KM and Carey KB. (1998). "Psychometric properties of the Drug Abuse Screening Test in psychiatric outpatients." *Psychological Assessment* 10(4): 408-414.
- Curry SJ, Ludman EJ, et al. (2003). "A randomized trial of a brief primary-care-based intervention for reducing at-risk drinking practices." *Health Psychology* 22(2): 156-165.
- Diaz FJ, Jané M, et al. (2005). "A brief measure of high nicotine dependence for busy clinicians and large epidemiological surveys." *Australian and New Zealand Journal of Psychiatry* 39(3): 161-168.
- Donovan DM, Rosengren DB, et al. (2001). "Attrition prevention with individuals awaiting publicly funded drug treatment." *Addiction* 96(8): 1149-1160.
- Dunn C. (2003). "Brief motivational interviewing interventions targeting substance abuse in the acute care medical setting." *Seminars in Clinical Neuropsychiatry* 8(3): 188-196.
- Dunn C, Deroo L, et al. (2001). "The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review." *Addiction* 96(12): 1725-1742.
- Dunn C and Ostafin B. (2005). "Brief interventions for hospitalized trauma patients." *Journal of Trauma* 59(3 Suppl): S88-93.
- Dunn CW, Donovan DM, et al. (1997). "Practical guidelines for performing alcohol interventions in trauma centers." *Journal of Trauma* 42: 299-304.

- Dunn CW and Ries R. (1997). "Linking substance abuse services with general medical care: Integrated, brief interventions with hospitalized patients." *American Journal of Drug & Alcohol Abuse* 23(1): 1-13.
- Estee S and He L. (2007). Use of alcohol and other drugs declined among emergency department patients who received brief interventions for substance use disorders through WASBIRT. Olympia, WA, Washington State Department of Social and Health Services.
- Field C, Hungerford DW, et al. (2005). "Brief Motivational Interventions: An Introduction." *Journal of Trauma* 59(3 Suppl): S21-S26.
- Fornili K and Alemi F. (2007). "Medicaid reimbursement for screening and brief intervention: Amending the medicaid state plan and approving state appropriations for the medicaid state match." *Journal of Addictions Nursing* 18(4): 225 - 232.
- Gallardo E, & Queiroz JA. (2008). "The role of alternative specimens in toxicological analysis." *Biomedical Chromatography* 22: 795-821.
- Gavin DR, Ross HE, et al. (1989). "Diagnostic validity of the Drug Abuse Screening Test in the assessment of DSM-III drug disorders." *British Journal of Addiction* 84(3): 301-307.
- Gentilello LM. (2007). "Alcohol and injury: American College of Surgeons Committee on trauma requirements for trauma center intervention." *Journal of Trauma* 62(6 Suppl): S44-45.
- Gentilello LM, Donovan DM, et al. (1995). "Alcohol interventions in trauma centers: Current practice and future directions." *JAMA: Journal of the American Medical Association* 274(13): 1043-1048.
- Gentilello LM, Ebel BE, et al. (2005). "Alcohol interventions for trauma patients treated in emergency departments and hospitals: A cost benefit analysis." *Annals of Surgery* 241(4): 541-550.
- Gentilello LM, Rivara FP, et al. (1999). "Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence." *Annals of Surgery* 230(4): 473-480.
- Goodyear-Smith F, NM. Coupe, et al. (2008). "Case finding of lifestyle and mental health disorders in primary care: validation of the 'CHAT' tool." *British Journal of General Practice* 58: 26-31.
- Han E, Yang W, Lee J, Park Y, Kim E, Lim M, & Chung H. (2005). "Correlation of methamphetamine results and concentrations between head, axillary, and pubic hair." *Forensic Science International* 147: 21-24.
- Hatcher RL and Gillaspay JA. (2006). "Development and validation of a revised short version of the Working Alliance Inventory." *Psychotherapy Research* 16(1): 12-25.
- Heatherton TF, Kozlowski LT, et al. (1991). "The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire." *British Journal of Addiction* 86(9): 1119-1127.
- Hegstad S, Khiabani HZ, Kristoffersen L, Lobmaier PP, & Christophersen AS. (2008). "Drug screenings of hair by liquid chromatography-tandem mass spectrometry." *Journal of Analytical Toxicology* 32: 364-372.

- Humeniuk R, Ali R, et al. (2008). "Validation of the Alcohol, Smoking And Substance Involvement Screening Test (ASSIST)." *Addiction* 103(6): 1039-1047.
- Humphreys K, Greenbaum MA, et al. (1996). "Reliability, validity, and normative data for a short version of the Understanding of Alcoholism Scale." *Psychology of Addictive Behaviors* 10(1): 38-44.
- Jennison C and Turnbull BW. (2000). *Group sequential methods with applications to clinical trials*, Chapman & Hall.
- Kintz P, Villain M, & Cirimele V. (2006). "Hair analysis for drug detection." *The Drug Monit* 28: 442-446.
- Kraemer, KL. (2007). "The cost-effectiveness and cost-benefit of screening and brief intervention for unhealthy alcohol use in medical settings." *Substance Abuse* 28(3): 67 - 77.
- Lan KKG and DeMets DL. (1983). "Discrete sequential boundaries for clinical trials." *Biometrika* 70: 659-663.
- Ledgerwood DM, Goldberger BA, Risk NK, Lewis CE, & Price R. (2008). "Comparison between self-report and hair analysis of illicit drug use in a community sample of middle-aged men." *Addictive Behaviors* 33: 1131-1139.
- Longabaugh R, Woolard RE, et al. (2001). "Evaluating the effects of a brief motivational intervention for injured drinkers in the emergency department." *Journal of Studies on Alcohol* 62(6): 806-816.
- Lucas CE. (2005). "The impact of street drugs on trauma care." *Journal of Trauma* 59(3 Suppl): S57-60.
- Madras BK, Compton WM, et al. (2009). "Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites: Comparison at intake and 6 months later." *Drug and Alcohol Dependence* 99: 280-295.
- Marsden J, Stillwell G, et al. (2006). "An evaluation of a brief motivational intervention among young ecstasy and cocaine users: no effect on substance and alcohol use outcomes." *Addiction* 101(7): 1014-1026.
- McCambridge J. and Strang J. (2005). "Deterioration over time in effect of Motivational Interviewing in reducing drug consumption and related risk among young people." *Addiction* 100(4): 470-478.
- McLellan AT, Alterman AI, et al. (1992). "A new measure of substance abuse treatment. Initial studies of the treatment services review." *J Nerv Ment Dis* 180(2): 101-110.
- Mello MJ, Longabaugh R, et al. (2008). "DIAL: A telephone brief intervention for high-risk alcohol use with injured emergency department patients." *Annals of Emergency Medicine* 51(6): 755-764.
- Mieczkowski T, & Newel R. (2000). "Statistical examination of hair color as a potential biasing factor in hair analysis." *Forensic Science International* 107: 13-38.

Miller WR, Yahne CE, et al. (2003). "Motivational interviewing in drug abuse services: a randomized trial." *J Consult Clin Psychol.* 71(4): 754-763.

Miller WR, Zweben A, et al. (1992). *Motivational enhancement therapy manual: A clinical research guide for therapists treating individuals with alcohol abuse and dependence.* Rockville, MD, National Institute on Alcohol Abuse and Alcoholism.

Mokdad AH, Marks JS, et al. (2004). "Actual causes of death in the United States, 2000." *JAMA : Journal of the American Medical Association* 291(10): 1238-1245.

Moyers TB, Martin T, et al. (2005). "Assessing competence in the use of motivational interviewing." *Journal of Substance Abuse Treatment* 28(1): 19-26.

Moyers TB and Miller WR. (1993). "Therapists' conceptualizations of alcoholism: Measurement and implications for treatment decisions." *Psychology of Addictive Behaviors* 7(4): 238-245.

Nilsen P, Baird J, et al. (2008). "A systematic review of emergency care brief alcohol interventions for injury patients." *Journal of Substance Abuse Treatment* 35(2): 184-201.

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

Pelander A, Ristimaa J, Rasanen I, Vuori E, & Ojanpera I. (2008). "Screening for basic drugs in hair of drug addicts by liquid chromatography/time-of-flight mass spectrometry." *The Drug Monit* 30: 717-724.

Rapp RC, Xu J, et al. (2006). "Treatment barriers identified by substance abusers assessed at a centralized intake unit." *J Subst Abuse Treat* 30(3): 227-235.

Rockett IRH, Putnam SL, et al. (2005). "Unmet substance abuse treatment need, health services utilization, and cost: A population-based emergency department study." *Annals of Emergency Medicine* 45(2): 118-127.

Rockett IRH, Putnam SL, et al. (2006). "Declared and undeclared substance use among emergency department patients: a population-based study." *Addiction* 101(5): 706-712.

Saitz R. (2007). "Screening and brief intervention enter their 5th decade." *Substance Abuse* 28(3): 3-6.

Sise MJ, Sise CB, et al. (2005). "Implementing screening, brief intervention, and referral for alcohol and drug use: The trauma service perspective." *Journal of Trauma* 59(3 Suppl): S112-118.

Skinner HA. (1982). "The Drug Abuse Screening Test." *Addictive Behaviors* 7(4): 363-371.

Sobell LC, Brown J, et al. (1996). "The reliability of the Alcohol Timeline Followback when administered by telephone and by computer." *Drug and Alcohol Dependence* 42(1): 49-54.

Sobell LC and Sobell MB. (1992). *Timeline follow-back: A technique for assessing self-reported alcohol consumption. Measuring alcohol consumption: Psychosocial and biological methods.* R. A. Litten and J. P. Allen. Totowa, NJ, Humana Press.



Sobell LC and Sobell MB. (1996). *Timeline Follow Back: A calendar method for assessing alcohol and drug use (User's Guide)*. Toronto, Addiction Research Foundation.

Sobell LC, Sobell MB, et al. (1988). "The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past." *Journal of Studies on Alcohol* 49(3): 225-232.

Stein MD, Herman DS, et al. (2009). "A motivational intervention trial to reduce cocaine use." *Journal of Substance Abuse Treatment* 36(1): 118-125.

Swanson SM., Sise CB, et al. (2007). "The scourge of methamphetamine: impact on a level I trauma center." *Journal of Trauma* 63(3): 531-537.

Tait RJ, Hulse GK, et al. (2004). "Effectiveness of a brief-intervention and continuity of care in enhancing attendance for treatment by adolescent substance users." *Drug and Alcohol Dependence* 74(3): 289-296.

Tassiopoulos K, Bernstein J, Heeren T, Levenson S, Hingson R, & Bernstein E. (2004). "Hair testing and self-report of cocaine use by heroin users." *Addiction* 99: 590-597.

The InSight Project Research Group (2009). "SBIRT outcomes in Houston: Final report on InSight, a hospital district-based program for patient at risk for alcohol or drug use problems." *Alcoholism: Clinical and Experimental Research* 33(8): 1374-1381.

Tracey TJ and Kokotovic AM. (1989). "Factor structure of the Working Alliance Inventory." *Psychological Assessment: A Journal of Consulting and Clinical Psychology* 1(3): 207-210.

U.S. Preventive Services Task Force (2004). "Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: Recommendation statement." *Annals of Internal Medicine* 140: 554-556.

Yudko E, Lozhkina O, et al. (2007). "A comprehensive review of the psychometric properties of the Drug Abuse Screening Test." *Journal of Substance Abuse Treatment* 32(2): 189-198.

Zahradnik A, Otto C, et al. (2009). "Randomized controlled trial of a brief intervention for problematic prescription drug use in non-treatment-seeking patients." *Addiction* 104(1): 109-117.

## 18.0 APPENDIX A

# Adverse Event Reporting Definitions and Procedures

## Definition of Adverse Event and Serious Adverse Event

**Adverse Event:** An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered study-related or clinically significant. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. A thorough history during the eligibility assessment phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. The AE form is used to capture reportable AEs (as defined in the protocol) and also used to record follow-up information for unresolved events reported on previous visits. A study investigator will identify and characterize each AE, and follow appropriate reporting procedures.

**Serious Adverse Event (SAE):** A serious adverse event is defined as any untoward physical or psychological occurrence during the study that suggests a significant hazard, side effect, or precaution will be defined as an SAE. This includes, but may not be limited to any of the following events:

- 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
- Persistent or significant disability or incapacity,
- Congenital anomaly/birth defect.
- An event that required intervention to prevent one of the above outcomes.

## Unexpected Adverse Event

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

## Pregnancy

As there is no medication intervention, pregnancy will not be followed within the context of this study.

## Laboratory Results

Laboratory results are obtained only from hair analysis and will not be used clinically or reported as an adverse event.

**Eliciting and Monitoring Adverse Events:** Qualified research staff will elicit participant reporting of reportable AEs/SAEs at study assessment visit designated to collect AEs. Adverse events (medical

and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. 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. 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.

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, and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor 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 given 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.

