Women's Treatment for Trauma and Substance Use Disorders: A Randomized Clinical Trial

Protocol 0015 Version 8.0

National Institute on Drug Abuse
Clinical Trials Network

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LIST OF ABBREVIATIONS

CAPS=Clinical Assessment of Posttraumatic Stress Disorder
CGI=Clinician Global Impression
CIDI=Clinical Interview for DSM-IV
PCM=Prior and Concominant Medications Form
GT=Greater than
HAQC or T=Helping Alliance Questionnaire, Counselor or Therapist Version
IOP=Intensive Outpatient
LE=Less than or equal to
MMSE=Mini Mental State Exam
NSMS=Non-Study Medical Services
ODF=Outpatient Drug Free
PTSD=Posttraumatic Stress Disorder
RBA=Risk Behavior Assessment
RESID=Residential
RPT=Relapse Prevention
PSS-SR=Possttraumatic Stress Symptom-Self Report
SPTSD=Subthreshold PTSD
SS=Seeking Safety
SUD=Substance Use Disorders
SUI=Substance Use Inventory
TAU=Treatment-as-Usual
TX=Treatment

SYNOPSIS

The impetus of the current study comes from research findings demonstrating that 1) co-occurring Substance Use Disorder (SUD) and Posttraumatic Stress Disorder (PTSD) are common, particularly among women, 2) those with both disorders have a more severe clinical profile than those with just one of these disorders, and 3) the comorbidity of SUD and PTSD has a significant negative effect on the course of treatment and treatment outcomes. These data highlight the importance of finding effective and accessible treatments that target the unique needs of this high-risk population. Preliminary studies show Seeking Safety, a cognitive-behavioral substance abuse treatment specifically designed for women with trauma, to be a viable option in need of further empirical study.

This study will assess the effectiveness of adding Seeking Safety (SS) to standard substance abuse treatment (TAU). The treatment groups will include 1) an enhanced treatment condition—Seeking Safety (SS) plus TAU, and 2) a non-specific attention-control condition—Women's Health Education (WHE) plus TAU. Subjects will be approximately 480 drug dependent women with at least one traumatic event in their lifetimes, meeting current DSM-IV criteria for PTSD, either full or subthreshold (SPTSD). The DSM-IV lists six criteria, labeled A, B, C, D, E, and F, which must be fulfilled for a diagnosis of PTSD. Sub-threshold PTSD is defined by fulfilling criteria A, B, (either C or D), E and F. Trained counselors will conduct the two group treatments twice weekly over an approximate 6-week period (12 sessions total for both treatments). The study is a prospective, randomized, controlled, repeated measures intent-to-treat design to assess Treatment (SS+TAU vs. WHE+TAU) differences over Time (pre vs. post-treatment). To further assess differences between the two treatments over time, the design will include 1-week, 3, 6, and 12-month post-treatment follow-up assessments. Primary outcomes to be assessed will be: (1) substance use abstinence; and (2) PTSD symptom severity. Secondary outcomes will be: (3) treatment retention and adherence; (4) global psychiatric symptom severity and (5) HIV-risk sexual behaviors.

Table 1. Time and Event Table

Instrument		**Purpose/Domain**	**Time Estimate**		**Rater**	**When Rated**					
Name	**Times done**		**Inter View**	**Self-report**		**BS**	**Sc**	**BL**	**In TX Wk**	**1-Wk FU**	**3,6, 12 Mo FU**
Brief Screening	1	Identify Potential Participants	5 mins		RA/IA	X					
Study Enrollment	1	Document Informed Consent		1 min	RA/IA		X				
Demographics	1	Characterize Sample	5 mins		RA/IA		X				
Substance Use Disorders (CIDI)	1	Assess substance use diagnoses	20 mins		RA/IA		X				
CAPS Part 1-Life Events Checklist	1	Screen for PTSD Criterion A	10 mins		RA/IA		X				
PRISM Suicide and Homicide Questions	1	Screen for suicidality, homicidality, and psychosis	10 mins		RA/IA		X				
MMSE	1	Screen for cognitive deficits	10 mins		RA/IA		X				
Prior & Con/Medication Form (PCM)	6	Document Pre-existing and Concomitant Use of Medications; Predictor	2 mins		RA/IA		X	X		X	X
CAPS Part 2-PTSD symptoms	5	Diagnosis and Primary outcome	30 mins		IA		X			X	X
Inclusion/Exclusion Form	1	Establish 1st level eligibility, document reasons for ineligibility		5 min	RA/IA		X				
ASI-Lite	5	Secondary outcome: SUD	20 mins		IA			X		X	X
SUI	11	Primary outcome: SUD	5 mins		P/RA/ IA			X	X	X	X
PSS-SR	11	Secondary outcome: PTSD	10 mins		P/RA IA			X	X	X	X
Addendum	5	Predictor of outcome: Gender Specific	10 mins		IA			X		X	X
BSI	5	Predictor of outcome: Psychiatric Severity	10 mins		IA			X		X	X
RBS	5	Secondary outcome: HIV	10 mins		IA			X		X	X
NSMS	11	Secondary outcome: TX Adherence; Predictor of outcome: TX Utilization	5 mins		P/RA IA			X	X	X	X
Trauma Specific Tx	**4**	**Predictor of outcome: Tx Utilization**	**1 min**		**IA**				**X**	**X**	**X**
Adverse Events	11	Document Adverse Events			RA/ IA/~~PI~~ MD			X	X	X	X

Urine Drug Screen Saliva Alcohol Screen	11	Primary outcome: SUD	5 mins		RA/ IA			X	X	X	X
CGI	5	Secondary outcome: SUD, PTSD	5 mins		IA			X		X	X
Eating Disorder Examination Questionnaire (optional assessment)	2	Predictor	10 mins		IA			X		X	
Randomization Form	1	Document Group Assignment		2 min	RA			X			
Study Blind Integrity	4	Document integrity of IA Study Blind		1 min	IA					X	X
Termination Form	1 or 2	Document Reasons for Study Termination – TX and FU		2 min	RA/ IA				X		X
Treatment Attendance (TSA)	12	Document Session Attendance of Participants		2 min	RA				X		
Participant Feedback Ratings (SSQ, WHQ)	1	Process measure		2 mins	P/RA				Wk 6		
HAQ-II Counselor and Participant Versions	2	Process measure: Therapeutic alliance		2 mins	C/RA/ P				Wk 2, 6		
Adherence and Competence Scales	Wkly	Process measure: Quality control of TX delivery/ TX integrity		90 min	CS				X		
Post TX Counselor/Supervisor Focus Group	**1**	**Process: Therapist experience**	**90 min**								

C=Counselor; CS=Counselor Supervisor; IA=Blinded Independent Assessor; RA=Research Assistant; P=Participant; MD=Study Clinician; TX=Treatment; WK=Weekly.

1.0. INTRODUCTION

1.1. Background

Substance abuse is a widespread and significant problem among women. Recent epidemiological studies show that up to 30% of those in substance abuse treatment are female. Further, studies (i.e., Chatham et al., 1999; Griffin et al. 1989; Wilsnak, 1984) have also demonstrated gender-specific risk factors, correlates and consequences for women, strongly suggesting the need for tailored interventions in drug abuse programs. Substance-dependent women who have been exposed to interpersonal trauma and violence represent a particularly high-risk subgroup, revealing poorer treatment retention and outcomes (Zweben et al., 1994). Prevalence estimates suggest that as many as 80% of women seeking treatment for chemical dependency report lifetime histories of sexual and/or physical assault (Dansky et. al, 1995; Fullilove et al., 1993; Hien et al., 1996; Paone et al., 1992). Thus, for the majority of women, integrated interventions that address both substance use and trauma are strongly indicated. Research that focuses on the implementation of such integrated treatment models and their effectiveness for women in drug treatment is critical to address the needs of this population.

1.1.1 Description of Psychotherapy Treatment

"Seeking Safety" (SS) is a short-term, manualized cognitive-behavioral treatment specifically designed to integrate attention to both trauma and substance abuse among women in group or individual modalities. In this integrated model, both disorders are treated at the same time by the same clinician. Seeking Safety was developed to fill the major gap between what has widely been recommended as optimal treatment for substance-abusing women with trauma and what has actually been available. It was also designed as a treatment that could be empirically examined and standardized. Seeking Safety is the first psychotherapy program for women with trauma and SUD to be undergoing empirical evaluation and to have published outcome results available.

The Seeking Safety Program was developed under a National Institute on Drug Abuse Behavioral Therapies Development grant. This program is a manualized 12-week (12 or 24 session) intervention which applies cognitive-behavioral strategies to the goals of attaining abstinence from substances and decreasing PTSD. It is highly adaptable to different contexts and has been used in a variety of formats (Najavits, 2002). Seeking Safety can be delivered in an individual or group format. Seeking Safety is based on five central ideas: (1) Safety as the priority; (2) Integrated treatment of PTSD and SUD; (3) A focus on ideals; (4) four content areas; cognitive, behavioral, interpersonal, and case management; and (5) Attention to therapist processes. The content of each session is structured to provide a theme relevant to both SUD and PTSD, and a specific CBT skill to learn. The treatment is comprised of five basic units. The Introductory Unit (2 sessions) goals are to provide the patient with basic education on PTSD and SUD as well to orient her to treatment and begin to build a relationship with the therapist. The Behavioral Skills Unit (3 sessions) is designed to teach action skills to prevent drug use and to control PTSD symptoms. The Cognitive Unit (3 sessions) provides education and practice in cognitive restructuring, with particular attention to maladaptive thoughts associated with PTSD and SUD, and the integration of previously learned behavioral techniques. The Interpersonal Unit (2 sessions) focuses on relationship issues specific to this population (e.g., difficulty trusting others, problems in managing conflict) and on developing communication skills and a healthy support network. The Review/Termination Unit (2 sessions) focuses on processing the ending of treatment and solidifying aftercare plans.

1.1.2. Clinical Profile

1.1.2.1. Clinical Efficacy

Seeking Safety is currently being evaluated in seven other funded studies of patients with PTSD and SUD. In addition to some of our work at Smithers on urban women (Hien, 1997, Hien et al., under review), other studies being conducted include those with outpatient women (Najavits, et al.1998), adolescent girls (Najavits, 1998), women in prison (Zlotnick, 1999), female combat veterans (Rosenheck, 1999), male combat veterans (Ruzek & Wilser, 2000), and men with a history of childhood physical/sexual

abuse (Najavits & Weiss, 2000). Significant results for SS have been found in a variety of domains (Najavits et al., 1996, 1998, under review; Hien & Litt, 2000; Hien et al., under review), with virtually all indicating improvement among completers (those who attended at least twelve sessions). Specifically results showed significant improvements in substance use, trauma related symptoms, suicide risk, suicidal thoughts, social adjustment, family functioning, problem-solving, depression, cognitions about substance use, and didactic knowledge related to the treatment. In addition to symptom reduction, the treatment also appeared to be highly appealing to the women, and demonstrated a 67% attendance rate (Najavits et al., 1996). Strong ratings of patient alliance and satisfaction indicate that patients felt helped by the treatment. These findings indicate that, when provided with treatment adapted to their specific needs, women are highly responsive to treatment and show marked improvements.

Results from a clinical trial conducted by our research group (Hien et al., under review) in which we compared Seeking Safety (SS), Relapse Prevention (RPT) and community care (CC) in women with addictions and post-traumatic stress disorder also reveal empirical support for the efficacy of SS. The treatments consisted of 12 weeks of twice weekly, manual-guided individual psychotherapy, either using the SS or RPT protocols. Data on 107 “intent-to-treat” participants addressed the relative efficacy of each of the two randomized treatments when compared to a non-randomized community care condition. The two main outcomes of interest were: 1) substance use frequency and intensity (determined by a composite score consisting of Clinician Global Impression [CGI] ratings, ASI alcohol and drug scales and Substance Use Inventory), and 2) severity of PTSD (composite of the CAPS and CGI). A secondary outcome of global psychiatric symptoms (composite of the Hamilton Rating Scale for Depression, CGI and Brief Symptom Inventory) was also examined. Repeated measure assessments were conducted at baseline, end-of-treatment, 6 months post-baseline and 9-months post-baseline.

Table 2. presents means and standard deviations for comparisons between treatment groups at end-of-treatment and over the follow-up periods on primary outcomes. There were no significant differences between any of the three study groups on baseline primary outcome measures. For both SS and RPT in comparison to CC, findings revealed significant reductions in all symptom areas at end-of-treatment, and sustained significant effects at the 6- and 9-month follow-ups for substance use and PTSD symptoms. Those in SS also sustained reductions in psychiatric severity at the 9-month follow-up in comparison to CC. There were no statistically significant differences between SS and RPT in any outcome domain at any assessment timepoint.

Table 2. Means and standard deviations for Seeking Safety (SS) and Relapse Prevention (RPT) in comparison to Community Care (CC) at baseline, end-of-treatment, 6-and 9-month post-baseline follow-ups on primary outcomes (N=107).

	Substance Use Severity			**PTSD Severity**		
	SS N=41	RPT N=34	CC N=32	SS N=41	RPT N=34	CC N=32
Baseline	-.08 (.68)	-.22 (.60)	+.19 (1.0)	+.03 (.81)	-.14 (.59)	+.12 (.73)

End-of-TX	-.15 (.65)[a]	-.26 (.52)[b]	+.36 (.78) [a, b]	-.11 (.59) [c]	-.17 (.65)[d]	+.25 (.61)[c,d]
6 mo. FU	-.12 (.61)[e]	-.30 (.58) [f]	+.19 (.72) [e,f]	-.10 (.67) [g]	-.24 (.78) [h]	+.31 (.79)[g,h]
9 mo. FU	-.08 (.54)[i]	-.18 (.76)[j]	+.21 (.76)[i,j]	-.02 (.63) †	-.25 (.86)[k]	+.39 (.86)[k, †]

Means with same letters are significantly different. † Indicates trend level differences between means. [a,b] $F=8.49_{2,100}$, $p<.001$, $r^2=.45$, [c,d] $F=4.71_{2,100}$, $p<.01$, $r^2=.42$; [e,f] $F=4.82_{2,100}$, $p<.01$, $r^2=.36$, [g,h] $F=4.94_{2,100}$, $p<.01$, $r^2=.28$; [i,j] $F=2.87_{2,100}$, $p=.06$, $r^2=.35$; [k] $F= 5.51_{2,100}$, $p<.01$, $r^2=.22$. Post-Hoc equivalence testing for SS vs. RPT revealed no statistically significant differences between the two active treatments.

Examining the findings of outcome and retention together also provides an empirical justification for conducting a 12-session version of the treatment. Once treatment type and baseline severity were controlled, number of sessions was not a salient predictor of any of the outcomes. However, since the average number of sessions attended in this study was 12, and the findings revealed significant treatment effects for SS, we expect that selecting 12 sessions as a target dose will be (a) more feasible and (b) will be expected to yield favorable outcomes. A dose of 12 sessions was also reported to be effective by Najavits et. al. (1998) in their pre-post test design study.

Summary: Seeking Safety meets criteria as a "probably efficacious treatment."
The Hien et al. (under review) study described above was a Phase IB trial designed to provide a preliminary test of an integrated model (as opposed to a phase-based model) of treatment for women with the dual disorders of trauma and substance use. Since RPT had been empirically-validated for the treatment of SUD, *but had never been tested specifically in relation to the dual diagnoses of PTSD and SUD*, it was selected as a credible alternative treatment with which to compare SS.

Our primary research question was: How effective would an integrated CBT treatment model with a direct PTSD psychoeducational component (SS) be in impacting substance use, PTSD and psychiatric severity in comparison to standard CBT (RPT) for this dually-diagnosed population? The rationale for this research question originated from controversy existing in both trauma and addictions fields regarding the optimal time to begin addressing the underlying "comorbid" (in this case, PTSD) disorder—with the most commonly held belief that addressing PTSD directly in early recovery would "open the Pandora's box" and **worsen** the person's progress in addictions treatment. In contrast, following from a self medication model, we believed that treating the PTSD using an integrated CBT model would **not worsen** the individual's SUD, and ultimately, might improve outcomes in some or all domains.

Indeed, the two-armed RCT component which compared SS and RPT did find equivalence (defined as no statistically significant differences between two treatments, Chambless & Hollen, 1998; Kazdin, 1998) in the sample (n=41 in SS vs. 34 in RPT). The importance of equivalence of treatments has been underscored by the American Psychological Association's Division 12 (Clinical Psychology) efforts to define empirically supported treatments (EST). The APA's Task Force on Promotion and Dissemination of Psychological Procedures (Task Force, 1995) systematically defined

criteria for determining treatment efficacy. In its most recent explication of the standards for ESTs (Chambless et al., 1998, Chambless & Hollen, 1998), the Task Force described two categories: Well-Established Treatments and Probably Efficacious Treatments. **Notably, one of the main recommended criteria for identifying treatment efficacy is "equivalence to an already established treatment"** (See Chambless & Hollen, 1998, Criterion IB).

1.1.2.2. Clinician and Patient Acceptability

Seeking Safety has evidenced an exceptional level of clinician and patient acceptability in a short time frame. From a clinical practitioner perspective, treatment providers report feeling discouraged that they do not have adequate tools to help their clients with PTSD and associated issues. This further supports the need to develop and test trauma-focused treatments. Existing alliance and satisfaction data point to the SS treatment as being well accepted by both the patients and their clinicians (Najavits, Weiss Shaw & Muenz, 1998; Zlotnick, Najavits & Rosenhow, under review). Also, in Najavits' 1998 study SS completer group's retention (63%) and attendance ratings (67%) are higher than those of substance abuse populations in most other studies, suggesting that once engaged these women attended frequently and felt helped by the treatment. In the Zlotnick et al. study, the attendance was even higher at 83% of available sessions. These findings indicate that when provided with treatment adapted to their specific needs, women are more committed and responsive to treatment.

Moreover, in a very short period of time (given that the first published study on SS was in 1998, and the manual published only last year, 2002), the treatment has been adopted in a number of state and national services research contexts:

- In a CSAT study on Women and Violence, nine sites were offered a choice of three treatment models for PTSD/SUD; more chose SS than any other treatment model.
- In a State of Connecticut trauma initiative to provide trauma-informed services, three models were offered, and SS was selected as one of them. Seven agencies chose SS for this year-long project.
- In a Veterans Affairs 10-site project on homeless women veterans, SS was selected as the sole treatment to be compared to "treatment-as-usual".
- While it will take years for results on any of these projects to be known, thus far, the report is that SS has been extremely well accepted by both clinicians and patients (communications from Sharon Cadiz, PhD; Vivian Brown, PhD; Frances Hutchins, PhD; Norma Finkelstein, PhD; Tracey Rogers, PhD, et al.).
- Clinically, SS has been implemented in a wide variety of programs thus far, with reports of very strong positive patient ratings on the end-of-treatment questionnaire: e.g., the D.C. Vet Center (Carey Smith, LICSW), the Menlo Park VA (Robin Walser, PhD), Harborview Medical Center (Laura Holdcraft, PhD, Holdcraft & Comtois, in press).
- In all of these studies, the patient populations were considered "difficult to treat", with chronic, complex PTSD and SUD.

While this groundswell of clinical acceptability is not a final determinant of a treatment's efficacy, it is nonetheless extremely important.

1.1.2.3. Stage of Science

Following from the Division 12 Task Force criteria (Chambless et al., 1998) for determining treatment efficacy, the Hien et al. Phase IB study examined:

1. the equivalence of SS with standard CBT (RPT), and
2. the superiority of SS to standard non-manualized TAU.

The Hien et al. findings provide initial support for both propositions. Using the intent-to-treat analyses, the tests for treatment equivalence were upheld, as were the tests of superiority to a no-treatment control group.

Based on the Division 12 Task Force criteria (1995), Seeking Safety meets Criterion II for Probably Efficacious Treatments (the Hien et al. study). Under the Well Established Criteria, the treatment meets both IA and IB (from the Hien et al. investigative team). SS also has positive results in pilot studies and smaller n studies conducted by independent investigating teams (Criterion V for Well-Established Treatments; e.g., Najavits et al., 1998 (N=17), Zlotnick et al. 1999 (N=17)). At this point in order for Seeking Safety to meet the "Well Established" criteria, another investigative team would need to report on an RCT (N of at least 25 per arm) in which SS was tested against either an alternate treatment and found to be either equivalent or superior OR, compared with a no-treatment control group and found to be superior.

Finally and in sum, based on the Hien et al. findings, the Najavits et al. and Zlotnick et al. smaller N studies, and the lack of any other studies with which to contradict these findings, the preponderance of evidence provides ample support for the promise of the use of this integrated CBT treatment of PTSD among drug-involved women, and the need for its further testing and development.

2.0 STUDY RATIONALE

The rationale for this research is based on findings that the majority of substance-dependent women seeking treatment has been exposed to chronic interpersonal violence and suffers psychiatric sequelae of trauma in the form of posttraumatic stress disorder symptoms. Interpersonal violence appears to be a gender-specific risk factor for women with SUD's. Moreover, women with trauma histories and substance use disorders present significant challenges to clinicians who routinely observe poorer treatment outcomes in this group, including poor treatment engagement and retention, higher frequency of relapse, use of multiple substances, co-occurring psychiatric diagnoses, and treatment drop-out (i.e., Dansky et al.1995, Hien et al., 2000; Zweben et al.1994).

While substance abuse programs are well aware of the ubiquity and relevance of

trauma for their patients, the majority of substance abuse programs do not regularly assess for nor address interpersonal violence histories, so women do not receive treatment for co-existing trauma-related problems (Brown et al., 1999). Yet, an integrated model is recommended by both clinicians and researchers as more likely to succeed, more cost-effective, and more sensitive to these patient's unique needs (Brady et al., 1994; Evans et al., 1995; Najavits et al., 1996; Sullivan & Evans, 1994). Patients also favor this type of comprehensive treatment and perceive a connection between their substance use and traumatic experiences (Brown et al., 1998). All of these factors indicate the need for an integrated substance abuse/trauma treatment in drug abuse treatment settings.

Following from our own findings (Hien et al., under review), one of the next steps is to advance a larger RCT in which SS is compared to an attention control group. Additionally, based on our findings that PTSD symptoms did not fully remit during the course of our previous study—where, importantly, the participants received almost no other addictions treatment—a logical next step will be to compare the treatment efficacy of SS in the context of ongoing community-based substance abuse treatment. The Clinical Trials Network provides an ideal context in which to conduct this study.

2.1 Rationale for Selection of the Current Study Design

The design we have selected will use a randomized clinical trial to compare Seeking Safety to Women's Health Education, an attention control comparison group. However, following from our preliminary findings, one could easily argue that the most rigorous design would be to add a relapse prevention condition as a third study arm. Following from our previous work, a 3-armed design would potentially serve as an important replication and advancement of our previous findings. However, from the point of view of CTN feasibility and overall cost, a 3-armed trial would be prohibitive.[1] Therefore, we have selected the Women's Health Education as a credible comparison condition serving to control for all non-specific treatment elements (attention, dose, education, and gender-specific focus).

The reasons for continuing to develop and test Seeking Safety for this population are multiple. Based on the Hien et al. findings, RPT may be considered a reasonable early treatment choice for women with SUD and PTSD, because it appears to be effective in the short-term and is already used in the addictions field. However, the fact that the majority of women will present for addictions treatment with a co-existing trauma-related

[1] Ultimately, however, we could not use Relapse Prevention as the comparison treatment for reasons of feasibility. As our data have shown us there were no statistically significant differences between Seeking Safety and Relapse Prevention. This means that the effect sizes of the differences between the two treatments were very small. Thus, to launch a trial with the main comparison being SS vs. RPT, we would need a large sample size. Even using our current power calculations based on a small-moderate effect size between Seeking Safety and Treatment-as-Usual, we need to conduct the treatment in at least 8 CTP's (480 participants) over the course of 1-2 years of data collection. If we were to lengthen the study period, that too would become prohibitive from a budget perspective in that the study would cost too much to any individual CTP. Thus, these are main reasons why RPT, an excellent choice as the comparison treatment from a design point of view, is not a feasible one, from a CTN point of view.

disorder remains a strong rationale for continuing to develop and modify treatments that can more directly address the trauma-related problems. Moreover, though RPT has been demonstrated to be an efficacious treatment in more than 24 replicated randomized controlled clinical trials (Carroll, 1996), “transfer of technology” from research to practice of RPT represents many significant challenges (Carroll, 1997), and may be most appropriate for particular subgroups such as those with smoking problems, higher levels of impairment, or therapists with more vs. less training (Carroll, 2001).

Seeking Safety has the crucial qualitative **advantage** of answering the need for tailoring treatment to the trauma-driven struggles of female drug users. The prevalence of trauma experiences and symptoms, and their link to substance use in women, is a common observation of researchers and providers working with female drug users. It has prompted a widespread call for gender-specific substance abuse treatment programs that integrate these issues into their usual emphasis on building coping skills for abstinence. As we stated above, from a clinical practitioner perspective, reports of discouragement from providers who do not feel that they have adequate tools to help their clients with PTSD and associated issues further supports the need to develop and test PTSD-specific treatments. This is evident from the speed with which Seeking Safety is being disseminated within the addictions community (see listing above of all federal and state initiatives launched over the past few years using Seeking Safety as a model treatment, 1.1.2.2. Clinician and Patient Acceptability).

Similarly, the call for trauma-related treatment is an urgent issue expressed by the participants in the CTN. For example, this protocol was initially ranked Number One by CTPs expressing interest in which 3rd Wave Protocol Concepts to develop further. At present, out of the 9 Nodes that have identified which protocols they would like to participate in, 18 CTPs in 9 Nodes have identified this protocol as one of their top choices. It is the protocol that currently has the greatest number of both CTPs across the CTN and Nodes expressing interest.

3.0 OBJECTIVES

3.1 Primary Objective

The primary objective of this behavioral treatment study is to implement and evaluate the effectiveness of Seeking Safety—a cognitive-behavioral substance abuse treatment for women with trauma—in comparison to a control treatment for women in standard substance abuse treatment on treatment outcomes for women with PTSD/SPTSD.

The primary hypothesis is:

Enhanced treatment (SS plus TAU) will be more effective than control treatment (WHE+TAU) for substance-using women with PTSD/SPTSD on outcomes including substance use and PTSD severity.

3.2 Secondary Objectives

The secondary objectives of this effectiveness study will allow for examination of impact of enhanced treatment vs. control treatment on: (1) treatment adherence, (2) secondary measures of substance use and PTSD outcome; (3) measures of psychiatric severity; (4) measures of HIV sexual risk behaviors. We will also explore delivery of drug abuse treatment for women by examining various characteristics of the sites (CTPs) for their potential effect on the efficacy of the intervention and on the retention of subjects in treatment. In addition, in an exploratory fashion we will study the effect of various baseline demographic and individual characteristics on the inferences made for the primary hypotheses.

4.0 STUDY DESIGN

Pre-treatment (1-4 weeks)	**Treatment - (approx 6 weeks)**	**Follow up (12 months)**
Assessment	Treatment	Assessment
Screen Baseline		1 Week, 3-, 6-, and 12-month follow ups

The study will use a randomized, controlled, repeated measures design to assess the effectiveness of Seeking Safety Treatment plus standard substance abuse treatment (SS+TAU) in comparison to a control treatment plus standard substance abuse treatment (WHE+TAU) over an approximate 6-week period. To further assess differences between the two treatments over time, the design will include a 1-week, 3, 6, and 12-month post-treatment follow-up assessments.

The study population will consist of treatment-seeking, substance abusing or dependent women with at least one traumatic event in their lifetime and who meet DSM-IV criteria for PTSD either full or subthreshold (SPTSD). Sub-threshold PTSD is defined by fulfilling a sub-set of the DSM IV criteria for PTSD. Specifically, the subset is criteria A, B, (either C or D), E and F. Outcomes assessed will be (1) substance use abstinence and symptoms and (2) PTSD symptoms, and secondarily, (3) treatment retention and adherence; (4) general psychiatric symptomatology; and (5) HIV-risk sexual behaviors.

A number of design considerations have been made in response to the internal validity threats posed by variability in the TAU conditions. It is our desire to be as inclusive of CTPs as possible without compromising study integrity. In general, the strategy for dealing with variations in TAU will be to measure the anticipated confounding variables adequately and to include the variables as covariates in the data analyses. This should allow us to address the extent to which factors other than the active treatment itself contributed to predicting outcomes. The factors we have considered a priori include:

- Definition of traumatic stressor. DSM-IV PTSD criterion A stipulates that an individual must have been exposed to a traumatic event in which both of the following were present: 1) The individual experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others; 2) The individual's response involved intense fear, helplessness, or horror (or in children, this may be expressed

instead by disorganized or agitated behavior). We have chosen not to define a specific type of trauma for inclusion in this study for a variety of reasons. First, although there is some evidence for differential risk of PTSD based on type of trauma exposure (namely rape, childhood physical abuse and childhood neglect), this information is inconsistent. Second, based on our preliminary studies, 80% of our target population will have been exposed to multiple traumas. Limiting our sample to only those with a single type of trauma exposure would seriously threaten the study's external validity. Third, the PTSD literature suggests that the risk of PTSD associated with any one event alone is usually less powerful than the lifetime risk of PTSD associated with multiple events. Thus the severity, duration, and proximity of an individual's exposure to the traumatic event are the most important factors affecting the likelihood of PTSD rather than the event per se. Our preliminary statistical analyses will examine our CTP samples for variability (within and between sites) in type of events leading to PTSD, as well as other trauma characteristics that may systematically differ across sites

- Dose of treatment. The general strategy for dealing with dose/response issues will be to carefully measure the dose of both active treatments, and of TAU. The inclusion of the WHE control group allows us to control for non-specific factors including dose of enhanced treatment.

- Site-specific CTP characteristics. The study is powered to enable us to examine both between subgroup differences, as well as within subgroup effects (see Statistical analysis section 11.5.5 for more detail). Site-specific characteristics we plan to examine include standard level of psychotherapy intervention, gender-specific vs. mixed gender settings, type of setting (level of care), and location (rural vs. urban).

- Inclusion of subthreshold PTSD (SPTSD) participants. We broadened our original inclusion criteria as a response to the Clinical Treatment Programs' numerous requests that participants with trauma history (not necessarily with current PTSD diagnoses) be included in the study. Given empirical evidence linking PTSD to subthreshold PTSD, we will include those who meet subthreshold criteria as defined by fulfillment of Criterion A (traumatic event), Criterion B (re-experiencing), EITHER [Criterion C (Numbing) OR Criterion D (Hyperarousal)], and Criterion E (Month duration symptoms) and Criterion F (functional impairment). Marshall and colleagues (2001) in their American Journal of Psychiatry report analyzed National Anxiety Disorders screening data (N=2,608). Their findings provide strong support that a syndrome exists which can be measured using these stringent criteria. In their analyses, individuals with subthreshold PTSD were at greater risk for greater impairment, comorbidity and suicidal ideation than those without PTSD.

  In our own study (Hien et al., under review), the only difference between those with full PTSD and our "subthreshold" participants was that those in the subthreshold group did not meet all four symptom cluster criteria, but only 3. They were, however,

required to meet the hallmark symptom clusters (Criterion A presence of a trauma), and B (re-experiencing). If they fully met either Criterion C (numbing) OR Criterion D (hyperarousal) symptom sets they were included in our study. Our subthreshold participants were also required to meet Criterion E (functional impairment for longer than one month). Therefore, the criteria we used to include those with subthreshold PTSD were highly conservative. Of the total sample for that study (N=107), 88% met full criteria for current DSM-IV with the remainder (only 12%) meeting the "subthreshold" criteria. Comparative analyses between those with full and subthreshold PTSD failed to yield differences in overall substance use, PTSD and psychiatric severity. Nor were there differences in distribution of subthreshold PTSD across the three study groups. Therefore, we do not believe that our inclusion of subthreshold participants compromises the study integrity or limits interpretation of our study in any way.

Finally, it can also be noted that in their study of over 225 subjects, Schutzwohl & Maercker (1999), also concluded that "the findings did not support the diagnostic boundaries as defined by the DSM-IV…The concept of partial PTSD appeared to be the most appropriate way to provide diagnostic coverage of those who did not meet full DSM-IV criteria" (pg. 155). We believe that by allowing participation of this particular subgroup, we are increasing the external validity of our study, in addition to being responsive to the requests of the CTPs in the CTN.

- Additionally anticipated subgroup individual differences: e.g., length of time in treatment prior to study participation, differences in participants by definition of trauma (full vs. subthreshold, and severity of symptoms). Other individual-specific factors that will be examined include age, abuse characteristics including severity and duration, severity of substance use disorder and PTSD at baseline, severity of other psychiatric symptoms, and previous treatment history. See Statistical analysis sections 11.5.4 and 11.5.5 for more details.

5.0 STUDY POPULATION

5.1 Number of Sites and Subjects

The study will be conducted at approximately eight substance abuse treatment sites. Each participating site will enter approximately 60 eligible participants into the study (3 - 8 patients per group). The treatment groups will be open enrollment format and expected to operate continuously for, on average, 36 weeks. Each treatment group will begin when at least 3 participants are enrolled. We anticipate that the CTP needs to be able to recruit approximately 2 patients per week who meet screening eligibility criteria (see section 5.4 below).

5.2 Duration of Study and Visit Schedule

The total duration of the study is expected to be about 2 years at each CTP. We expect that both the Seeking Safety and Women's Health Education groups will be running

simultaneously at each site. On average, we expect that screening, baseline assessment and random assignment to each group will be conducted over approximately a one-to-four week period. We will conduct groups with open, rolling enrollment so that upon randomization, a participant will immediately enter either SS or WHE group. It should be noted, arrangements may need to be made for the final few participants enrolled in the treatment groups, as there is the possibility of participants tapering off until only one remains with sessions to complete. The following exceptions can be made: 1) conduct individualized sessions with the final participant(s) or 2) create a cohort with the last few participants so that they will start and end treatment at the same time. Prior to entrance into a group, participants will meet individually for about 45-60 minutes with a counselor. The purpose of this session is to disclose condition assignment, build rapport, introduce the group and treatment format, and answer questions regarding treatment. For each condition, groups will last about 75-90 minutes and be held two times per week. During this time, CTPs will continue to screen participants and enroll them into the study. Participants will also be scheduled for post-treatment assessments at the 1-week, 3-month, 6-month and 1-year post-treatment time points. Follow-up contact and locator information will be reviewed at baseline, during treatment and at each follow-up time point.

5.3 Informed Consent

At both screening (level 1 consent for screening interview) and entry into the main intervention trial (level 2 consent for baseline interview, treatment participation and follow-up assessments), the Research Assistant (RA)/Independent Assessor (IA) will obtain informed consent and HIPAA authorization (as needed) for study participation. The RA/IA and the participant will discuss the basic features described in the informed consent form. These include: purpose; procedures; randomization; confidentiality; voluntary nature of participation and freedom to withdraw without consequences to clinic services received; audio and videotaping; risks; and benefits.

We will also obtain informed consent during the training procedures involved in the study (described below in Section 6.2 Selection and Training of Therapists). To protect the counselors and supervisors participating in the study, as well as the participants who will take part in the training activities, we will obtain informed consent.

If a person consents, but doesn't complete the screening or doesn't show up for the baseline after completing the screening, they will have 30 days to do so before needing to be re-consented and complete the process again. The same holds for the baseline. If they consent for the study, but don't finish the baseline, they have 30 days to complete it before needing to be re-consented and complete all of the assessments again, including the screening. However, assessments that gather historical information (these include the Life Events Checklist, CIDI, Demographics questionnaire, Addendum) will not have to be readministered in their entirety. Rather on these instruments, the interviewer should focus on any changes since the participant was last assessed. All other assessments will need to be readministered in their entirety.

5.4 Screening and Inclusion Criteria

Participants will be referred to the study through several recruitment methods, including by CTP treatment staff who will be informed about the study through staff meetings, brochures, and flyers. Entry to this study is open to women participating in substance abuse treatment at one of the participating centers, and to all racial and ethnic subgroups. CTPs can decide the best way to recruit patients depending on local needs and regulations.

To be eligible for the study, participants must:

1) range in age from 18 - 65,
2) be female,
3) have used an illicit substance within the past six months and have a current diagnosis of illicit drug abuse or dependence or have used alcohol within the past six months and have a current diagnosis of alcohol abuse or dependence
4) have either full or subthreshold DSM-IV PTSD (as defined above),
5) be capable to give informed consent,
6) be enrolled in treatment at the participating CTP,
7) not meet any of the exclusion criteria.

5.5 Exclusion Criteria

A participant will be excluded from the study, if the participant has:
(1) advanced stage medical disease (e.g. AIDS,TB) as indicated by global physical deterioration and incapacitation,
(2) impaired mental status as measured by the Mini-Mental Status Exam (score # 21),
(3) significant risk of suicidal/homicidal intent or behavior or history,
(4) a history of a schizophrenia-spectrum diagnosis,
(5) a history of active (past two months) psychosis,
(6) involved in litigation involving PTSD,
(7) refusal to be audio or videotaped.

5.6 Subject Discontinuation Criteria

Study discontinuation is at the discretion of the clinical staff, Protocol Manager and Protocol PI, at each CTP who may discontinue a patient from participating in the study if they deem it clinically appropriate. During the treatment phase of the study a participant may be discontinued from the study for a variety of reasons including a serious concurrent illness, a serious or unexpected adverse experience which places her at risk if study participation is continued, or non-compliance with clinic policy or study protocol. However, as advised in the consent form, a participant who does not attend 4 sessions of consecutively scheduled visits (with no contact regarding her absence) will be

considered non-compliant with the protocol and should be discontinued from treatment. Additionally, a participant may withdraw from this study anytime she wishes.

5.6.1 Required Termination

The study must be terminated for a participant if, in the opinion of the investigator, the IRB, or the CTN DSMB, 1) continuation of the study would present a serious medical or psychological risk to the participants or 2) for other administrative reasons. In the event that a patient is discontinued prematurely from the study she will continue to be eligible for standard substance abuse treatment at the discretion of the CTP. Study participants who enter treatment randomization but are discontinued or terminated from treatment will be contacted to complete the end of study assessments at 1-week and 3- 6- and 12-month follow-up. In the event that such individuals refuse to make a face-to-face appointment, the option of a phone assessment will be presented.

5.6.2 Consideration of Early Termination

Consideration for early study termination will be made jointly by the counselor, research supervisor, Protocol Manager and Protocol PI.

5.6.3 Procedures for Discontinuation

Once a participant has been randomized and the decision for early study discontinuation has been made as described above, the participant will be notified by the Site PI (or Protocol Manager) and the counselor jointly. They will be given an appropriate local treatment referral in the event that the participant is no longer enrolled in the CTP. They will, however, continue to be outreached by the RA to receive all study follow-up assessments.

5.7 Replacement of Subjects

Subjects who drop out of the study after randomization will not be replaced.

6.0 STUDY TREATMENTS

Both Seeking Safety and Women's Health Education will ideally be delivered in a twice-weekly format for a period of 6 weeks (12 sessions total). Treatment sessions will be about 75-90 minute group sessions (2-8 participants per group) led by experienced CTP counselors who have received training in their respective model. In each treatment, groups will be held on a rolling admissions basis. Study groups will not begin at a site until at least 3 participants are enrolled in each treatment. Once the study groups have begun, if enrollment drops below 3 participants in either group, the group will be temporarily suspended until 3 participants are again enrolled. For any given group session to be conducted, a minimum of 2 enrolled participants must be present. If only 1 participant shows up for a given session, that session will be postponed until the next scheduled group meeting. Ideally, new participants should start their treatment group on

the first session of the week, unless it is in the best interest of the participant or group to have the participant start on the second session of the week.

All study treatment sessions will be videotaped to evaluate fidelity and so participants can view by videotape missed seasons, ideally prior to attending the next session.

6.1 Study Therapies

Seeking Safety Treatment (SS). The Seeking Safety treatment was developed under a National Institute on Drug Abuse Behavioral Therapies Development grant. This intervention applies cognitive-behavioral strategies to the goals of attaining abstinence from substances and decreasing the negative impact of trauma exposure. It is highly adaptable to different contexts and has been used in a variety of formats (Najavits, 2002). The Seeking Safety manual is currently in use by several investigators (specified in Background section) in a range of treatment outcome studies. Videotaped training modules have been developed by Dr. Lisa Najavits (author of the manual) and will be used to aid training, therapist competence and adherence.

Structure of Seeking Safety. The basic format of each session remains consistent. Each session is a sequence of four steps (1) the check in: allows the therapist to find out how the patient is doing, to identify issues the therapist can incorporate into main content of the session, and to provide a consistent start to each session. As part of the check-in the patient reports any “unsafe” behaviors (i.e., substance use, high risk sexual behavior, domestic violence) since the last session and the patient also reports ways she used coping skills, (2) the session quotation: provides a brief point of inspiration to affectively engage the patient and a link to the session topic that can be remembered in the future, (3) relating the material to the patients’ lives: this is the majority of the session with the goal of meaningfully connecting the session topic to the patient’s experience by using specific and current examples from the patient’s life and offering intensive rehearsal of the material and skills. Patients are provided with session sheet(s) summarizing the material, (4) the check out: provides opportunity for the therapist to reinforce the patient’s progress and to provide feedback. At the end of each session during the check out the patient is asked to commit to a specific skills practice exercise to continue work on new coping strategies in-between sessions. Possible obstacles to successfully carrying out the commitment are discussed.

Control Treatment: Women’s Health Education (WHE). Women’s Health Education treatment is the non-specific short-term manualized psychological treatment control that will be provided as a comparison treatment. As a non-specific manualized treatment we have selected WHE to serve as an attention control group in the present study. This condition will control for the Hawthorne effect and reduce the likelihood that effects of the Seeking Safety treatment can be attributed to its nonspecific features. In addition, the fact that all subjects will receive an intervention should reduce the likelihood of differential attrition between conditions. It is a short-term manualized treatment that focuses on topics such as understanding the women’s body, human sexual behavior, pregnancy and childbirth, STD’s, HIV, and AIDS. Currently, WHE is also being used in a

treatment trial for intravenous drug users (Tross, 1998). WHE will provide equivalent facilitator attention, expectancy of benefit and issue oriented focus, but will not provide theory driven techniques of Seeking Safety such as cognitive behavioral therapy, and psychoeducation specific to substance abuse and posttraumatic stress disorder.

Our intervention design (i.e., goals, scope, structure) will be based on the Women's Health Education Treatment protocol for women, which was developed in the context of a treatment grant for female partners of injection drug users (Tross, 1998). Both interventions (SS and WHE) will be equivalent on all major design features, other than the treatment technique (CBT) that is the experimental factor being tested in the trial.

Structure of Women's Health Education. All sessions have the following common format: (1) introduction of topic, (2) review of group rules, (3) review of between session assignment, (4) topic presentation using mini-lecture, video, story-telling and/or text readings, (5) topic exercises in a variety of formats to facilitate group discussion and application of session material or skills to their lives, (6) setting of between-session goals.

Standard Treatment (TAU). All study participants will also participate in usual care within their drug-free outpatient substance abuse program. These programs will consist of a variety of individual and group treatment components, reflecting varying orientations and philosophies of addiction treatment. Each subject must attend the standard treatment offered during the six weeks of psychosocial intervention.

Recognizing that standard treatment may vary greatly across sites in frequency of sessions, program philosophy, staffing, etc, we plan to gather program information about each participating CTP. We will also gather information about dose and types of treatment received on a weekly basis using the modified, brief NSMS. By gathering information about general types of treatment received, we will be able to statistically examine the characteristics and components of general drug abuse programs, potentially controlling for confounds such as receiving focal PTSD evaluation and treatment. (See Statistical Analysis sections 11.5.2, 11.5.4 and 11.5.5 for a delineation of all planned analyses of site-specific variables). Adding the comparison condition strengthens our design, by providing us with the ability to (1) assess comparative outcomes for a sample of female drug abusers with diagnosed PTSD, given manualized, attention control treatment and (2) facilitate the interpretation of our enhanced treatment findings.

6.2 Selection and Training of Therapists

Selection: Potential female therapists for the two study groups (SS and WHE) will be identified by Site PI in conjunction with CTP supervisors. After successfully completing a screening session, they will be randomized to one of the two conditions, and participate in a national training program led by the Lead Node and LI specific to their treatment condition. All training sessions conducted by trainees for selection and certification will be audio or videotaped.

Training: The behavioral therapy training will be completed prior to study initiation. An effort will be made to minimize the length of time between training and study initiation. Therapists will be briefed about the general study aim of evaluating trauma treatments in substance abuse settings; however, efforts will be made to keep them blind to the specific hypotheses, primary/secondary outcomes and specific assessment measures. All CTP counselors and their on-site supervisors will be selected, trained and certified in their assigned therapies by the Lead Node expert training group. Counselors hired after centralized training will be trained at their local site with consultation from the Lead Node training group. Replacement counselors or supervisors will not be randomized.

The Lead Node expert training group will provide comparable training for both SS and WHE conditions. The counselors responsible for implementing the behavioral therapies, as well as the counselor supervisors, will complete the following three phases of training: (1) Pre-Training: includes conducting an audiotaped practice individual session that will serve as a screening tape, (2) Training: involves attending Centralized Training provided by the Lead Node that will include didactic review of manualized intervention, observation and practice of role-plays. (3) Post-Training: involves practice and completion of a training case (a group with at least 3 women), which will be rated by the Lead Note for Certification.

Before counselors and supervisors are randomized to a treatment condition, each will conduct an individual practice session. The LI expert training group will provide brief instructions about how to conduct the session. If the CTP counselor or on-site supervisor can follow the basic structure of one session, then she will continue with the full training. Lisa Najavits, developer of the treatment and trainer for many studies, has found that therapists who can easily follow the basic structure of a session (check in, quotation, topic areas, commitment and wrap-up) are best suited to complete the full training (Najavits, 2000). If a counselor or on-site supervisor cannot follow the basic structure, she will be ineligible to be a study therapist or supervisor.

The Lead Node will conduct a 3-day centralized training for counselors and counselor supervisors. After the training is completed, counselors and supervisors are requested to get as much experience with the intervention as possible before conducting a training case, with supervisory support and consultation from the Lead Node. The training case will entail conducting at least four group sessions of the treatment to which the counselors/supervisors are assigned with at least three group members. A Lead Node expert trainer will rate the sessions for adherence to the manual. The Seeking Safety Adherence Scale (Najavits, unpublished) is a 21-item scale, with 10 items reflecting essential components of the treatment and 11 items reflecting general therapeutic skills, the last of which is an overall adequacy rating. Each variable is rated on a 0-3 scale, with 0 being “Not Done” or “Harmful” and 3 being “Done thoroughly” or “Very helpful.” If the trainee has a mean rating of 2.0 on items 1-10 and 21, she will be permitted to start running study groups. Otherwise, the lead node will provide additional training via teleconference, and the trainee and supervisor will complete additional mock intervention sessions until she meets the criterion of achieving at least a 2.0 rating on those designated items of adherence scales. WHE has its own adherence rating scale,

with ratings ranging from 1 (poor) to 5 (excellent). Counselors and site supervisors will be required to obtain mean ratings of 3.0 on the WHE adherence scales to meet the competency criterion.

In addition to the 3-day centralized therapy training, Node and/or CTP treatment supervisors will also attend a half-day centralized training. This train the trainer component will focus on providing supervision and using the adherence scales to rate videotaped sessions. After achieving competency as a clinician (as described above), the supervisors will use the adherence scales to rate a four-session training case. Those ratings will be compared to ratings made by a Lead Node expert trainer in the applicable treatment. Item level, inter-rater reliability of .70 (computed with the intraclass correlation coefficient [ICC]) will be required for certification. Performance below ICC=.70 will lead to additional training until ratings reach the acceptable criterion. Specific information about training materials and staff turnover can be found in the Training Plan.

6.3 Administration of Study Therapies

6.3.1 Randomization

Participants satisfying screening eligibility from each CTP site and completing the baseline assessment will be randomized to one of the two enhanced treatment groups. The two treatment groups are 1) Seeking Safety (SS) plus Standard Treatment (TAU), and 2) a comparison condition—Women's Health Education (WHE) plus TAU. Each participating CTP clinic will randomize approximately 60 participants. Given that our study focuses on women only, stratification by gender will not be necessary. We will examine other potential confounding variables in the analyses (e.g., individual- and site-specific characteristics).

A statistician at the Long Island Node will generate one blocked randomization list (block size will be known only to this statistician) for the entire study, starting with randomization number 1001. The randomization list will be generated so that at the end of the specified block; and, after every 60 numbers, the treatment assignment will be balanced. A block of 60 sequential randomization numbers will be assigned to each CTP *a priori*. Each CTP will receive a set of 60 sealed, tamper evident, security envelopes, each containing one randomization number and the corresponding treatment assignment. Although each CTP will have the full set of randomization numbers, knowledge of treatment assignment will not be known. In addition, each site will receive a second set of randomization envelopes specifically for participants eligible under the new alcohol abuse or dependence criterion (this addition coincides with the eligibility criterion change in version 6.0 of this protocol). This will ensure equal distribution across the two treatment conditions for participants meeting this eligibility criterion. The creation of these randomization envelopes will follow similar guidelines as the original envelopes.

Randomization will be stratified by receipt of psychotropic medication at each CTP. Eligible participants not receiving psychotropic medication will be assigned randomization numbers in ascending order, starting with the smallest number (within the block of numbers assigned to the CTP); and, participants receiving psychotropic medication will be assigned numbers in descending order, starting with the largest number (within the block of numbers assigned to the CTP). This method of stratification should permit the study to achieve balance between the two treatment groups with respect to receipt of psychotropic medication, CTP and overall, and alcohol/illicit substance abuse and dependence, while allowing for each CTP to enroll a varying number of individuals receiving psychotropic medications. All participants who are randomized will receive a randomization number.

The randomization procedure will involve 4 steps: 1) after the Independent Assessor (IA) has completed the baseline assessment and determined that all final eligibility criteria are met, she will inform the Research Assistant (RA) that the participant needs to be randomized; 2) the RA (to keep the IA blinded to condition assignment) will then randomize the eligible participant (ideally within one business day if not sooner); 3) the RA will notify the participant to schedule the individual counseling session as soon as possible after randomization; 4) at the individual session, the counselor will inform the participant of her group assignment.

6.3.2 Blinding

Independent assessors (IA) performing all baseline and follow-up assessments should to the extent possible be blind to participant's treatment assignment. The counselors will be blind to the study hypotheses, although they will be familiar with the design of the study and the two experimental treatments. During the protocol specific training, procedures for handling and documenting any instances of IA "corruption" will be reviewed. Additionally the IA will not attend training on specifics of the randomization procedure.

6.3.3 Quality Control of Therapies Administered

Ongoing Supervision of Counselors. During the study, counselors will receive weekly individual supervision that will include review and discussion of randomly selected, videotaped sessions. Female supervisors will rate the sessions for adherence prior to the individual meeting with the counselor. Should review of a session indicate that a counselor is falling below the adherence criterion (i.e., mean score of 2.0 on the rating scales for SS or 3.0 for WHE) then additional supervision will be provided, including an increase in the number of sessions reviewed. If the counselor falls below the adherence criterion for seven consecutive sessions (to allow for variability that may occur due to group dynamics and the opportunity for therapists to demonstrate adherence as group composition changes), the supervisor will join the group as the primary therapist for six sessions. After six sessions, the counselor, with the supervisor still present, will resume the primary therapist role in the group. If the counselor still fails to meet the 2.0 cut-off, the supervisor will resume the role of primary therapist for another six sessions.

Ongoing Supervision of Supervisors. In order to ensure ongoing supervisor competency, supervisors will have conference calls with experts in the intervention to answer questions that arise about the treatment and supervision. These calls will initially be held weekly and then decrease to biweekly over the course of the study. Supervisors will also submit adherence ratings for expert review. The Lead Node will co-rate 25% of the sessions to assure supervisor fidelity. Supervisors must demonstrate agreement with training experts at the level of ICC=.70.

6.3.4 Other Procedures to Minimize Potential Biases in Administration of Therapies

The cross-contamination threat is potentially problematic. We aim to address this problem in a number of ways, recognizing that none are perfect solutions. Whenever possible, we will encourage programs to have study participants sit in different waiting rooms. However, there's no guarantee participants will be able **not to** discuss their treatment, especially if their treatment raises issues that are then brought into other groups. Likewise, there are concerns about cross-contamination coming from program staff (i.e. counselor learns SS or WHE and communicates to other counselors who begin to incorporate elements into other TAU groups). These issues will be addressed during centralized training. Overall, because the SS treatment is unique and has so many structured sessions and elements, we believe that it is unlikely that much of the treatment will be absorbed by the WHE participants or program staff.

7.0 CONCOMITANT THERAPY

7.1 General Considerations

While there is no medication component to the study, many participants may be taking prescribed psychotropic and other medications. We will document psychotropic medications on a prior and concomitant medications form (PCM) in order to consider psychotropic medication use as a component of TAU. Stratification for whether or not the participant is taking psychotropic medications at the time of randomization is planned. Since there are no known efficacious medication treatments in the absence of a behavioral intervention specifically for PTSD in this SUD population, we will not specify either any particular medication protocol OR prohibit participants from taking prescribed medications during the course of the study. However, we plan to monitor psychotropic medication usage during the course of study and will statistically control for differences in medication usage across CTP sites and treatment groups. We do not expect that most participants will have access to *any other* treatment for PTSD, as they are not widely available. In the event of severe symptoms that require additional treatment CTPs will be instructed to use their usual assessment and referral procedures for psychiatric disorders to determine appropriate level of care.

7.2 Medications Prohibited During the Trial

Because this population of women may be frequently in need of pharmacological adjunctive treatment for comorbid disorders, we are unable to impose a restriction on participants' medication usage while they are taking part in the study. Nor can we control variations in the use of medications in the TAU group. Therefore, while we will recommend that participants in the study remain on a stable medication dose, we will not exclude anyone on any class of antidepressants. Again, variability across treatment groups and sites, which may include psychotropic medication use will be statistically examined.

7.3 Medications Allowed During the Trial

No specific restrictions.

8.0 MEASUREMENTS, EVALUATIONS, AND METHODS

Study procedures will consist of: 1) pre-screening; 2) screening; 3) baseline assessment; 4) randomization and treatment; 5) immediate post-treatment assessment; and 6) three- six- and twelve-month post-treatment follow-up interview.

8.1 Pre-Screening

Typically, research staff at each CTP will be responsible for the pre-screening (brief screen assessment) of interested potential participants enrolled in or presenting for substance abuse treatment. However, depending on local CTP staffing, clinic intake staff may also provide pre-screening provided that they have received the required Good Research Practices (GRP) and Human Subjects Training. Potential participants will respond to a brief screen questionnaire that ascertains their status on study criteria to provide CTP research staff with a preliminary evaluation of their eligibility. Potential participants that meet these preliminary criteria will be provided with more information about the study and a time will be scheduled for the purpose of obtaining the first level of informed consent and a full screening for study inclusion. This may occur immediately following the initial participant pre-screening or by appointment within a reasonable number of days (preferably within 7 days).

8.2 First Level Informed Consent and Screening

Prior to the collection of any screening assessments or initiation of research procedures, the RA/IA, or Study Coordinator at each CTP will obtain informed consent for screening participation. Each individual CTP may decide whether to combine first level and second level consents. Participants will be provided with a consent form describing the study's purpose, general procedures, risks and benefits, and the participants' role in the study. The consent procedure will inform participants that descriptive information about them obtained during the screening assessment on the

Basic Data and Locator Questionnaires may be shared with outreach workers on the research staff at the CTP to facilitate finding patients for follow-up evaluations. Potential volunteers will be encouraged to ask questions and encouraged to take the Informed Consent Form home to review with family or significant others if they wish. HIPAA authorizations, as needed, will be presented at the same time as the 1st level consent form. They should understand that they can ask questions any time during the study. Screening evaluations will assess the domains of demographics and treatment history, substance use diagnoses and severity, exposure to traumatic life events, and other eligibility measures (see measures in Section 8.4.1). All assessment interviews will be audio taped. Note that in the event that a participant refuses to consent to audio or videotaping, she will be ineligible for the study.

In terms of PTSD diagnostic criteria, potential participants will be screened with the CAPS. The CAPS-Part 1, the Life Events Checklist, administered by the Research Assistant (RA) or by the Independent Assessor (IA), is a partial screen for PTSD, identifying DSM-IV Criterion A exposure to at least one qualifying traumatic event. If the participant is eligible after the first part of the screening (Demographics, CIDI, CAPS Part 1, PRISM, MMSE, and PCM) , she will go on to complete the CAPS-Part 2. Only the IA may administer the CAPS-Part 2. After the CAPS-Part 2, the diagnosis of PTSD/SPTSD can be made. Because there is empirical evidence linking PTSD to subthreshold PTSD, we will include those who meet subthreshold criteria as defined by fulfillment of Criterion A (traumatic event), Criterion B (re-experiencing), EITHER Criterion C (Numbing) OR Criterion D (Hyperarousal), Criterion E (Month duration symptoms) and Criterion F (functional impairment). The CAPS-Part 2 should ideally be completed during the screening session, but may be completed at a second session (for example, on the day of the baseline) if the IA is unavailable. If the participant does not meet criteria for PTSD or sub-threshold PTSD, the participant is ineligible for the study, the interview is concluded, and the participant is thanked for participating.

8.3 Second Level Informed Consent and Randomization

If the participant is given the diagnosis of PTSD or sub-threshold PTSD, then they are given the assessments for the baseline measures. If they are not given the PTSD/SPTSD diagnosis, then they will not be assessed further. Note that these assessments are made prior to treatment assignment, in order to avoid bias. Participants who meet diagnostic eligibility criteria (determined by the IA) at the time of pre-randomization will be presented the level-2 consent form explaining randomization, treatment types and all study procedures by the RA/IA. Participants will be given adequate time to understand the level 2 informed consent before signing. Those who consent to participation will receive the full baseline assessment and, if eligible, be randomized.

Approximately 8 sites (CTPs) will be recruiting approximately 60 participants per site for a total of 480 participants. Within each site 60 participants will be randomized to one of two groups. The treatments (SS+TAU and WHE+TAU) will be open to rolling admissions following a one session post-randomization orientation to group treatment

specific to each study treatment group and conducted by the counselor assigned to each condition.

8.4 Assessment

8.4.1. Measures

In the baseline assessment, measures of substance use, PTSD symptoms, psychiatric symptoms and HIV-risk sexual behaviors will be recorded and then, the same assessment will be repeated four times over a one-year follow-up period (see Time and Event Table for more details). All assessment interviews will be audio taped. In addition to the assessment points at pre-screening, screening, baseline, post-treatment and follow-up, participants will also be asked to fill out a brief selection of self-reports on a weekly basis to more frequently gather data on primary outcomes. Optimally, weekly treatment assessments should be conducted directly after the 1st or 2nd treatment session during a given week. These assessments should be given in a group format, whereby the RA reads the questions and the participants complete the CRFs, however RAs may conduct assessments individually with participants if necessary and choose to either have the participant complete the questionnaires or administer the questionnaires to the participant. The RA will also collect the weekly urine and saliva samples. Thus, participants will complete the NSMS, SUI, and PSS-SR (see below) and be asked to provide urine for screening and to take a saliva test. Participants will also complete the Helping Alliance Questionnaire at weeks 2 and 6 and a brief feedback questionnaire about the helpfulness of topics covered in the groups at the end of treatment. If necessary, the HAQ may be completed by the participant during week 3 of treatment and at the 1-week post treatment respectively. Separately, counselors will complete the Helping Alliance Questionnaire at the end of week 2 and week 6 (for any week they have a participant in treatment week 2 or 6). These assessments are expected to take 10-15 minutes for participants and 5 minutes for the counselors. Note that participants will be paid for all assessments (though not for their time in treatment). Each participant receives $10 for completing weekly treatment assessments. The RA administering the treatment assessments at the final session should also schedule the 1-week follow-up assessment.

8.4.1.1 Screening

Study Enrollment Form will be completed by the RA/IA documenting informed consent.

Demographics form will be administered from the common assessment battery.

Composite International Diagnostic Interview for DSM-IV (CIDI) is an interviewer-administered assessment that is part of the Common Assessment Battery. It will be used to determine lifetime and current substance use disorder diagnoses for alcohol, cocaine, heroin, marijuana, methamphetamine and sedatives.

Clinician Administered PTSD Life Events Checklist (CAPS-Part I) is a structured, clinician-rated interview for diagnosing and assessing traumatic life events meeting

DSM-IV PTSD Criterion A.

Suicide and Homicide Screening Form is a structured, clinician-rated reliable interview modified from the *Psychiatric Research Interview for Substance and Mental Disorders- PRISM* (Hasin, Trautman, Miele, Smith, Samet & Endicott, 1997).

Mini-Mental State Exam (MMSE) a widely-used, clinician-rated measure of several key domains of intellectual function including orientation, attention-concentration, short-term recall, fund of knowledge, language, visuospatial organization and visuomotor ability, and spontaneous mental processing. A criterion of less than or equal to 21 will be used as the cut off for study exclusion.

Prior and Concomitant Medications Form (PCM) will be used to document pre-existing and concomitant medications that a participant takes during the study.

Inclusion/Exclusion Form will be completed by the RA/IA to document eligibility and reasons for ineligibility.

Randomization Form will be completed by the RA only to document group assignment.

8.4.1.2 Primary Outcomes

Clinician Administered PTSD Scale (CAPS-Part II) measures frequency and intensity of signs and symptoms of PTSD and overall symptom severity over time and has been designed to be used as a measure of DSM-IV PTSD diagnosis (which will determine final study eligibility) and treatment outcome.

Urine Drug Screen will test for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, methadone, morphine (opiates), PCP THC, and TCA (Tricyclic Antidepressants). Rating of outcome will consist of the ratio of positive/negative urines corrected for time since last assessment.

Saliva test will assess for recent alcohol use. Rating of outcome will consist of the ratio of positive/negative saliva tests corrected for time since last assessment.

Substance Use Inventory (SUI) consists of a series of self-report questions about quantity (i.e. in dollars spent per day) and frequency (i.e. in days) of various substances used over the time period of the past week. Craving intensity is also assessed. This method adapts the Time-Line Followback Assessment Method for alcohol use first used by Sobell et. al (1980). Substances include: opiates, cocaine, alcohol, marijuana, amphetamines, sedatives, PCP, and prescription medications.

8.4.1.3 Secondary Outcomes

Addiction Severity Index (ASI-Lite). The ASI is a standardized, multidimensional, semi-structured, comprehensive clinical interview that provides clinical information important for formulating treatment plans as well as problem severity profiles in six domains commonly affected in substance abusers. The domains covered are chemical abuse (alcohol and drug), medical, psychiatric, legal, family/social and employment/support. Composite Scores for each problem domain are derived mathematically. A revised version of the ASI Fifth Edition, 1997 version (ASI-CTN) that includes only those questions used to derive the composite scores along with some demographic information will be administered by a research staff member. Composite

scores will be calculated according to the procedures described by McGahan *et al.* (1982) and Carroll *et al.* (1994).

Risk Behavior Scale (RBS) is based on the Risk Assessment Battery (Booth et al., 1994). It is an interviewer administered questionnaire that assesses HIV risk behavior. Information on recent injection drug use and sexual activity are queried. There is no scoring associated with this assessment.

Clinical Global Impression Rating Scales (CGI) are 7 point Likert scales which will serve as a *clinician-rated* secondary measure of severity (a) use of cocaine, opiates, other drugs, and alcohol (b) PTSD symptomatology and (c) depression. Rating of response will use the average rating over the time period of the last four weeks prior to the end point under analysis, or over the time period of the last four weeks prior to the patient's last assessment, for drop-outs.

Non-Study Medical Services (NSMS) is a brief version of the interview eliciting the variety and intensity of services received during the past week. This instrument will be used to evaluate the secondary outcome of treatment adherence.

Post Traumatic Stress Disorder Symptom Scale-Self Report (PSS-SR) is a self-report inventory that assesses the frequency and severity of PTSD symptoms corresponding to DSM-IV diagnostic criteria.

8.4.1.4 Predictors of Outcome

Brief Symptom Inventory. The Brief Symptom Inventory (Derogatis, 1993) is a self-report scale that was developed from its longer parent instrument, the Symptom Checklist 90 (SCL-90), to assess for psychological problems. It includes 53 items, rated on a 5-point scale, with each item representing a symptom or a negative state of mind. Symptoms are scored along 9 primary dimensions: somatization, obsessiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Three global indices can also be obtained: *Global Severity Index*, Positive Symptom Distress Index, and Positive Symptom Total. Both test-retest and internal reliabilities have been shown to be very good for the primary symptom dimensions of the BSI. Factor analytic studies of the structure of the scale support its construct validity.

Non-Study Medical Services (NSMS – described above) will also be used to evaluate exposure to diffusion/contamination, as well as to determine potential covariates during statistical analysis of the data. **In addition, a trauma specific treatment question was added.**

Prior and Concomitant Medications Form (PCM - described above) is also used to document concomitant treatment and will be used to record psychotropic medications that a participant takes during the study.

Addendum contains gender specific questions covering physical health and psychosocial areas not covered in the other standardized assessment forms.

Eating Disorder Examination Questionnaire is a 38-item, 7-point scale assessing the frequency of key behavioral features such as binge eating and self-induced vomiting and associated eating disorder pathology. (optional assessment)

8.4.1.5 Safety Measures

Adverse Events Log (AE Log) is a source document used to record the occurrence of adverse events during study participation.

Adverse Events Form (AE CRF) will be used to document the occurrence of any study-related and/or serious adverse events during study participation.

Serious Adverse Events Form (SAE Form) will be used to document the occurrence of serious adverse events during study participation in more detail.

Serious Adverse Events Summary Report (SAE Summary Report) contains demographic information and event narrative. It is completed by the study clinician (MD, Ph.D., PI).

8.4.1.6 Process Measures

Helping Alliance Questionnaire (HAQ-II-C/T). Defined by Bordin (1979) as consisting of agreement on goals, agreement on tasks, and development of bonds between therapist and participant, the therapeutic alliance has proven to be a promising variable for predicting outcome from psychotherapy for substance abuse (Connors, Carroll et al., 1997) and other disorders (Horvath & Luborsky, 1993). In this study, the revised Helping Alliance Questionnaire (Luborsky et al., 1996), a well-validated measure of this construct will be completed by each participant at weeks 2 and 6 (and may be done at week 3 and 1-week post treatment respectively) and by counselors for any week they have a participant in treatment week 2 or 6.

Participant Feedback Questionnaire At the end of treatment participants will complete this brief questionnaire that asks them to rate the overall helpfulness of the intervention they received as well as the helpfulness of each of the specific topics covered.

Post Treatment Therapist/Supervisor Focus Group. As soon as possible after the final intervention sessions are completed at a given site, a focus group should convene with the 2 therapists (SS/WHE) and the 2 supervisors (SS/WHE) to 1) process the experience of participating in the study, and 2) discuss elements of the treatments and the potential for continuation of the treatments within the CTP. The focus group should last approximately 90 minutes and be facilitated by an individual at the node or CTP level designated by the site team.

8.5 Research Assistant/Independent Assessor Training

Training Plan: Because the nodes are responsible for providing core training, the core training component will not be described here. The Lead Node will provide centralized protocol-specific assessment training for the Research Assistant (RA) and **blinded** Independent Assessor (IA). The RA/IA's will be female individuals in an appropriately related field with some clinical and research training. Additionally, the IA must be able to conduct a diagnostic interview and make other clinical decisions. There should be no differences between RA and IA in supervision, but the IA must, to the extent possible, be blind to participant treatment condition throughout the course of the study. Each will receive training on the assessments relevant to their roles on the project.

During protocol specific training the RA, IA and Research Coordinator will receive training on all study measures. Thus, although the RA will not administer the CAPS part 2, any other baseline interviews or counselor assessments, RAs will generally have responsibility for checking the completeness and accuracy of all CRFs and, thus, need to have a good understanding of all study measures. IAs, although not primarily responsible for conducting screening assessments, will be trained to administer them since IAs may perform screening assessments as needed at individual sites. IAs, however, will not be trained on specific randomization procedures in order to help ensure that they remain blind to this process. Finally, the research supervisory staff (Research Coordinators) will complete all of the protocol specific modules to ensure that they can provide appropriate supervision and, if necessary, serve as a back-up for the RA.

Reliability of PTSD diagnosis will specifically be monitored for all IAs following standard procedures, including individual on-site supervision and teleconference supervision. The LI training team will determine reliability of diagnoses by reviewing 10% of all baseline and 10% of all follow-up CAPS-Part 2 assessments. Kappa's on diagnosis and ICC's on severity will be computed between IA and expert ratings. Raters should have a .70 level of agreement. If agreement levels fall below .70, the IA supervisor will conduct joint rated interviews with the IA until a .70 level is achieved in three consecutive interviews.

Ongoing training and supervision will be provided by the IA supervisors (Research Coordinator) and the Lead Node training team via biweekly protocol teleconferences. Specific information about training materials and staff turnover can be found in the Training Plan.

8.6 Prevention of Study Drop-outs

We plan to conduct extensive outreach efforts so participants are not lost at key assessment points. RA's will provide reminder calls and contact participants and other contacts on a regular basis to keep participants engaged and to track and document any changes in living situation or status that will facilitate follow-up. We also plan to provide options for participants who are unable or unwilling to come to the CTP for follow-up assessments to be interviewed in their homes, at a designated public location or over the telephone. Independent assessors will conduct all follow-up assessment interviews.

8.7 Post Treatment Follow-up

At the end of the approximate 6-week therapy administration period participants will be assessed again using the same measures given at the baseline interview at 1-week post treatment. Participants will then be asked to come back at 3 months, 6 months and 12 months (post-treatment) for additional follow-up assessments that will consist of these same measures (See Table 1). All post treatment follow-up interviews will be

scheduled based on the last day of treatment, that is the day after their last treatment session will start the follow up count, unless the participants did not attend any treatment groups in which case the follow-up dates are based on the randomization date. The 3-month follow-up needs to be scheduled 12 weeks after the date of the last treatment session. The 6-month follow-up needs to be scheduled 24 weeks after the date of the last treatment session. The 12-month follow-up needs to be scheduled 48 weeks after the last treatment session. There are windows of opportunity for completing the post treatment follow-up interviews. Once a window has closed, that interview should not be completed and contact procedures should begin for the next interview. There is a 5-week window for the 1-week follow-up, an 8-week window for the 3-month follow-up, and a 12-week window for the 6 and 12-month follow-ups.

8.8 Participant Reimbursement

Participants will be compensated with cash or scrip (cash equivalent in retail vouchers or coupons) as follows: $20 in scrip or cash upon completing the screening ($20x133=$2,660), and on completing the baseline interview ($20x67=$1,340) procedures. At each follow up assessment, it is suggested that compensation increase by $10 for every time point so that upon completing the 1-week post-treatment follow-up assessment participants will receive $20 in scrip or cash ($20x60=$1,200), upon completing the 3-month follow-up assessment participants will receive $30 in script or cash ($30x60=$1,800), upon completing the 6-month follow-up assessment participants will receive $40 in script or cash ($40x60=$2,400), and upon completing the 12-month follow-up assessment participants will receive $50 in script or cash ($50x60=$3,000). However, with Lead Node approval, each site may decide on alternate follow up incentive amounts based on their location’s specific requirements. In addition, participants in each treatment group will receive $10 in scrip or cash following the completion of each weekly self-report assessment ($10x60x6=$3,600). Thus, the maximum amount that any individual subject can receive is $240 if they complete the entire study. Sites may also use other minor stipends to assist participants with transportation, childcare or other potential barriers to participation as necessary.

8.9 Participant Confidentiality

Procedures to assure confidentiality will be strictly observed. All data will be 1) kept in confidential locked files; 2) identified by subject number only; and 3) kept separately from identifying information used for subject tracking and follow-up contacts. Identifying information will be kept in separate locked files. No identifying information will be disclosed in reports, publications or presentations. As an additional safeguard of confidentiality, the investigators will obtain a Federal Certificate of Confidentiality from NIH.

9.0 ASSESSMENT AND REPORTING OF ADVERSE EVENTS

An adverse event is defined as any reaction, side effect, diagnosis or untoward event that either a) occurs during the course of the clinical trial and was not present at

baseline; or b) was present at baseline and appears to worsen during the study. All AE's will be assessed by the study clinician (MD, Ph.D., PI) from baseline through the last follow-up assessment at 12-months. During weekly assessments the RA will inquire about AEs and complete an AE CRF for each participant. In the event that the participant is experiencing a worsening of symptoms, the RA will inform appropriate study and clinical staff. The Study Clinician and the participant's counselor should determine if the AE places the participant at risk if study treatment is continued. The distribution of severity codes within each intervention condition will be compared.

The risks expected from trials employing behavioral interventions are presumed minimal relative to pharmacologic interventions. However, for this trial specifically, the population studied is a vulnerable population and possibly high risk given the nature of the disorders, i.e. SUD and PTSD. Participants are seeking treatment for their SUD and are approached for consideration for being enrolled into this study, which specifically screens for a PTSD diagnosis. Risks of invoking clinical deterioration and psychologic/psychiatric decompensations must be anticipated. Thus, in accordance with OHRP and NIH requirements for human subject protection, the collection and reporting of AE/SAEs are specified below.

All adverse events, with the exception of clinically insignificant events and minor common illnesses and injuries (e.g., cold/flu, scrapes, upset stomach, low-grade headaches) will be documented on the *AE Log.* The AE Log is a source document and this information will not be entered into the study database. The study clinician (MD, Ph.D., PI) will regularly review the AE Log. Any AEs determined to be serious and/or study-related by the study clinician will require the completion of an *AE CRF*. The RA/IA may gather much of the information but a clinician must review the CRF information, make all medical determinations and sign the CRF. If an AE is determined to be serious, an *SAE Form* and an *SAE Summary Report* containing demographic information and the event narrative must also be completed and signed by the study clinician.

During protocol specific training procedures for AE identification, collection and reporting will be reviewed in detail. Training will cover definition and grading of AEs, criteria for an AE to be considered serious, how and when to complete the AE Log, AE CRF, SAE Form, and the SAE Summary Report (narrative) and where and when to report this information.

Study staff will be trained to provide crisis intervention and referral as is standard operating procedure within each CTP for such situations, should they become dangerous or life-threatening (i.e. suicidal ideation or attempts). The local Node Protocol Manager and a covering study clinician (MD, Ph.D., PI) will be available to respond to a need for consultation within 24 hours in order to fully assess untoward reactions or severe symptoms, including suicidality. In addition, all study assessments contain modules concerning psychoeducation and coping strategies that can alert the study staff to evolving risk.

9.1 Assessment of Adverse Event Severity and Relationship to Treatment

Adverse events will be categorized using severity codes of mild, moderate or severe. In this protocol potential study related AEs include 1) worsening of PTSD symptoms, 2) worsening of SUD symptoms, and 3) worsening of depressive symptoms. For this reason, participants will be assessed weekly on current symptom measures of PTSD and SUD (PSS-SR and SUI) to observe any signs of severe symptoms of SUD, PTSD, depression (PSS-SR also measures some overlapping depression symptoms). Additionally, participants are advised to observe any signs of worsening PTSD, SUD and depression symptoms and to discuss these with study staff. If the level of symptom worsening becomes dangerous or life threatening (e.g. drug overdose or suicidal ideation or attempt, any symptom worsening requiring inpatient hospitalization) these will be classified as SAEs and require further documentation (See section 9.3 below). Study staff will be trained to provide crisis intervention and referral for such situations. In addition, all study assessments contain modules concerning psychoeducation and coping strategies that can alert the study staff to evolving risk. In the case that a participant is worsening over the course of treatment, consideration for early termination or study discontinuation will be conducted following procedures outlined in Section 5.

9.2 Monitoring Adverse Events

Monitoring of known adverse events will be conducted by Protocol PIs, Study Project Managers, NIDA liaison and Members of the DSMB.

9.3 Definition and Reporting of Serious Adverse Events

Each Adverse Event will be categorized as serious or not. Serious adverse events are defined as any fatal, life-threatening, permanently and/or substantially disabling condition; or one that is a congenital anomaly, requires an initial hospitalization or prolongs a hospitalization, or is an event which requires intervention to prevent permanent impairment or damage. Note that all hospital admissions will be considered an SAE (this includes normal pregnancies and pre-planned medical procedures). Emergency room visits, however, should not be considered SAEs unless there is a resulting hospital admission. The designated study clinician (MD, Ph.D., PI) should be consulted if questions arise as to whether an AE should be categorized as serious. **Any Serious Adverse Event which does occur during the course of study must be reported within 24 hours to the NIDA Medical Officer and to the Lead Investigator.** Initial notification of an SAE is to be followed by submission of the Serious Adverse Event Form within 24 hours to the above individuals. The study clinician (MD, Ph.D., PI) will be responsible for generating an SAE Summary Report which includes a brief narrative and description of the SAE. Within 14 days the AE CRF, SAE Form and SAE Summary Report should be sent to the NIDA Medical Officer, Lead Investigator, Lead Node Project Manager, Lead Node PI, Protocol PI, & Local Node PI, and Local Node IRB (In accordance with local IRB requirements). Failure to comply with reporting requirements can result in serious negative consequences, including criminal and/or civil penalties.

9.4 Reporting of Subject Death

Subject death will be reported by the Node and Study LI following SAE guidelines as described above.

9.5 Known Adverse Events Relating to the Underlying Clinical Condition

Exclusion criteria are designed to minimize the psychiatric and medical risks to the subjects, such as those who are acutely suicidal or require medication intervention. The study assessments and interventions consist of techniques that have been widely used in similar forms with comparable populations with minimal problems for the subjects. Previous research experience suggests that subjects generally perceive these discussions positively. There is, however, some risk that discussing sensitive topics, especially drug use and trauma, will cause distress in some subjects. Women may become emotionally fatigued or stressed during the interviews. Yet these risks do not exceed those which are a normal part of any clinical interview or treatment session. The use of individual assessment procedures has not been shown to be either harmful or directly helpful to psychiatric/substance abusing patients. All clinical interviewers and research therapists will be trained to assess for level of distress and will be attentive to patient's needs. Appropriate breaks will be given, and if necessary, additional support at the end of the interview or session.

Participants who do become emotionally stressed will be encouraged to talk to their counselors and interviewers about their feelings. In the event that any subject is assessed to be in need of extra support, appropriate referrals will be given. At each site, there will be a well-established protocol for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or other acutely distressed patients. The Protocol Manager and a covering study clinician (MD, Ph.D., PI) will be available within 24 hours for consultation about untoward reactions or severe symptoms, including suicidality. Participants can be evaluated at any time should that prove necessary.

9.6 Data Safety Monitoring Board

NIDA's DSMB will review the data of enrolled patients on a regular basis to advise on implementation of the protocol, to examine safety data, to make recommendations for a discontinuation of study for an individual patient based on adverse experience or to recommend early termination of the trial because of safety issues.

10.0 DEPARTURES FROM PROTOCOL

All departures from protocol will be documented following appropriate CTN SOP forms, as well as Node-specific IRB reporting requirements.

11.0 STATISTICAL ANALYSIS

11.1 Objectives of Analysis

The data analysis will be guided by the specific hypotheses of the study. This trial is intended to test the effectiveness of SS and WHE as an adjunct to Treatment-as-Usual on the primary outcomes of substance use abstinence and PTSD severity for women with comorbid substance use disorders and PTSD. The secondary objectives of this effectiveness study is to examine the impact of enhanced treatment on: (1) retention in substance use treatment (2) secondary measures of substance use and PTSD outcome; (3) measures of psychiatric severity; (4) measures of HIV sexual risk behaviors. We will also explore delivery of drug abuse treatment for women by examining various characteristics of the sites (CTPs) for their potential effect on the efficacy of the intervention and on the retention of subjects in treatment. In addition, in an exploratory fashion we will study the effect of various baseline demographic and diagnostic characteristics on the inferences made for the primary hypotheses.

11.2 Efficacy Measures

Primary Efficacy Measures

There are two primary efficacy measures for this study, one for drug abuse and one for PTSD. Abstinence from drug of abuse, defined using self-report, and urine/saliva-confirmed results, will be the primary efficacy measure for drug abuse. The total score from the CAPS part 2 will be the primary efficacy measure for PTSD. Self-report of drug use and urine/saliva results are collected at baseline, weekly throughout the treatment phase of the study and at all follow-up time points. Only baseline and follow up data will be considered in the primary analyses. Abstinence from drug of abuse for a given baseline or follow-up time point will be defined as self report of no use during the prior month, a negative urine drug screen and a negative saliva for that visit. The CAPS part 2 is administered at baseline, end of treatment and all follow-up time points.

Because there are two primary efficacy variables being analyzed, each will be evaluated at the 0.025 level of significance. By testing each hypothesis at the 0.025 level, the overall type-I error rate will be controlled at 0.05.

Secondary Efficacy Measures

Retention in treatment, the ASI composite scores for alcohol and drugs, weekly scores from the PSS-SR, SUI and biological measures, and the overall drug craving severity score from the Substance Use Inventory, will be additional outcome measures.

Abstinence from drug of abuse for a given week during the treatment phase will be defined as self report of no use during the week, a negative urine drug screen, and a negative saliva alcohol screen; otherwise the subject will be considered not abstinent for that week. Weeks during which no information is available will be considered non-abstinent; and, will be handled by the analytic methodology.

Additional Predictors

The remaining ASI composite scores; summary scores from the NSMS; CGI interviewer assessments of drug use, PTSD symptoms, and psychiatric symptoms; the 9 primary

dimension scores and 3 global indices from the BSI; and gender specific variables from the Addendum will be additional measures.

11.3 Statistical Analyses

11.3.1 Intention to Treat and Minimal Treatment Analysis

The primary efficacy analysis will be based on data from all randomized participants ("intent-to-treat analysis" participants).

A confirmatory analysis will be based on data from all randomized participants who completed at least six of the twelve sessions (SS or WHE) -- minimal treatment analysis.

11.3.2 Missing Data and Dropout

For the analysis of the intent-to-treat sample multiple imputation methods will be used (Lavori, Dawson & Shera, 1995) for subjects who do not have any observations after baseline. In the analysis we will employ statistical methods (Mixed Effects Models, Diggle, Liang, & Zeger, 1994) that do not relay on complete observation from all subjects and thus all randomized subjects will be included in the analysis. The validity of the inference from these methods, however, depends on the assumption that missing and dropout occur 'at random' [Little and Rubin, 1989], i.e. the missingness/ dropout does not depend on the outcome that was not observed (because the subject missed a visit or dropped out completely); for example, if a urine test for abstinence is missing it is not because the subjects used substances prior to the urine collection, but it is for some reason not associated with substance use, such as her/his mother got ill and she/he was taking care of her at the time when the assessment was supposed to take place. The assumption of missingness/dropout happening 'at random' is usually untestable and it seems to be likely to be violated in our study. Therefore, we plan to conduct a sensitivity analysis in order to assess the sensitivity of the results from the hypotheses testing to this assumption. We plan to impute the missing data using several strategies (last observation carried forward, multiple imputation (using Solas [Solas™ 3.0 (2000) Statistical Solutions. Ltd. 8 South Bank, Crosse's Green, Cork, Ireland) and imputation of most conservative value, i.e. lack of abstinence when urine is missing) and to compare the results from the analysis on each of these data sets. Consistency of the inference from the hypotheses testing using each all of these data sets will lend validity to results. Lack of consistency will obscure interpretation and explanation of the findings from the different methods of accounting for missing data and dropout.

11.3.3 Significance Testing

All tests performed will be two-sided and significance will be judged at level α=0.05 everywhere, except for the two primary hypotheses concerning the outcome measures for substance use and PTSD severity. Each of the two primary hypotheses will be tested using the Holm's sequentially rejective test to determine level of significance.

11.3.4 Statistical Methods

Mixed Effects Models (MEMs) will be used to analyze continuous outcome measures. The statistical issues arising from clustering of subjects within a site requires appropriate statistical methods for analysis of clustered data, namely Mixed Effects Models (MEM). Mixed effects models are sometimes referred to as hierarchical models (Brown & Prescott, 1999; Bryk & Raudenbush, 1992). MEMs are also used to analyze repeated measurements of data over time (Diggle, Liang & Zeger, 1994). The repeated measurement on an individual over time are usually correlated and thus represent another cluster in addition to the clustering of subjects within a site. Also, the group nature of the therapy represents another cluster with correlated data. However, the groups have a rolling enrollment and are expected to have changing groups each week at the expected recruitment rate. The number of parameters needed to estimate the correlation for this cluster is expected to be large and thus clustering for therapy group will not be considered in the model.

The use of MEMs allows us to estimate the random effects corresponding to the participating sites and to explore the relationship between these random effects and site-specific characteristics, such as frequency or order of the therapeutic sessions. In addition, MEMs do not require complete data on all subjects. Incomplete or missing data are handled by the model, providing that the missing data are assumed to be "missing at random."

In all mixed effects models, site (or more explicitly, CTP) will be a random effect reflecting our desire to make a global inference among all CTPs, as opposed to treating them as fixed effects which would correspond to local inference related to only the particular CTPs used in the study. The estimated variance of the random effects corresponding to sites and site by treatment interaction will give a measure of the expected variability in the efficacy of SS between CTPs. PROC MIXED in SAS® [SAS Institute Inc. Cary, NC] will be used to carry out the MEM analysis.

The covariance structure for any particular model will be determined by modeling several possible covariance structures. For example, the course of an efficacy measure over time will be modeled as auto-regressive of order one, compound symmetry, and unstructured. Selection of which structure to be used will be based upon review of both Akaike's Information Criteria and Schwarz's Bayesian Criteria. An auto-regressive covariance structure has the property that observations taken close in time are more correlated than observations taken further apart in time. A compound symmetric

covariance structure has the property that all observations are equally correlated, no matter how much time has elapsed between observations. Compound symmetry covariance structure is appropriate for modeling the correlation between subjects within sites and corresponds to a random effect for site. An unstructured covariance has no restrictions on the correlation between the repeated measurements; however, it does estimate many more parameters than the other two covariance structures and is often inefficient.

Generalized Log-Linear Mixed Models (GLLMM) (Lang & Agresti, 1994; Ten Have & Morabia, 1999; Tutz & Hennevogl, 1996) The GLLMMs are an analog of the MEMs for analysis of categorical and count data. They are appropriate for the analysis of categorical and count data in all situations where clustering and correlation between the observations is present. These situations are discussed above in the description of MEMs. The GLLMMs include the method of analysis Generalized Estimating Equations (GEE) described in the next paragraph. GLLMMs model both the marginal expectations (as GEE) and the associations due to repeated observations on a subject or clustering of subjects within sites or some other design feature.

Generalized estimating equations (GEEs) will be used to analyze binary outcome measures. The statistical issues arising from clustering of subjects within a site requires appropriate statistical methods for analysis of clustered binary data (Brown & Prescott, 1999). Generalized estimating equations allow for the analysis of binary data which may be missing for some subjects either because of a missed week or due to drop-out, thus complete information for all subjects is not needed. The GLIMMIX macro and PROC GENMOD in SAS® [SAS Institute Inc. Cary, NC] will be used to carry out these analyses.

Survival analysis. Time to dropout from therapy will be analyzed using survival analysis techniques. Survival analyses will be performed using a Cox Proportional Hazards model [Cox, 1972). The Cox proportional hazards model permits the evaluation of the effects of covariates in the analyses. The survival distribution functions will be estimated using the Kaplan-Meier estimator and the results will be plotted for graphical presentations (Lee, 1992; Lawless, 1982).

χ^2 test for comparison of proportions. For the comparison of proportions in the two treatment groups, a Mantel-Haenszel chi-square analysis, controlling for (stratified by) CTP site will be used (Agresti, 1990).

11.4 Sample Size and Statistical Power

The sample size proposed in this study has been decided based on the treatment effects that have clinical importance and have been observed in preliminary studies.

Power computations for detecting differences with respect to abstinence.
The abstinence outcome measure (urine/saliva confirmed self-report of abstinence in the last 4 weeks) was not assessed in the pilot study of SS, reported in 1.1.2.1. The

abstinence measure that will be used in the proposed study has been previously used in a clinical trial of drug treatment for depressed cocaine users [Ned Nunes (2001) personal communication]. The observed abstinence rates in this clinical trial were between 10 and 15%. The power computations for this outcome measure are based on these rates. We assume that the abstinence rates between sites will differ and the magnitude of the difference between sites will correspond to odds ratios ranging from 0.4 to 2.4 (for example, if the abstinence rate in one site is 9% and in the other is 20%, the odds ratio between the sites is 2.4). We also assume that the response rates in the WHE+TAU group will not exceed 15%. The table below gives the overall odds ratio odds(abstinence|SS+TAU)/odds(abstinence|WHE+TAU) for which there is at least 80% power of a significance test with α=0.025.

Table 3. Odds ratio for abstinence SS+TAU vs. WHE+TAU that can be detected with 80% power of a significance test with α=0.025, assuming the response rates between the 8 sites vary.

Response in the WHE+TAU group	5%	10%	15%
odds(abstinence|SS+TAU)/odds(abstinence|WHE+TAU)	2.9	2.3	2.0

Power computations for detecting differences with respect to frequency of substance use. In the preliminary study reported in 1.1.2.1 Clinical Efficacy the difference between SS and TAU (i.e. the treatment effect) with respect to substance use frequency was 0.45 (see Table 2). The observed standard deviation (square root of error variances) of this measure in both groups was almost the same (0.67 and 0.77 respectively). The design of the proposed study calls for the involvement of 8 sites (CTPs). In order to compute the required number of subjects recruited in each of these 8 sites, the between sites variance of the treatment effects is needed. This variance is not available so we need to make some assumption regarding this variance. Unfortunately, the scientific literature reporting results from multi-site studies rarely reports the values of between centers variation of the estimated effects and information of this variation for the measures that will be used in our study is completely absent. However, statistical investigations regarding multi-site variability in treatment differences suggests that this variation is usually small compared to the within site variation of the outcome measure (Donner, Brown, & Brasher, 1990; Gail et al., 1996; Raudenbush & Liu, 2000).

Therefore, we assume that the between sites variation in the treatment difference is 5%-10% of the within site variance of the outcome measure. In terms of standard deviation this translates in assuming that the between sites standard deviation of the treatment effect is between 20% and 30% of the within site standard deviation in the outcome measure. For example, if the standard deviation of the outcome measure is 0.77, the standard deviation of the between sites treatment effect is allowed to be as large as 0.3 *0.77=0.23. In addition, we assume that the within site variances of the outcome measures are the same for all 8 sites. If this later assumption is not made, a design with different number of subjects per site would be a more efficient design; information about differences in the outcome measure between sites, however is not available so we compute the sample size per site under these two assumptions: 1) between sites

variation in treatment differences is between 5% and 10% of the within site variance of the outcome measure; and 2) the within site variation of the outcome measure is the same across all sites. Sample size is estimated for detecting treatment effects equal to the treatment effect observed in the pilot study (0.45) and a bit smaller, but still clinically meaningful (0.4). Table 4 below gives the number of subjects in each of the 8 sites needed in order to have 80% power to detect the specified treatment effects with a significance test with α=0.025 (this level of significance is chosen in order to account for the two main outcome measures: substance use and PTSD symptoms). The sample size is computed using formulas given in Brown & Prescott (1999), and in Raudenbush & Liu (2000).

Table 4: Number of subjects per site necessary to detect differences between the two treatments with respect to substance use measure as a function of the variance of the substance use measure within site (σ^2) and the variance of the treatment effect between sites (τ^2). Sample size is computed for power 80% of significance test with α=0.025.

	Treatment effect=0.40					Treatment effect=0.45				
	τ					τ				
σ	0.14	0.15	0.17	0.19	0.20	0.14	0.15	0.17	0.19	0.20
0.70	40	44	60	104	172	28	28	36	48	56
0.75	44	52	68	116	196	32	32	40	52	64
0.80	52	56	76	132	220	36	40	44	60	72
0.85	56	64	88	152	252	40	44	52	68	84

This table can be used in the following way. Suppose the common within site standard deviation of the outcome measure is 0.80 and the standard deviation of the treatment effect between sites is 0.15. If the true treatment effect is 0.4, then we need 56 subjects in each of the 8 sites in order to have 80% power of a significance test with α=0.025 to detect the true treatment effect. If the true treatment effect is 0.45, then we need only 40 subjects per site. From this table the strong effect of both the treatment effect and the between sites variance of the treatment effect are apparent. If the variance of the treatment effect between sites is large, increasing the number of subjects per site will not increase the power appreciably; in such case, increasing the number of sites is more beneficial. Allowing the between sites variance of the treatment effect to be 10% of the within site variance of the outcome measure corresponds to between sites variations observed in other multi-site studies of effectiveness and evidence-based practices implementation experiments. Thus, with 60 subjects per site we have assured adequate power for our main hypotheses.

Power computations for detecting differences with respect to severity of PTSD symptoms. In a similar way, we estimate the number of subjects recruited in each of the 8 sites to ensure sufficient power for the second primary hypothesis. Table 5 is modeled after Table 4. The treatment effect with respect to PTSD symptoms observed in the pilot study is 0.27 at the end of the treatment and 0.53 at 6 months follow up. The observed standard deviations were between 0.56 and 0.71. Allowing for the between sites variance of the treatment effect to be between 5% and 10% of the within site

variance of the outcome measure, results in a between sites standard deviation for the treatment effect between 0.11 and 0.21. If the treatment effect is only 0.25, however, such variation between sites will make it impossible to detect the treatment effect with only 8 sites. That is why, for treatment effect 0.25 we have computed the number of subjects needed to be recruited in each of the 8 sites assuming smaller variability between sites – allowing it to be only about 1% of the within site variance, i.e., the between sites standard deviation is assumed to be between 0.05 and 0.1. If the between sites variability in treatment effect is larger, there will not be sufficient power to detect treatment effect as small as 0.25. For treatment effect 0.4, the between sites variation is allowed to be as large as 10% of the within site variation of the CAPS measure.

Table 5: Number of subjects per site necessary to detect differences between the two treatments with respect to PTSD severity measure as a function of the variance of the substance use measure within site (σ^2) and the variance of the treatment effect between sites (τ^2). Sample size is computed for power 80% of significance test with α=0.025.

	Treatment effect=0.25					Treatment effect=0.40				
	τ					τ				
σ	0.02	0.03	0.04	0.05	0.06	0.14	0.15	0.16	0.17	0.18
0.55	36	36	38	40	44	24	26	30	36	46
0.60	42	44	46	48	52	28	32	36	44	54
0.65	50	50	52	56	60	34	38	42	50	64
0.70	58	58	62	64	70	38	44	50	58	74
0.75	66	68	70	74	80	44	50	56	68	64

From Table 5 it is evident that with 60 subjects recruited from each of the 8 sites, there will be sufficient power to detect treatment effect as small as 0.25, provided that the between sites variance of the treatment effect is no larger than 1% of the within site variance of the PTSD severity outcome measure. If the variability of the treatment effect between sites is larger, there will not be sufficient power to detect treatment effect equal to 0.25. For larger treatment effects, such as observed at 6 months follow up in the pilot study and even smaller, 60 subjects per site provide sufficient power of the test.

Using ANCOVA on the end score adjusting for baseline, instead of ANOVA without adjustment might increase the sensitivity by reducing the within site variance of the outcome measure and thus increase the power of the tests. This gain in power however will have only limited advantage, because the between sites variation will not be affected by such approach. Identifying and adjusting for site-level characteristics that contribute to the between sites variation in treatment effect have the potential to decrease this variability. Such analysis, however, is going to be exploratory and will only benefit the design and execution of future studies.

The power computation were based on Brown & Prescott (1999)(pages 183-189), and in Raudenbush & Liu (2000) and were performed programming the procedures in Splus.

The following presents our expectations at each CTP site for patient flow throughout the entire study and assessment period.

- 133 women will meet initial criteria on the Prescreening form.
- •50% (N = 67) of these women will meet PTSD or subthreshold PTSD and qualify based on the Screening Assessment.
- 90% (N = 60) of these women will be randomized to study treatments.
- 30% (N = 42) attrition rate over the 12-month FU

This will result in an Intent to Treat sample size of 480 participants and a final sample size (all data points) of 42X8 CTP's=336 or 168 per group.

Power computations and sample sizes for detecting treatment vs. control differences using a fixed effects model. The power computations presented above in the protocol corresponded to testing hypotheses based on coefficients of mixed linear and generalized linear models that treat sites as random effects. The use of random effects models allows for making global inferences regarding the efficacy of the experimental intervention compared to the control, referring to the population of *all sites*. When the efficacy hypotheses are tested on the basis of models that treat the sites as fixed (rather than random effects), the scope of the possible inference becomes narrower – conclusions about the efficacy may be drawn only to the study sites and not generalized to the whole population of sites. Such inference is called *local* in contrast to *global* inference.

The benefit of a fixed effects model in contrast to a random effects model with respect to the current project is that by applying a fixed effect model, we would able to have the same power to detect experimental/control differences at the same planned significance levels with fewer participants. In the event that fewer than the eight sites remain in the study, we will apply the fixed effects model to our data analytic plan in order to insure statistical conclusion validity.

Below are presented effects that can be detected with 80% power of two-sided significance test with alpha=0.05 when only 6 sites (or N=360) participate in the study and models treating site as fixed effects are used to test the efficacy hypothesis.

This further analysis is presented for the categorical outcome (odds ratios) of abstinence with the assumption that power for the continuous outcome variables (substance use and PTSD severity) will be greater.

For the purpose of this power analysis, we suppose that the probabilities of occurrence for the control groups are 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.11, 0.12, 0.13, 0.14, 0.15 respectively. Every subject will be observed four times at: 7 weeks, 3 months, 7 months and 1 year respectively. Further, we suppose that there is no correlation between different subjects within the same site (center), and that the within person correlation for the four observations of a subject to be 0.2, 0.25, 0.3, 0.35, 0.4, 0.45 and 0.5.

We calculate the odds ratios (experimental vs. control) in order to achieve 80% power of a test for differences between the two interventions. The method is from the formula on

p. 31, Analysis of Longitudinal Data, Second Edition, by P. J. Diggle, P. Heagerty, J.-Y. Liang and S. L. Zeger.

Table 6. displays the calculated odds ratios (experimental vs. control). The first row are probabilities of occurrence for the control group. The first column are the within person correlations. As can be seen, with a final sample size of 360, more than adequate power (corresponding to Table 3. above for the random effects models) exists to detect differences that significantly differ between the treatment and control groups. Again, note that power for the continuous outcome variables (substance use and PTSD severity) is expected to be greater.

Table. 6. Proportion of response in the control group

corr	0.05	0.06	0.07	0.08	0.09	0.1	0.11	0.12	0.13	0.14	0.15
0.2	2.1	1.99	1.92	1.84	1.8	1.75	1.72	1.7	1.67	1.65	1.63
0.25	2.16	2.03	1.95	1.9	1.84	1.8	1.77	1.73	1.7	1.68	1.67
0.3	2.2	2.1	2.01	1.93	1.88	1.84	1.8	1.77	1.73	1.72	1.7
0.35	2.27	2.16	2.05	1.99	1.93	1.88	1.84	1.8	1.77	1.75	1.72
0.4	2.34	2.2	2.1	2.03	1.97	1.92	1.88	1.84	1.8	1.79	1.75
0.45	2.39	2.25	2.16	2.08	2.01	1.95	1.92	1.88	1.84	1.8	1.79
0.5	2.44	2.29	2.2	2.12	2.05	1.99	1.95	1.9	1.88	1.84	1.82

11.5 Statistical analysis

11.5.1 Preliminary analysis

Prior to the analysis of the main hypothesis we will generate the appropriate statistical and graphic presentations (frequency distributions, histograms, scatterplots, box plots, codescriptives, etc.) of the distributions of values for each variable. These presentations will be used to detect potential outliers and possible data entry errors. For example, if a variable should only have values in the range of 0-3, but values of 99 are present we would question if a value of 99 were used as a missing value code.

11.5.2 Demographic and Baseline Characteristics

The number of participants enrolled into the study will be summarized by CTP site, treatment group, and by receipt of psychotropic medications. For participants who are screened but not randomized, a distribution of the reasons for non-randomization will be provided for each site separately and overall. Also, the distribution of reasons for dropout from the study will be summarized overall and for each site separately.

Treatment groups will be described with regard to baseline characteristics (e.g., age, sex, race, diagnosis, and receipt of psychotropic medications) using proportions when

the data are categorical or means and standard deviations when the data are quantitative. These descriptive statistics are being computed to describe the subjects in the different randomization strata (CTP, treatment group, receipt of psychotropic medications, and alcohol/illicit substance abuse and dependence).

The categorical demographic variables to be examined are: sex, ethnicity, and age group. The quantitative demographic variables to be examined are age in years, years of education, substance use in the past 30 days, as well as, use of substances during the participant's lifetime.

For Baseline efficacy measures, the following quantitative variables will be examined: the seven composite scores from the ASI (medical, employment, alcohol, drug, legal, family and psychiatric); BSI scores, baseline severity of substance use and PTSD, and severity of depression.

11.5.3 Analysis of Primary Efficacy Measures

Hypothesis 1: At the end of the treatment SS+TAU will be more effective than WHE+TAU with respect to substance use outcome and this response will continue to be superior during one year of follow-up.

This hypothesis will be tested using generalized log-linear models with random effects CTP site will be a random effect in the model. Treatment group, time and time-by-treatment group interaction will be fixed effects. The interaction between CTP site and treatment group and time will also be included in the model. Linear functions of time will be used to represent the course of drug use during the study; however if necessary, quadratic terms could easily be incorporated. We anticipate that there will be a significant interaction of treatment and time, which would correspond to difference in the decrease of symptoms over time between SS+TAU and WHE+TAU, which would result in a difference between the treatments at end of the treatment and at follow up. Time will be defined as number of days relative to randomization; information prior to randomization will have a negative value and information after randomization will have a positive number. Comparisons between the two groups will be made using contrast statements. Comparisons between end of treatment and each of the follow-up times will be made for each group separately using contrast statements. Estimates for treatment groups, and time-by-treatment group will be computed using estimate statements. Finally, the results will be translated from odds ratios to difference of proportions for interpretational purposes.

Hypothesis 2: At the end of the treatment SS+TAU will be more effective than WHE+TAU with respect to PTSD symptom outcome and this response will continue to be superior during one year of follow-up.

This hypothesis will be tested using MEMs as described under Hypothesis 1. Random effects for CTN will be included in the model. Treatment group, time and time-by-treatment group interaction will be fixed effects. The interaction between CTP site and

treatment group and time will also be included in the model. Linear functions of time will be used to represent the course of drug use during the study; however if necessary, quadratic terms could easily be incorporated. We anticipate that there will be a significant interaction of treatment and time, which would correspond to difference in the decrease of symptoms over time between SS+TAU and WHE+TAU, which would result in a difference between the treatments at end of the treatment and at follow up. Time will be defined as number of days relative to randomization; time prior to randomization will take negative values and randomization time will be at 0 for all subjects. Comparisons between the two groups will be made using contrast.

11.5.4 Analysis of Secondary Efficacy Measures

Hypothesis 3: At the end of the treatment SS+TAU will be more effective than WHE+TAU with respect to measures of retention in treatment and this response will continue to be superior during one year of follow-up.

The proportion of dropouts in the two treatment groups will be compared using Mantel-Haenszel chi-square test for independence with the sites being the strata on which the test conditions. In addition, the two treatment groups will be compared with respect to time to dropout from treatment using a Cox Proportional Hazards model. Treatment group will be a covariate in the model. CTP will be entered into the model as a stratification variable. Since survival analysis is based upon events occurring, the event of interest is time of discontinuation from treatment. Participants who drop out of treatment will be considered to have “the event of interest” at the time of their last clinic visit. Participants who complete treatment will be censored at that time.

Hypothesis 4: At the end of the treatment SS+TAU will be more effective than WHE+TAU with respect to secondary outcome measures for drug use, PTSD, and psychiatric symptoms and this response will continue to be superior during one year of follow-up.

The approach to testing this hypothesis will be as described for Hypothesis 2. The analysis will be done on all secondary outcome measures listed above.

Hypothesis 5: The superiority of SS+TAU as compared to WHE+TAU will be more pronounced among women with PTSD than among women with sub-threshold PTSD (SPTSD) and this response will continue to be superior during one year of follow-up.

Presence of PTSD or SPTSD will be used as a covariate in the analysis of the primary Hypotheses 1-4 above. Interaction terms between treatment and PTSD/SPTSD will be included in the models and the significance of these interactions will correspond to different treatment effects among participants with PTSD and SPTSD. We anticipate larger treatment differences between participants with PTSD than among women with sub-threshold PTSD.

11.5.5 Exploratory Analyses

This study offers the opportunity to explore several important questions related to the delivery and the efficacy of drug abuse treatment for women. We will explore various characteristics of the sites (CTPs) related to the delivery of TAU for their potential effect on the efficacy of the intervention and on the retention of subjects in treatment. Site characteristics that will be studied include: frequency and length of the TAU sessions; number of individuals in a therapeutic group; type of TAU therapy, such as self-help, psychotherapy, or addiction therapy; proportion of patients on medication; presence or absence (or amount) of gender specific intervention; and presence or absence (or amount) of trauma focused therapy. Hierarchical models (Bryk & Raudenbush, 1992), a special case of MEMs, will be used to study these characteristics. We are aware that with only 8 study sites there will be limited power for identifying important site-level factors predictive of outcome. The results from this analysis will be used for hypotheses generation and design of future studies.

In addition, in an exploratory fashion we will study the effect of various baseline demographic and diagnostic characteristics on the inference made for *Hypotheses 1-5*, by including these baseline factors in the models described above. Factors to be studied include severity, type, and duration of substance use and PTSD symptoms (and SPTSD vs. PTSD), use of psychotropic medications, ethnicity and group characteristics such as order of treatment sessions or number of individuals in group. In all of these analyses, we will explore potential effects by adjusting for the variable of interest and testing the significance of this effect with a 95% confidence interval. Finally, we will model the course of drug use and PTSD symptoms over time as a function of treatment, time and other time-varying psychological characteristics, such as those measured by SUI and PSS-SR.

Comparisons of baseline characteristics between those who complete the active phase of the study and those who do not will be performed. This comparison will be performed to determine if any characteristics differ between the two groups and to determine if there may be any predictors of early drop out that should be considered in future studies.

11.6 Analysis of Safety Measures

For each individual adverse experience, each participant will be categorized by the maximal severity reported during the randomization phase. Adverse experiences occurring during screening but ending prior to randomization, or those starting during screening and continuing into the randomization phase with the same or less severity will be excluded. All adverse events will be examined separately. The severity categories are: none (if the participant never had the adverse experience), mild, moderate, or severe. If a participant has an adverse experience more than once, then the adverse effect with most severe rating will be used in the analysis.

It may be necessary to group the individual adverse experiences before any analysis can be performed. If this is necessary, then the coding will be performed at the Long Island node. The Long Island node currently utilizes the Costart coding convention.

11.7 Interim Analyses

All studies meeting one or more of the following criteria must have an interim analysis plan included in the protocol that will allow presentation of efficacy data by treatment group to the DSMB on an ongoing basis:

- enrolling >1000 subjects (all treatment groups combined) or
- enrolling any number of subjects for > 6 months of active treatment or
- measuring deaths, serious adverse events, or significant morbidity as an efficacy outcome or
- testing a pharmacological treatment (including alternative dosage forms) not currently approved by the FDA for the treatment of the addiction under study

Since our study does not meet any of the criteria listed above, we have elected not to perform an interim analysis for the present study. Further, the rationale for this decision comes from consideration of two other issues relevant to the present study: first, that of harm and second, that of futility. From an ethical standpoint in a behavioral trial such as the one proposed, one credible reason to propose an interim analysis would be if there were a precedent for the expectation of harm to come to study participants (viewed as a group) as a potential consequence of study participation. In the case of the present study, given the treatment modality and content, no such presumption of harm can be made. In contrast to the so-called “trauma-processing” therapies which are known to increase short term distress in the process of therapy (ultimately leading to longer term reductions in PTSD symptoms), the Seeking Safety intervention—which focuses on providing psychoeducational strategies for managing distress and minimizing the “uncovering” of traumatic material—has not been shown to have any negative acceptability from either participants or therapists. All efficacy data point to reductions in distress levels at all points during the treatment. Moreover, we will assess for adverse events, and have clear-cut safety monitoring plans and safety analyses that will enable us to examine the potential for “harm” on an individual and group level during the course of the treatment trial.

The other issue for consideration with respect to presenting a rationale for conducting an interim analysis involves the potential of “futility.” The ethical perspective on this point is focused upon minimizing needless restrictions to patients that may be imposed by participation in a clinical trial. These restrictions may include adhering to rigid study protocol requirements, or subjecting participants to multiple, time consuming assessments when there is no evidence that direct benefits may be experienced by participants on a group level. Again, in the case of the present study, given that there is no evidence of harm through study participation, this ethical concern is somewhat minimized. Similarly, the course of treatment is relatively short (six weeks duration) and

participants receive reasonable and fair monetary reimbursements for all assessment time. Moreover, because of study participation they stand to benefit in that their therapists and therapists' supervisors will all be receiving ongoing clinical training and supervision, above and beyond that which is provided at their CTP site. Thus, in both study treatment conditions, for the period of study participation, we expect that on average participants will be receiving a high level of care. This expectation of benefit also outweighs concerns about futility.

However, should the DSMB recommend an interim analyses, we will amend the protocol to set forth prospective rules for such an analysis following guidance from the DSMB.

12.0 STUDY TIMETABLE

Estimated study start date	1/1/2004
Estimated date when 50% of subjects will be completed	6/1/2004
Estimated study end date	**12/31/2006**

13.0 DISCONTINUATION OF STUDY

The study may be terminated at any time if, in the opinion of the investigator, the IRB, or the CTN Steering Committee, 1) continuation of the study would present a serious medical risk to the participants or 2) for other administrative reasons.

14.0 DISCLOSURE OF DATA

It is understood by the investigator that the information and data included in this protocol may be disclosed to and used by the investigator's staff and associates as may be necessary to conduct this clinical study. All proper HIPAA authorizations will be signed and filed in accordance with mandated federal regulations for protecting research participants' privacy.

15.0 ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

The ethical and regulatory requirements must be observed to comply with Principles of Good Clinical Practice for the conduct and monitoring of clinical investigations. By signing this protocol, the investigator agrees to adhere to these requirements. The study should be reviewed by the Institutional Review Board. Written informed consent is required for all subjects. The ethical and regulatory requirements must be observed to

comply with Principles of Good Clinical Practice for the conduct and monitoring of clinical investigations.

15.1 IRB Approval

Prior to initiating the study, the Principal Investigator at each study site will obtain written IRB approval to conduct both the counselor training and the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the Principal Investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials (Homework Sheets and Self-help Handout Material) given to the subject.

15.2 Informed Consent

The informed consent document provides a summary of the research study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant.

15.3 HIPAA Authorization

Following the newly mandated federal HIPAA regulations, authorizations will be provided to all research participants at the time of presentation of 1st level consent, as needed (see Section 8.2) which detail all potential risks of disclosure and individuals and organizations who may have access to participant research data.

15.4 Investigator Assurances

Prior to initiating the study, the Principal Investigator at each study site will sign a protocol signature page, providing assurances that the study be performed according to the standards stipulated therein. The original signed copy of this document will be sent to the Lead Investigator site for record keeping and a copy will be maintained in the site's regulatory binder.

15.5 Outside Monitoring

The NIDA-CTN Data and Safety Monitoring Board, NIDA-CTN contracted Clinical Monitors, representatives from the Lead Investigators Node, and Quality Assurance representatives from the participating Node, will be given access to facilities and records to review and verify data pertinent to the study.

15.5.1. Clinical Monitors

All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding

source documents for each subject. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to inform the sponsor of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and good clinical practice's guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals, more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will advise on storage of study records. All sites should anticipate visits by NIDA and the Lead Investigator's Protocol Team.

15.5.2 Quality Assurance

The Quality Assurance (QA) Subcommittee has developed a minimal set of standards to be used for each protocol. In general, 100% of the informed consent forms, 100% of Inclusion/Exclusion criteria for all participants, all case report forms for the first 10 participants, and all case report forms for participants experiencing a serious adverse event. In addition, the minimal standards require a review of all case report forms for a random sample of 10% of the remaining participants. The QA Subcommittee has also developed a standard monitoring report template that permits the randomization process to be reviewed at each monitoring visit to ensure that the protocol procedures are being followed. For this protocol, we will require that the randomization process be reviewed at each monitoring visit; and, a 100% review of all primary efficacy measures (substance use inventory, urine drug screens, saliva alcohol screens, and CAPS, Part 2).

16.0 DISPOSITION OF DATA

The Long Island Node Data Management Center (DMC) will coordinate data management activities and provide ongoing consultation and assistance to participating nodes through out the study. All procedures will be in accordance with the Standard Operating Procedures (SOPs) developed by the CTN Data Management & Analysis Subcommittee (DMAS). The DMAS SOPs are in accordance with the Food & Drug Administration regulations, which NIDA has adopted as the data collection and management standards for all CTN studies.

16.1 Lead Node Responsibilities

The Long Island Node Data Management Center will provide final Case Report Form (CRF) specifications for the collection of all data required by the study. While the study data content of the CRFs cannot be changed, it is understood that CRFs may be modified for incorporation into each participating node data management system as appropriate. The Long Island Node DMC will also provide data dictionaries for each CRF that will comprehensively define each data element. The data dictionary will specify missing, illogical, out of range, and inconsistent value checks for each data element as well as within-CRF logic checks and across-CRF logic checks. The data dictionaries provide the specifications necessary for each node to develop an automated data acquisition and management system that will be designed in accordance with standards established by DMAS. The Long Island Node Data Management Center will also provide specifications necessary to conduct data monitoring activities and meet the requirements of all other DMAS SOPs.

16.2 Data Collection

Data will be collected at the study sites on either electronic (paperless) or paper case report forms (CRFs). Forms completion instructions will also be provided for each CRF.

Each participating node Date Management Center (DMC) will coordinate the preparation of paper CRFs and the distribution of these CRFs to participating Community Treatment Programs (CTPs) within their node. These forms are to be completed on an ongoing basis during the study. Forms should be completed according to the instructions provided. Each node is responsible for maintaining accurate, complete and up-to-date records and for tracking CRFs for each participant. Paper CRFs must be completed legibly with black ballpoint pen. Any corrections must be made by striking through the incorrect entry with a single line using a ballpoint pen and entering the correct information adjacent to the incorrect entry. Corrections to paper CRFs must be initialed and dated by the person making the correction.

16.3 Data Submission, Editing and Monitoring

Completed forms/electronic data will be submitted to each participating node DMC in accordance with Data Timeliness and Completeness SOP established by the DMAS. Only authorized individuals, in accordance with each participating node's DMC policies, shall perform data entered into electronic CRFs. Corrections to electronic CRFs must be tracked electronically with time, date, individual making the change, both the old data value and new data value, and the reason for the correction. Each node DMC will implement comprehensive error checking and data management procedures as per the Error Tracking SOP established by DMAS. Data monitoring will be the responsibility of the DMC at each node. Data monitoring will be performed as specified in the Data Timeliness and Completeness SOP, Data Accuracy and Validation SOP, Participant Progress Monitoring SOP, and other data monitoring SOPs as published by the DMAS.

16.4 Automated Data Acquisition and Management Systems

Each node is responsible for the development of a comprehensive automated data acquisition and management system in accordance with guidelines and SOPs published by NIDA and DMAS. The Long Island node DMC is willing to discuss the use of the Long Island automated data acquisition and management system if it is not desirable or cost effective for a node to develop an independent data acquisition and management system.

16.5 Central Data Repository

Data will be transmitted by the participating node DMC to the NIDA central data repository on the 1st of every month. The Long Island Node DMC will receive aggregated data from the NIDA central data repository on a monthly basis for data completeness, timeliness and accuracy quality assurance review. At the completion of the study, all data will be transmitted from the NIDA central data repository to the Long Island Node DMC for data analysis and the development of the final study report. The Long Island DMC will conduct final data quality assurance checks and “lock” the study database from further modification in accordance with the Database Lock SOP developed by the DMAS. The Long Island DMC will send the final analysis dataset back to NIDA for storage and archive.

SPONSOR
NIDA will ensure that the trial will be conducted in compliance with the protocol and all necessary regulatory guidelines

_____

Betty Tai, Ph.D., Director, CCTN (or designee) Date

LEAD INVESTIGATOR
The Lead Investigator will supervise the overall conduct of the trial to ensure compliance with the protocol and all necessary regulatory guidelines

_____

Name/Signature Date

NODE PRINCIPAL INVESTIGATOR
The Node Principal Investigator will supervise the conduct of the trial within the Node to ensure compliance with the protocol and all necessary regulatory authorities.

_____

Name/Signature Date

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor and Lead Investigator except when necessary to protect the safety, rights, or welfare of subjects.

I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.

I agree to report to the sponsor and Lead Investigator adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.

I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, following reporting requirements of the local IRB. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I agree to comply with all the applicable federal, state and local regulations regarding the obligations of clinical investigators as required by DHSS, the state and the IRB.

_____

Protocol Principal Investigator Name/Signature Date

_____

Investigator #1 Name/Signature Date

_____

Investigator #2 Name/Signature Date

(Add additional lines / pages for further other Investigators)

17.0 REFERENCES

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18.0 AMENDMENTS

18.1 Not applicable