PROTOCOL: Treating Co-Occurring PTSD and Substance Abuse in High Risk Transition Age Youth

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SPECIFIC AIMS

The overriding purpose of the proposed project is to develop and conduct a pilot evaluation of an integrated treatment for co-occurring substance use and posttraumatic stress disorder (PTSD) among an extremely high-risk clinical population – emerging adults. Over the past few years, data have emerged indicating that emerging adults (aged 18-25) have higher rates of initiation and increases in substance use than any other age group (SAMHSA, 2009). Further, although this population experiences a range of mental health problems, PTSD has been identified as a particularly problematic psychiatric disorder for these youth, as it is linked to the development and exacerbation of substance use disorders (SUDs). Indeed, in a large-scale longitudinal study, transition age youth with PTSD were five times more likely than those without PTSD to develop a new SUD, even after controlling for other SUD risk factors, such as gender, ethnicity, education, and socioeconomic status (Reed, Anthony, & Breslau, 2007). PTSD also predicts higher relapse rates and poorer outcomes among individuals in treatment for SUDs (Kessler et al., 2005; Tomlinson, Brown, & Abrantes, 2004). Thus, substance use problems are highly prevalent among emerging adults, and the transition from experimental use to the development of a SUD is exacerbated by co-occurring PTSD symptoms. Nevertheless, **surprisingly little attention has been devoted to developing integrated SUD/PTSD treatment protocols for this age group.**

A majority of transition age youth with serious mental health concerns like PTSD will be arrested by age 25, and most will have multiple arrests, often with serious charges (Davis & Koroloff, 2007; Fisher, Silver, & Wolff, 2006). Further, among adolescent and young adult offenders, up to 49% meet criteria for current PTSD, and up to 73% meet criteria for a current SUD (see Vermeiren, 2003) as compared to the rates of 3.4% for current PTSD and 6.6% for current drug abuse disorders found in community samples of young adults (Tanner et al., 2007). Given the elevated single-disorder rates, the overall rates of SUD/PTSD comorbidity are also substantially higher in this subgroup than in community samples. **Therefore, development and validation of a SUD/PTSD treatment for this subgroup will target youth at the highest risk for this comorbidity and its negative sequelae.**

The integrated approach to treating SUDs and PTSD proposed in this application combines two evidence-based interventions for PTSD (**Prolonged Exposure Therapy**; Foa, Hembree, & Rothbaum, 2007) and SUDs (**Contingency Management**; Higgins, Silverman, & Heil, 2008). Results from multiple studies support the efficacy of these treatments. Recent studies have demonstrated the advantages of integrated approaches that target SUDs and PTSD simultaneously for comorbid populations (e.g., Back, 2010; Back, Brady, Sonne, & Verduin, 2006). The current study provides the opportunity to develop and evaluate an integrated SUD/PTSD treatment approach for emerging adults, a group that arguably demonstrates the greatest need for such a treatment. Delivering an integrated SUD/PTSD treatment to this high-risk population may present multiple challenges as a result of competing clinical needs (i.e., severe behavioral and psychosocial problems) and frequent involvement with the criminal justice system. Thus, the specific aims of the study are:

Aim 1: To develop and implement an integrated SUD/PTSD treatment that is developmentally appropriate and integrates evidence-based treatments for SUD/PTSD (Contingency Management, Prolonged Exposure).

Aim 2: To evaluate feasibility, acceptability, and safety of the integrated treatment among emerging adults and clinicians using qualitative and quantitative methods.

Aim 3: To conduct preliminary analyses exploring whether emerging adults who receive the intervention demonstrate improvement in key symptom domains. Specifically, 40 youth will be randomized to either the integrated treatment or standard care. Primary outcomes will include substance abuse and PTSD. Secondary outcomes will include criminal justice involvement, adaptive functioning, and other mental health symptoms.

The results of the study will have a **significant impact on public health** by informing treatments for co-occurring SUD/PTSD among justice-involved transition age youth, a group at the highest risk for these problems. Demonstrating the efficacy of an integrated treatment approach will provide a valuable clinical tool for community-based therapists to employ in the context of existing evidence-based treatments. Further, should compelling indications of efficacy be found and safety and acceptability be established, these aims will position the research to advance to an appropriately powered randomized controlled trial.

A. SIGNIFICANCE

Prevalence and consequences of substance use problems among emerging adults. Transition age youth (i.e., emerging adults, ages 18-25) represent the age group with the **highest rates of initiation of substance use, increases in substance use, and progression of substance use into substance use disorders** (Chassin, Flora, & King, 2004; Delucchi, Matzger, & Weisner, 2008; SAMHSA, 2009). Substance use plays a significant role in many serious problems during this developmental period, including suicide (SAMHSA, 2010), automobile accidents (Hingson, Heeren, Winter, & Wechsler, 2005), and other lethal events. Emerging adults with SUDs also have increased rates of risky sexual behavior, increasing their chances of contracting HIV and other STDs (King, Nguyen, Kosterman, Bailey, & Hawkins, 2012). Further, SUDs significantly impede successful negotiation of important developmental tasks of this transitional age, leading to increased rates of unemployment and job instability and decreased college attendance (Bray et al., 2000; Mangione et al., 1999). Finally, emerging adults with SUDs represent a greatly underserved population, with a high likelihood of "slipping through the cracks" as they transition from child to adult substance use service providers (Davis, Green, & Hoffman, 2009). **Thus, this group has a very high potential to present significant short- and long-term costs for individuals, families, and society.**

Comorbid SUDs and PTSD. Although emerging adults experience a range of mental health problems, PTSD has been identified as particularly problematic, predicting more severe and chronic substance use. In a longitudinal study of emerging adults, those with PTSD were **5 times as likely** as those without PTSD to develop a new SUD, even when controlling for possible confounding factors (Reed, Anthony, & Breslau, 2007). Further, among those in SUD treatment, PTSD is a complicating factor**, predicting high rates of relapse and low rates of treatment success** (Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Tomlinson, Brown, & Abrantes, 2004). Despite these sobering statistics, PTSD treatment is rarely offered in conjunction with evidence-based treatments for SUDs, and little attention has focused on developing and validating integrated treatments for emerging adults.

The group of emerging adults with the highest rates of SUD/PTSD comorbidity is those with justice system involvement. Almost half of adolescent and young adult offenders meet criteria for PTSD, and over 70% meet criteria for a SUD (Vermeiren, 2003), representing rates that are dramatically higher than those found in community samples of emerging adults (3.4% for PTSD, 6.6% for SUDs). These rates are not surprising given that 90% of justice-involved youth are exposed to at least one traumatic event in their lifetime, including high rates of physical and sexual assault, witnessed violence, and traumatic loss (Ford, Hartman, Hawke, & Chapman, 2008). Left untreated, offenders who abuse substances tend to engage in more severe delinquency, continue offending well into adulthood (Dembo, Wareham, & Schmeidler, 2007), and experience poor educational and occupational outcomes (Belenko & Dembo, 2003). Moreover, societal costs of SUDs are substantial. Annual costs for drug-related crime victims are $1.8 billion, with associated law enforcement and incarceration costs totaling $39 billion (NIDA, 2004). Further, justice-involved youth are very unlikely to receive an evidence-based treatment for SUDs (Chassin, 2008; Garland et al., 2005), and **no evidence-based approaches have been specifically tailored to treat SUD/PTSD in this group.**

Integrated Treatments for SUD/PTSD. Though SUDs and PTSD have been historically treated separately (often with the requirement of abstinence from substance use prior to treatment for PTSD), results of **recent studies suggest the advantage of an integrated approach** (see Back, 2010 for review). For example, a study of symptom change during treatment for co-morbid PTSD and alcohol dependence found that improvements in PTSD symptoms had a greater impact on improvements in symptoms of alcohol dependence than the reciprocal relationship (Back, Brady, Sonne, & Verduin, 2006), indicating the importance of targeting PTSD to improve substance use problems. Further, several promising integrated SUD/PTSD programs have been developed, and there is preliminary support for their effectiveness. Specifically, Concurrent Treatment of PTSD and SUDs with Prolonged Exposure (COPE; Killeen, Back, & Brady, 2011; Mills et al., 2012), which integrates an exposure-based treatment for PTSD and a cognitive behavioral approach to SUDs, has demonstrated safety, feasibility, and preliminary efficacy in treating adults with comorbid SUD/PTSD. In addition, Seeking Safety (Najavits, 2009), another cognitive behavioral approach to SUD/PTSD, has established effectiveness with adult populations (e.g., Morrissey et al., 2005).

Results of these studies highlight the importance of integrated approaches to comorbid SUD/PTSD and lay the groundwork for developing and validating treatments for high-risk emerging adults. Given the developmental features specific to this population (e.g., incomplete development of executive functions; Ernst, Pine, & Hardin, 2006; Yurgelun-Todd, 2007), the multiple psychosocial risk factors faced by high risk youth populations, and the

need for a treatment that is congruent with justice system requirements, it is expected that an approach that relies heavily on behavioral principles, as opposed to the cognitive emphasis of existing adult treatments, will be more effective for this population. Thus, **the current study aims to integrate and adapt evidence-based interventions for SUDs (Contingency Management) and PTSD (Prolonged Exposure)** to meet the needs of emerging adults, adapted to be congruent with the demands of justice system involvement (i.e., frequent drug testing, use of contingencies, collaboration with parole officers), which is frequently seen in this group. An effective SUD/PTSD treatment that could be used in this context would provide clinicians with the tools to treat this complex population and establish the building blocks to adapt SUD/PTSD treatments for other high-risk youth. **Given the high rates of SUD/PTSD in such populations and the deleterious effects of these problems on individuals and society, an evidence-based SUD/PTSD treatment for high-risk emerging adults has the potential for an enormous public health impact.**

B. INNOVATION

Focusing on a traditionally underserved, under-researched population that produces high costs

Other models for targeting comorbid SUD/PTSD were developed for traditional outpatient adult samples and may be limited in their applicability to high-risk youth given the stringent demands of the justice system. The proposed project focuses on treating individuals with complex comorbidities who: (a) make up a large proportion of those seen in community-based care; (b) are at the highest risk for deleterious long-term outcomes; and (c) produce the most significant societal costs. Specifically, this research targets co-occurring SUD/PTSD among justice-involved emerging adults. The specific foci on **justice involvement** and **emerging adults** are innovative:

- **Justice-involved** youth have very high rates of SUD/PTSD, yet there is a paucity of research on integrated treatments for this population. Though this study will not specifically recruit emerging adults from the criminal justice system, comprehensive assessments of past and current criminal justice involvement will allow for the examination of the impact of criminal justice involvement on treatment outcome.
- In addition, despite compelling evidence that **emerging adulthood** is a distinct age group with unique developmental goals (Arnett, 2000), almost no research has focused on interventions adapted for their needs. Adolescent treatments require substantial parental involvement and are inappropriate for use with emerging adults who are often transitioning from their family of origin to more independent living situations. Adult treatments fail to consider multiple developmental transitions faced by this age group (e.g., from family to independence; from formal education systems to higher education/work force).

Thus, designing integrated interventions adapted to meet the needs of this underserved, under-researched population is novel.

Extending integrated treatments for SUD/PTSD to high-risk emerging adults with multiple problems

Studies of adult outpatient populations have supported the hypothesis that integrated SUD/PTSD treatments are superior to sequential treatment that requires abstinence from substances prior to initiation of PTSD treatment (e.g., Back, Brady, Sonne, & Verduin, 2006). The proposed study will serve as the first step to extend the empirical evidence for this theoretical model to individuals in need of SUD/PTSD treatment while presenting with multiple problems (i.e., justice system involvement, significant psychosocial risk, additional comorbidities).

C. APPROACH

Preliminary Studies: This study builds on projects in which the candidate has had an active role.

Study 1: Longitudinal Study of Risk and Resilience among Low-Income Adolescents: As part of this NIMH-funded study (PI: Kobak), Dr. Zajac examined trauma exposure and mental health among low-income parents and their adolescent children (Zajac & Kobak, 2009; Kobak, Zajac, & Levine, 2009; Kobak, Zajac, & Smith, 2009; Kobak, Rosenthal, Zajac, & Madsen, 2007). Involvement in this longitudinal project afforded Dr. Zajac important experience with recruitment and retention of high-risk youth populations, conduct of statistical analyses for longitudinal research, and design and oversight of detailed assessment protocols.

Study 2: Prevalence and Correlates of Substance Use Problems among Youth: In this NICHD-funded study (PI: Kilpatrick) of a nationally representative sample of adolescents, Dr. Zajac collaborated on manuscripts focused on the prevalence and correlates of substance use, PTSD, and delinquency (Zajac, Ruggiero, Smith, Saunders, & Kilpatrick, 2011; Kofler, McCart, Zajac et al., 2011; McCart, Zajac et al., 2011; McCart, Zajac et al., 2012; Adams, McCart, Zajac et al., 2014). Results support the strong relationship between substance use and a range

of negative outcomes, including PTSD and revictimization. Further, this study provided Dr. Zajac with solid training in epidemiological methods and assessment approaches for SUDs and mental health problems in youth samples.

Study 3: Victimization, PTSD, and Substance Use among Teenage Mothers (intramurally funded; PI: Zajac): This developmental research examines the prevalence and correlates of victimization, PTSD, and substance use among teenage mothers through collection of detailed trauma history, substance abuse, mental health, and parenting assessments. Conduct of this study has added to Dr. Zajac's experience in recruiting youth populations, ethical conduct of research, IRB procedures, and use of detailed substance use measures.

Study 4: SUD and PTSD Outcomes in Multisystemic Therapy (MST) for Emerging Adults: Pilot studies of MST for Emerging Adults have focused on mental health, justice involvement, and vocational outcomes. However, examination of SUD and PTSD outcomes showed the need for additional treatment of these two problems. In a small pilot study of 11 youth, 4 (36%) met criteria for PTSD or subthreshold PTSD prior to MST treatment. Interestingly, at 12-month follow-up, 6 (55%) met criteria for full or subthreshold PTSD. In a larger ongoing trial, 9 of 23 (39%) met criteria for PTSD at baseline. Though data collection is still in process, 3 of 9 (33%) and 3 of 8 (37%) have continued to meet PTSD criteria at 1- and 4-months post-treatment, respectively. Similarly, in an ongoing study, 30 out of 38 (79%) youth had a substance use problem at intake, and 21 of 36 (58%) had continued substance use problems at discharge. These results indicate that, among justice-involved emerging adults receiving a treatment specifically adapted for this population, substance use and PTSD emerge as significant problems even after completion of treatment. Thus, there is a clear need for treatments that specifically target these co-occurring problems.

Overview of Design: The proposed research will adapt and integrate evidence-based interventions for SUD (Contingency Management) and PTSD (Prolonged Exposure) to target co-occurring SUD/PTSD among emerging adults. The execution of the project will take place in two steps and will adhere to procedures outlined in Stage I of the Stage Model of Behavioral Therapies Research (Carroll & Nuro, 2002), which focuses on initial manual writing, development of a training program and therapist adherence measures, and pilot feasibility/safety testing. An overview of the design is presented in the table below. In Step 1*,* Contingency Management and Prolonged Exposure will be integrated and adapted for use with this population, and training manuals and adherence ratings will be developed. In Step 2**,** a pilot feasibility trial of the treatment will be conducted through an substance use treatment clinic. If evidence of feasibility is found, data will be used to support a grant application evaluating the integrated SUD/PTSD treatment in an appropriately powered RCT (i.e., Stage II RCT). **Therefore, the project will result in three crucial products: 1) an adapted and integrated SUD/PTSD treatment for justice-involved emerging adults; 2) training materials and measures of therapist adherence specific to the treatment; and 3) preliminary data on feasibility, safety, and symptom reduction as a result of the intervention.**

Research Plan Timeline.

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<tr><th colspan="2">Year 1</th><th colspan="2"></th><th colspan="2">Year 2</th><th colspan="2"></th><th colspan="4">Year 3</th><th colspan="4">Year 4</th><th colspan="4">Year 5</th></tr>
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<tr><td colspan="2">Treatment development (Step 1)</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="4"></td><td colspan="4"></td><td colspan="4"></td></tr>
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<tr><td colspan="6"></td><td colspan="10">Participant recruitment and randomization (Step 3)
N = 40</td><td colspan="4"></td></tr>
<tr><td colspan="6"></td><td colspan="10">Assessments at baseline, post-treatment, and 3-month follow-up</td><td colspan="4"></td></tr>
<tr><td colspan="6"></td><td colspan="10"></td><td colspan="4">Data analysis, manuscript preparation, and grant submissions</td></tr>
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Procedure: Step 1, Treatment and Therapist Training Adaptation: Work on Step 1 will begin immediately upon receipt of the award and will include Dr. Zajac's training on evidence-based treatments for youth SUDs as well as completion of several critical tasks described in detail below, including integrating the SUD and PTSD interventions, tailoring the integrated treatment to meet the needs of emerging adults and to be appropriate for delivery in the context of justice system involvement, and development of training materials and an adherence measure for the integrated treatment. This process will take an iterative approach and will follow the steps of new treatment development outlined for Stage 1a and 1b behavioral therapy research (Carroll & Nuro, 2002).

Step 1a: Integration of SUD and PTSD treatments. Step 1a will involve integrating Contingency Management and Prolonged Exposure and specifying modifications for implementation with emerging adults. Prolonged Exposure was originally developed for adults, with multiple studies documenting its efficacy (see Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010 for a review). More recently, an RCT provided initial support for the efficacy of a Prolonged Exposure protocol modified for adolescents (Gilboa-Schechtman, Foa et al., 2010). Given that the developmental needs of emerging adults are likely to span adolescence and early adulthood, careful consideration will be given to which protocol is appropriate for this population, with expert input from the mentoring team. Similarly, versions of Contingency Management have been validated for both adolescents and adults. The adolescent version includes extensive caregiver involvement, whereas adult protocols focus on contingencies provided by the treatment program. In past studies of treatments for emerging adults (R34 MH081374; PI: Davis), the research team has noted low rates of caregiver involvement, despite substantial effort to engage social networks. Thus, the proposed project will utilize adult Contingency Management models. However, as Dr. Zajac will receive extensive training in a variety of treatments during the early stages of this project, she will be in an ideal position to consider alternatives to Contingency Management with the guidance of the mentoring team and substance abuse treatment experts.

Prolonged Exposure is a 10-session exposure-based behavioral treatment for PTSD based on Emotional Processing theory (Foa & Kozak, 1986), which proposes that pathological fear structures underlie the development and maintenance of anxiety disorders. The goals are to promote processing of the trauma memory and reduce distress and avoidance evoked by trauma reminders through four components: 1) psychoeducation; 2) breathing retraining; 3) in-vivo exposure (i.e., repeated prolonged exposure to anxiety-provoking people, places, or situations); and 4) imaginal exposure (i.e., repeated prolonged retelling of the trauma memory). Contingency Management procedures as specified by Petry and colleagues (2000; 2004) involve reinforcements for drug abstinence and withholding reinforcements when drug use occurs. An individualized menu is created using rewards that can compete with the client's substance use (e.g., gift cards from stores and restaurants). The client receives frequent random drug tests, an escalating reinforcement schedule for continuous abstinence,

and rapid reset to maintain motivation. The principles underlying Prolonged Exposure and Contingency Management are theoretically and logistically compatible (i.e., using behavioral principles to promote symptom reduction), making these treatments ideal for integration. Further, behavioral approaches are likely to best meet the needs of high-risk emerging adults due to their unique developmental characteristics, multiple psychosocial risk factors, and justice system-related requirements.

Step 1a will follow the stage model of treatment development specified by Carroll and Nuro (2002), which outlines seven sections integral to the development of a Stage I treatment manual. Dr. Zajac will take the lead on integrating the interventions with mentoring from Drs. Sheidow and Davis. Each mentor will review changes to the protocol and provide feedback. Dr. Zajac will integrate feedback, and the mentors will review the revised protocol. This process will continue until all mentors have agreed that the integrated protocol is: a) consistent with the Contingency Management and Prolonged Exposure models, b) developmentally appropriate, c) likely to meet the needs of the population, and d) meets the criteria specified by Carroll and Nuro (2002).

Step 1b: Specification of modifications for implementation with emerging adults. Modifications will be made to best meet the needs of emerging adults who are often involved with the criminal justice system. The process for these modifications will be similar to Step 1a, with Dr. Zajac taking the lead and eliciting feedback from mentors. Mentors will be asked to review, provide feedback, and approve the integrated protocol at the end of this step, with particular focus on ensuring that the treatment approach is compatible with the demands of ongoing probation and court involvement (e.g., frequent drug testing, use of contingencies, establishing collaborative relationships with probation officers). Attention will also be paid to the logistics of the treatment (e.g., specifying treatment length, number of sessions per week) as well as other necessary modifications based on the justice involvement of the clients.

Step 1c: Development of training materials. The Criterion-Based Development Model (CBDM; Carter, 2005) will be followed in the development of the training materials. CBDM uses an iterative process that includes: (a) operationally defining the targeted intervention skills; (b) identifying criteria for each skill; (c) developing training materials; and (d) implementing phased evaluation and revision of materials. Dr. Zajac will complete items a-c, routinely eliciting feedback from the mentoring team as specific skills are identified, criteria are selected, and materials are developed for each component of the treatment.

Procedure: Step 2, Feasibility Pilot Study with 40 Emerging Adults: A feasibility pilot study will be conducted with 40 emerging adults recruited through substance abuse treatment clinics and from the community. Recruitment of emerging adults will begin halfway through the second year of the study with the last participant being recruited by the end of the fourth year to allow for a 6 month follow up of each participant.

Subjects and settings: Subjects will be 40 patients seeking substance abuse treatment. In addition, up to 10 pilot participants will be recruited to test study procedures. Pilot participants will not be randomized and all will receive the experimental treatment – see below for additional details. A subset of patients will be recruited from the Farrell Center (New Britain, CT) and at The Village for Families & Children (Hartford, CT). These participants will receive study treatment at their respective treatment centers. Additional participants will be recruited through flyers at other substance abuse treatment centers in the area and through ads. These participants will receive the study treatment at UConn Health in Farmington.

To aid with study recruitment, participants who are randomized into the study will be given flyers to hand out to peers who are in their age group and who may use drugs or alcohol. Participation in the study will not be affected by whether or not a subject chooses to send referrals. The flyer will describe the study and include RA contact information. A unique code will be used to link returned flyers with the original participant. Subjects can earn $15 for each eligible recruit (up to 3 referrals) who attends an intake appointment regardless of whether the recruit consents to participate in the study.

Participant inclusion/exclusion criteria. Participants must meet the following inclusion criteria: (a) 18-25 years old; (b) meets diagnostic criteria for substance use disorder; (c) meets diagnostic criteria for full or subthreshold PTSD; (d) currently able to provide a urine drug screen that is negative for cocaine and non-prescribed methadone or opiates in the past 60 days (since we are not able to test for methadone or determine whether a positive test for opiates is from a prescribed or non-prescribed source, we will rely on patient self-reports to make final decisions about the methadone and opiate results); and (e) speaks English.

Exclusion criteria are: (a) significant cognitive impairment or serious uncontrolled psychiatric problem (other than PTSD); (b) in recovery from pathological gambling or current pathological gambling diagnosis and desiring

to stop or reduce gambling (because of potential concerns of similarity of prize reinforcers and gambling even though no increases in gambling have been reported; Petry & Alessi, 2010; Petry et al., 2006); and (c) in a current domestic violence relationship (as Prolonged Exposure is contraindicated for individuals in this situation; Foa, Hembree, & Rothbaum, 2007).

Informed consent will be obtained by a research assistant (RA) under supervision of the PI. Those who decide not to participate, or who are ineligible, will receive standard care at the clinic.

Assessments. After informed consent, patients will undergo a 3-hour assessment to assess inclusion/ exclusion criteria and outcomes. All measures except those with an asterisk (at baseline [BL] only) will be collected at BL, ~3-month post-baseline, and ~6-month post-baseline. Instruments were chosen based on psychometric properties, with briefer instruments chosen over lengthier ones when possible to minimize burden. Measures will be entered directly into UConn Health's REDCap system. Measures will be administered by Dr. Zajac or by an RA after training from Dr. Zajac. The RA will audio record all assessments, which Dr. Zajac will review randomly for quality control.

The DSM-5 criteria Checklist* (DSM) (APA, 2013) will be used to assess alcohol, cocaine, methamphetamine, opiate, benzodiazepine and marijuana use disorder. This instrument will be used to determine whether participants meet diagnostic criteria for a substance use disorder.

The National Opinion Research Center Diagnostic Screen (NODS)* assesses DSM-IV pathological gambling with high sensitivity and specificity (Gerstein et al., 1999). This instrument will be used to determine whether a participant needs to be excluded based on a history of pathological gambling.

The PTSD module of the Structured Clinical Interview for Diagnosis (Research Version) for DSM-V* (SCID-V; First, Williams, Karg, & Spitzer, 2015) is a structured diagnostic interview that has been updated to reflect the DSM-V diagnostic criteria. The PTSD module will be used to determine if participants meet criteria for either PTSD or subthreshold PTSD. The SCID is considered the gold standard for diagnosis of mental health disorders.

The Trauma Assessment for Adults (TAA; Gray, Elhai, Owen, & Monroe, 2009) will be used to screen for exposure to traumatic events, as the diagnosis of PTSD or subthreshold PTSD is contingent upon the experience of a qualifying traumatic event. In addition, the TAA assesses current involvement in violent relationships and will be used to assess the exclusion criteria "currently in a domestic violence relationship."

The National Stressful Events Survey PTSD Short Scale (NSESP-SS: Miller et al., 2013), a validated self-report measure of DSM-V PTSD symptoms, will be used to screen for PTSD. THE NSESP-SS is a 20-item measure including subscales for intrusion, avoidance, negative cognitive/mood alterations, and hyperarousal/reactivity. The reference period will be "since the crime event occurred" at the screening/BL assessment and "past month" for each subsequent assessment. It is likely that emerging adults with both clinical and sub-clinical levels of PTSD will benefit from this treatment; therefore, emerging adults will meet study criteria if they: (a) report an index trauma; (b) meet criteria for 2 of the 4 DSM-V PTSD symptom cluster and (d) have significant functional impairment (i.e., the recommendation for determining subthreshold PTSD using DSM-V criteria; McLaughlin et al., 2015). This instrument will be used at each of the assessments as well as once per week during the participant's scheduled sessions.

The Addiction Severity Index (ASI; McLellan et al., 1988) is a structured interview that assesses demographic information as well as areas affected by substance use disorders: alcohol use, drug use, medical status, legal status, psychiatric, employment, gambling, cigarette smoking, and social functioning. Adequate interrater and test-retest reliability, and concurrent and discriminant validity, have been established (McLellan et al., 1985; Zanis et al., 1994). An abbreviated version will be administered at follow-up.

Timeline Follow-back (TLFB; Sobell et al., 1980) uses calendar prompts to elicit specific information about the frequency and intensity of substance use over time intervals with good test-retest reliability and validity (Sobell & Sobell, 1992). It will assess days and quantity of alcohol use and days of cocaine, opioid, benzodiapine, marijuana or other drug use 3 months before treatment, every session throughout treatment, and since the last interview at follow-up.

The Psychiatric Diagnostic Screening Questionnaire (PDSQ; Zimmerman & Shereen, 2003) is a brief, psychometrically strong self-report scale that screens for the most common Axis I DSM-IV disorders encountered in outpatient settings. For the current study, modules for the following disorders will be used: 1) obsessive compulsive disorder; 2) panic disorder; 3) psychotic symptoms; 4) agoraphobia; 5) social phobia; 6) generalized anxiety disorder; 7) physical health problems; and 8) hypochondria.

The HIV Risk Behavior Scale (HRBS; Darke et al., 1991) assesses injection and sexual risk behaviors over time; it has adequate reliability and validity (Barry et al., 2008; Petry, 2001) and provides continuous summary scores. The HRBS will assess lifetime and past 3 months at baseline and the past 3 months at all other time points.

The Quality of Life Inventory (QOL; Frisch, et al., 1992) assesses satisfaction in 17 life areas (work, health, recreation, goals, etc). It has test-retest coefficients of .80-.91 and correlates with other measures of well-being (Frisch, et al., 1992); scores change in response to CM (Petry et al., 2007b).

The COPE Inventory (COPE; Carver, Scheier, & Weintraub, 1989) is a well validated measure of a broad range of coping responses that individuals use in response to stress. Five scales measure aspects of emotion-focused coping (e.g., seeking of emotional social support, positive reinterpretation, acceptance, denial, turning to religion); and three scales that measure less adaptive coping strategies (e.g., focusing on and venting of emotions, behavioral disengagement, mental disengagement).

The Center for Epidemiological Studies-Depressed Mood scale (CES-D; Radloff, 1977; Thomas et al., 2001) is a widely used, reliable and valid index for assessing depressive symptoms. This instrument will be used at each of the assessments as well as once per week during the participant's scheduled sessions.

The Self-Reported Offending Scale (SRO; Huizinga, 1991) was adapted from the Self-Reported Delinquency Scale (Elliott, Ageton, Huizinga, Knowles, & Canter, 1983) to be used for adult rather than juvenile offending (i.e., delinquency). The SRO will be used to assess the participant's involvement in delinquent acts during the past 90 days. The SRO includes a general delinquency scale as well as subscales that pertain to person offenses (e.g., assault) and property offenses (e.g., vandalism).

The Service Utilization Form (SU; Rosenheck et al., 1995) evaluates drug abuse, medical, and mental health treatments received at the clinic and elsewhere. It inquires about services in the past 12 months at baseline and since the last interview at other points. It also collects information about societal costs related to drug abuse (e.g., unemployment, homelessness, criminal justice involvement). It contains similar items as the Treatment Services Review (McLellan et al., 1992) but is more extensive. An abbreviated version will be administered at follow-up.

Objective indicators of substance use will be assessed at each evaluation and during treatment. We will assess recent alcohol use (e.g., Alcosensor IV Alcometer, Intoximeters, St. Louis, MO) and cocaine, amphetamine, methamphetamine, opiate, benzodiazepine, and marijuana use (e.g., iCup, Brooklyn, NY) at BL, all follow-ups, and every treatment session.

Treatment Feasibility. Individual qualitative interviews will be conducted with each participant to assess treatment feasibility, acceptability, and burden as well as acceptability and burden of the research protocol.

Scale	Data	Baseline	Weekly during sessions	3 month follow-up	6 month follow-up
DSM-5 Criteria Checklist	Substance use disorder	X*			
Trauma Assessment for Adults	Exposure to traumatic events	X*		X	X
Urine Toxicology, Breathalyzers	Substance Use	X*	X	X	X
National Stressful Events Survey PTSD Short Scale	PTSD symptoms	X	X	X	X
National Opinion Research Center Diagnostic Screen	Pathological gambling	X*			
Structured Clinical Interview for DSM-5 PTSD Module	PTSD Diagnosis	X*			
Timeline Follow-back	Substance use	X	X	X	X
Addiction Severity Index	Substance use & related problems, demographics	X		X	X
Center for Epidemiological Studies-Depressed Mood scale	Depression symptoms	X	X	X	X
Psychiatric Diagnostic Screening Questionnaire	Co-occurring mental health problems	X		X	X
HIV Risk Behavior Scale	HIV Risk Behaviors	X		X	X
Service Utilization Form	Use of community services	X		X	X
Self-reported Offending (SRO)	Criminal behavior	X		X	X
Quality of Life (QoL)	Life satisfaction	X		X	X
COPE Inventory (COPE)	Coping skills	X		X	X
Qualitative Interview with Participants	Treatment acceptability			X	

*indicates measures that will be used to assess inclusion/exclusion criteria

Follow-up assessments will be *scheduled* to take place immediately following treatment completion (i.e., 10-12 weeks of PE/CM for the active group, 10 weeks of sample drop-off for the control group) and about 6 months post-baseline. In this study population, patients are often difficult to contact (e.g., homelessness, unstable housing) or become unavailable for follow-up assessments (e.g., in controlled environment). We have many procedures in place to address these issues (e.g., collection of contact information, reminder calls and cards, etc.). Given these difficulties, some flexibility in scheduling follow-up interviews is required to protect participants from unnecessarily limiting study procedures to a specific calendar day. If a participant misses the follow-up evaluation, research staff will attempt to contact and reschedule the evaluation, but we anticipate late and missed appointments. Given these circumstances, completion of follow-up assessments is likely to occur at *about* 3 months and 6 months following study initiation. Study visits may be completed over the phone or mailed if needed. During the COVID-19 outbreak, participants who complete the follow-ups over the phone or through the mail will receive the full $100 follow-up payment.

Retention Strategies: Dr. Zajac and her mentoring team have been very successful at recruiting and retaining participants from extremely challenging clinical populations. These strategies will be used to promote excellent recruitment and retention rates. First, to establish a collaborative relationship, assessments will be scheduled at participants' convenience, contacts will be maximally personalized, participants will be reimbursed for completing assessments, and researchers will behave in a friendly and professional manner. Second, each time participants are assessed, they will be asked if they plan to move and for the names and contact information of three friends or relatives to facilitate tracking. When a participant cannot be located, the Research Assistant will immediately attempt to track them using this information. Third, contacts will be defined as confidential and independent of the treatment team so as to encourage disclosure. All reasons for failure to interview will be recorded to assess their impact on the proposed methods.

Incarceration: This is a minimal risk study that recruits non-prisoner patients from substance abuse treatment programs. However, a portion of the study patients are likely to be incarcerated during the study period due to illegal activities that are common in this population. If a patient is incarcerated during study participation, all study procedures are suspended except the evaluations. In the ICF, patients indicate whether or not they would like the evaluation questionnaires sent to them in prison. The mailing delivered to the incarcerated patient only contains the evaluation questionnaires and a cover letter indicating the questionnaires are follow-up to a study the patient participated in at UConn Health. A stamped and addressed return envelope is also provided with the questionnaires. If the patient completes and returns the questionnaires for Month 3 and 6, they will receive $25 in the form of a check. The patient will receive the check after their release from incarceration or they may designate a person to whom the check should be sent during their incarceration. The patient is notified in the ICF that their participation in this study while incarcerated will have no effect on their eligibility for parole.

Compensation: To compensate for their time, participants will be given a $50 giftcard for the baseline interview and $100 in their choice of a check or giftcard for each subsequent interview. Participants in the control group will be compensated $5 (check or giftcards) for each urine sample they provide during the treatment phase (i.e., two samples per week for ten weeks). Participants who travel to UConn for their study visits will be provided with $15 (check or giftcards) to cover the cost of travel (bus passes, gas, parking, etc). Participants may also earn up to $45 for eligible referrals ($15 each, up to 3 referrals).

Random Assignment occurs after the BL evaluation. A computerized urn randomization procedure (Stout et al., 1994) will balance patients on gender and submission of a positive sample for any illicit drug (i.e., cocaine, amphetamine, methamphetamine, opiate, benzodiazepine, or marijuana) at baseline, because positive samples at treatment initiation are related to poor outcomes (Preston et al., 1998; Silverman et al., 1998; Stitzer et al., 2007). Prior to randomizing participants, up to 10 pilot participants will complete a pilot study consent form and study procedures described for Group B below, through month 3 follow-up, for the purpose of monitoring staff on study procedures prior to the randomized trial.

Group A (Standard care [SC]; n=20) patients will receive SC at the substance use clinic where they are seeking treatment. This treatment approach typically consists of group therapy sessions, including daily planning, 12-Step treatment, relapse prevention, coping and life skills training, and AIDS education. Groups are led by recovering individuals, nurses, and masters level counselors. Very few individual sessions are provided at these clinics, and then only in cases of emergencies (e.g., suicidality). These clinics rarely conduct breathalyzers or urine testing for illicit drug use. Any such testing will occur as it normally would, and study procedures will not

impact standard care in any way. If the participant is not already enrolled in SC at a substance use clinic, they will be provided with referrals to clinics convenient to their home.

Study urine samples will be collected twice weekly. Patients will receive a $5 payment (check or gift cards) for each of 20 urine/breath sample submissions during weeks 1-10. In addition, they will be asked to complete the NSSEP-SS and the CES-D to assess PTSD symptoms and depression weekly. If patients cease attending groups, they will still be encouraged to attend these brief meetings for sample monitoring. To maintain consistency with standard care in these clinics, results from toxicology screens will not be discussed with providers.

Group B (SC + PE/CM Treatment; n=20) patients will receive the same SC groups as Group A. If they are currently enrolled in susbtance use treatment, they will continue with that treatment. If not, they will be provided with referrals for substance use treatment in the community. In addition, they will participate in an integrated Contingency Management (CM) and Prolonged Exposure (PE) treatment protocol described subsequently. Either the PI (Dr. Zajac) or Meredith Ginley, PhD, will serve as the study therapist for participants randomized to group B. For cases where Dr. Ginley serves as the therapist, Dr. Zajac will provide clinical supervision of study cases.

As in Group A, participants will undergo testing twice weekly with a breathalyzer and urine drug screen. In addition, during the first meeting of the week, participants will engage in both CM and PE components of treatment (described below). During the second meeting of the week, participants will engage in CM and a brief check-in on the components of PE that the participant is working on for homework that week but no new PE-related components will be introduced.

*Contingency Management Component***.** Participants in Group B will participate in CM to target abstinence from substance use. In prize CM protocols, participants earn opportunities to draw cards from a prize bowl. The cards differ in prize value, ranging from $0 to $100 in value, and participants can earn increasing numbers of draws with consecutive performance. The variable reinforcement amount feature of prize CM distinguishes it from other reinforcement systems such as voucher CM. Participants will be allowed to draw from the prize bowl if their urine drug screen is negative for opiates, methadone, cocaine, amphetamines, methamphetamines, and marijuana (see additional information about marijuana use below) and their breath screen is negative for alcohol.

The prize bowl contains 500 cards; 50% are winning and the remainder are non-winning (i.e., “Good Job”). The majority (209/500) of winning cards are small prizes (about $1 in value; e.g., small toiletries, food items); 40/500 cards are large prizes (up to $20 in value; e.g., small electronics, gift cards). One card (1/500) is a jumbo prize (up to $100 in value; e.g., MP3 players/iPod). The maximum number of draws is 132, with an expected average maximum earned per person of about $255 over 10 weeks. Slips are drawn consecutively (without replacement) within session and then replaced between sessions. This reinforcement approach has been used successfully in other treatment trials (Petry et al., 2004; 2005). Prize CM is equally effective as voucher CM (Petry et al., 2005) and it is more cost-effective than voucher CM (Olmstead & Petry, 2009).

At week 1, participants will earn 1 draw for the first negative sample and the number of draws will increase by 1 draw for each consecutive negative sample up to a cap of 8 draws. Once the cap of 8 draws is achieved, participants will continue to receive 8 draws for each consecutive negative sample. No draws are earned for positive samples, unexcused absences (e.g., no shows), or refused samples, and these events will reset the schedule to 1 draw for the next negative sample and escalation will resume as described above. Excused absences (e.g., court appearance, doctor’s appointment) will be accommodated with valid proof and will not reset the reinforcement schedule.

It is expected that, for some emerging adults, marijuana will be their drug of choice. Marijuana treatment requires a different CM schedule, as marijuana can continue to be detected on urine drug screens for up to 3-4 weeks following last use among heavy marijuana users. In these cases, participants will earn 1 draw simply for attending sessions and providing a urine sample for the first 4 weeks of CM treatment. Once the participant is able to provide a negative screen, they will begin to earn escalating rewards starting at the same level as their peers who are in treatment for other illicit drugs. For example, if a participant is positive for marijuana until week 3, s/he would receive one draw for each session attended leading up to the negative screen and then 5 draws for his/her negative urine drug screen in week 3. Once the participant tests negative for marijuana (or the 4 weeks has elapsed), s/he is subject to the same rules for negative and positive screens as other participants.

This adaptation allows us to engage marijuana users in the CM treatment process during the time that they are waiting for their urine drug screens to reflect their abstinence.

Prolonged Exposure Therapy. Participants in Group B will also engage in Prolonged Exposure (PE) therapy for the treatment of PTSD. PE is a well-established treatment for PTSD for a wide range of populations, including victims of sexual and/or physical assault, childhood trauma, accidents, and war veterans. A 2010 meta-analysis reviewed 13 randomized controlled trials evaluating PE over 20 years and concluded that this treatment approach "is a highly effective treatment for PTSD, resulting in substantial treatment gains that are maintained over time" (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). PE has also been evaluated with patients who have co-occurring PTSD and substance abuse disorders, resulting in evidence for its safety, feasibility, and efficacy with this patient population (Brady, Dansky, Back, Foa, & Carroll, 2001; Foa et al., 2013; Mills et al., 2012).

PE consists of 10 sessions and is based on Emotional Processing theory (Foa & Kozak, 1986), which proposes that pathological fear structures underlie the development and maintenance of anxiety disorders. The goals are to promote processing of the trauma memory and reduce distress and avoidance evoked by trauma reminders through four components: 1) psychoeducation; 2) breathing retraining; 3) in-vivo exposure (i.e., repeated prolonged exposure to anxiety-provoking people, places, or situations); and 4) imaginal exposure (i.e., repeated prolonged retelling of the trauma memory). **Psychoeducation** includes providing information to the participant about common reactions to trauma, how PTSD develops, and how exposure to trauma cues and reminders through PE can help reduce PTSD symptoms over time. As in other studies with substance using populations (e.g., Brady et al., 2001; Mills et al., 2012), psychoeducation will also be provided about the relationship between PTSD symptoms and substance abuse. **Breathing retraining** involves teaching patients how to use their breathing to calm down their bodies and thoughts. Patients are educated on the relationship between calm breathing and subjective feelings of distress and coached in a method for slowing down breathing. Patients are encouraged to practice breathing retraining between sessions to promote mastery. **In vivo exposure** involves the gradual exposure to people, places, situations, and other triggers that the patient is currently avoiding due to trauma-related distress. The patient and the therapist work together to construct an in vivo exposure hierarchy and then choose targets for the patient to work on. In vivo exposures are conducted for at least 30-45 minutes at a time to promote new learning and block avoidance. As in other studies of PE with substance using populations, in vivo exposures will be approached gradually. Finally, **imaginal exposure** helps patients to overcome avoidance of thinking and talking about the trauma and involves the repeated retelling of the traumatic memory. The patient engages in imaginal exposure during the PE sessions with the therapist, and the therapist coaches the patient on how to process the memory emotionally rather than blocking it or pushing it away. Sessions are audiotaped with participant permission and patients are encouraged to listen to these tapes between sessions to promote habituation to the traumatic memories. As in past studies using PE for substance using patients, the therapist emphasizes the importance of not using drugs or alcohol prior to the PE sessions or during the between-session homework, as this is likely to decrease the effectiveness of the exposure exercises. The therapist will also ensure that patients are proficient in effective coping techniques, including breathing retraining, prior to conducting an in vivo or imaginal exposure exercises.

Missed Sessions. When a participant misses a PE session, he or she will be encouraged to reschedule that session within the same week. To allow for the high likelihood of occasional missed sessions or scheduling conflicts that will result in a missed week of PE, participants will be given the opportunity to make up a missed session in the following week. However, session length will be capped at 12 weeks, regardless of the number of sessions completed.

Inclusion of Women and Minorities. Data from past studies with this clinical population (i.e., emerging adults seeking susbtance abuse treatment) suggests that 40% of the sample can be expected to be women. Thus, we anticipate that 16 of the 40 participants recruited will be women. Using the same data source, we estimate that 25% of the sample will identify as Hispanic, and 45% will identify as African American. Participants will be enrolled without regard to gender or minority status, and this study involves no gender or minority group exclusions. Because this is a feasibility study, our aim at this stage of development is to observe the capacity of our standardized recruitment protocol to engage females and minorities into the study. A higher rate of refusal for study participation in these groups will be examined. Similarly, apparent under-enrollment according to our

estimated enrollment rates will stimulate changes to protocols for subsequent applications.

Data Quality Control: Instruments chosen are reliable and valid for assessing substance use, PTSD, and related outcomes. To maximize consistency of measurement, careful training will precede study initiation. Our staff is experienced in conducting similar trials, and the majority of these instruments are being used in ongoing studies. Training of new personnel consists of 2-4 days of intense training and ≥5 supervised ratings. Reliability is assessed at outset of data collection and then spot-checked about monthly via review of audiotapes. Interrater reliability on each instrument is >80% before study initiation and throughout its duration; if not, more training occurs. Kappas are used for diagnostic assessments, and Shrout and Fleiss intraclass correlations for continuous variables.

Valid assessment requires that measures be obtained from different sources, including self-report and objective data, which will be compared. If discrepancies are noted, the most conservative index can be utilized with any index (self report or objective data) coding an individual as using substances for analysis purposes.

Strict separation of clinical (therapy) and research components (structured evaluations) and the use of multiple sources of information including objective indicators of substance use will help to reduce bias. Importantly, for Group B, Dr. Zajac will be implementing the treatment but a trained RA will conduct the research assessments. As in prior trials, checksheets will be kept, in which all data to be collected are listed, draws earned and their outcomes are recorded, and patients are informed of draws possible at their next session (Petry, 2011; Petry, Alessi, Ledgerwood, & Sierra 2010).

Data will be entered into electronic format (REDCap) and checked for out of range responses and missing data. Data cleaning procedures involve within and between file checks for inconsistencies, outliers, and missing data and nonresponse patterns.

Steps are taken to minimize follow-up contact bias: obtaining names, phone numbers and addresses of ≥3 locators and checking in regularly about changes. We generally achieve follow-up rates >90% at early follow-ups (through month 6), and >80% at each longer-term follow-up, with <6% of patients lost to follow-up completely (Petry, Martin, Cooney, & Kranzler, 2000; Petry et al., 2004; Petry, Alessi, Tedford, Austin, & Terdif, 2005; Petry, Alessi, Hanson, & Sierra 2007). We expect similarly high follow-up completion rates in this study.

Data Analysis Strategy:

Aim 1: To develop and implement an integrated SUD/PTSD treatment for high risk emerging adults. There are no data analyses associated with this aim.

Aim 2: To evaluate the feasibility, acceptability, and safety of the SUD/PTSD intervention for emerging adults. Feasibility measures relevant to recruitment and dropout proportions will be examined with 95% confidence intervals used to estimate the proportion of emerging adults who agree to participate out of the number deemed eligible and to compare those who complete versus do not complete the intervention. Feasibility will be evaluated by examining therapist adherence using ratings of taped sessions as well as emerging adults' responses to qualitative interviews. Measures of safety will include repeat trauma exposure, suicidal ideation, and risky substance use behaviors. Patterns of safety indicators will be examined using frequency distributions and descriptive statistics. In addition, rates of these indicators will be compared across Group A and Group B to determine if there is any increased risk posed by the active treatment compared to treatment as usual. These data will be used to make any necessary protocol changes.

Aim 3: To conduct a preliminary analysis of the efficacy of the integrated protocol in improving symptoms among emerging adults. Groups will be compared with respect to the primary outcome variables (substance use, PTSD symptoms) and secondary variables (delinquent behaviors, depression, adaptive functioning, HIV risk behaviors). An important issue preceding analyses is to identify baseline differences between groups despite random assignment. Differences between groups that may be related to outcome will be used as covariates or fixed factors, as appropriate. We will conduct intent-to-treat analyses, with all randomized patients and apply random regression models, also known as hierarchical linear models (HLM), to determine if patients improve differentially between groups over time (Raudenbush & Bryk, 2002). HLM is specifically designed for repeated measures designs with missing data, allowing for intra-subject serial correlation and unequal variance and covariance structures over time by incorporating available trend data for each individual with information on the group from which the subject is drawn. Maximum likelihood estimation enables analyses to be performed for the full trial without having to drop subjects with incomplete data, and both continuous and dichotomous variables can be analyzed. If data cannot be normalized, group by time effects will

be assessed with HLM, coding patients as improved or not at each time point. The main analyses will focus on during treatment effects (baseline through follow-up) but long-term effects (baseline to 3-month post-treatment follow-up) will also be analyzed (see follow-up section).

The primary outcomes are substance use is longest duration of abstinence from illicit drug use and symptoms of PTSD (NSESP-SS), continuous variables that can be transformed if needed. The primary substance use outcome is longest duration of abstinence from substances (LDA), the main outcome variable in most CM trials and the variable most strongly associated with long-term abstinence (Higgins et al., 1994, 2000, 2003; Petry et al., 2005). Linear regression will evaluate group differences in LDA, with condition as the independent variable (along with any important covariates). If data cannot be normalized, nonparametric tests will be used. While LDA is the primary substance use outcome measure, it is affected by retention as missing samples break a string of abstinence (unless preceded and followed by negative samples, and an excused 'miss' is obtained due to documented illness, court appearances, etc. usually comprising <5% of missed samples). Proportion of negative samples, in contrast, is unaffected by missing samples. Thus, we will also analyze proportion of samples negative for substances as a secondary outcome using similar analyses.

Analyses will focus on the 10-week during treatment effects, but long-term effects will also be analyzed. These will involve logistic regressions to predict substance abstinence at the 3-month follow-up, with treatment group and any important baseline characteristics (e.g., baseline sample result) included as independent variables. HLM analyses for dichotomous measures will also be conducted to evaluate substance abstinence over time between treatments from baseline throughout the 3-month follow-up. Additional secondary drug use outcomes will investigate abstinence from all substances concurrently and from each of the other drugs independently. These analyses will parallel those outlined above.

Effects of treatment on PTSD symptoms will be examined primarily using the weekly scores on the NSESP-SS. This is a continuous measure, with missing data likely. If no systematic differences in missing data are noted (the case in our prior studies), hierarchical linear models (HLM; Gibbons et al., 1993) using MIXREG (Hedeker, 1993) will analyze differences between groups over time. These analyses have advantages over repeated measures ANOVA as they estimate missing data via model parameter estimates and use real time, rather than scheduled time, of assessments. The model will include factors for group, time, and the interaction of group by time.

Secondary outcomes include delinquent behaviors (SRD), HIV risk behaviors (HRSB), adaptive functioning (SAS-SR), and depression (CES-D). Using the same HLM modeling described above, we will examine the impact of group, time, and group x time on each of these secondary outcomes to determine if the PE/CM treatment produces better outcomes than usual services.

Contingency Plan: If the intervention is not found to be feasible and/or produce symptom reduction, the candidate will work closely with mentors during Yr 5 to evaluate where positive outcomes are lacking and to refine the intervention using both quantitative and qualitative approaches. Assessment results will be evaluated to determine whether the intervention is equally effective across all areas targeted in treatment. If the intervention is found to be less effective in a specific area, modifications will be made to enhance the intervention in that area. Data will be examined to determine whether specific factors explain differential effects among participants. Input from participants will also be a critical source of information for improving the intervention.

PROTECTION OF HUMAN SUBJECTS

The proposed research does not meet the definition of a Phase III clinical trial (see http://www.drugabuse.gov/funding/clinical-research/guidelines-developing-data-safety-monitoring-plan), but a Detailed Data and Safety Monitoring Plan is provided following NIDA instructions. This plan includes continuous, close monitoring by the study investigators (including mentors) and prompt reporting procedures. All procedures and materials will be reviewed and approved by the Institutional Review Board at UConn Health prior to commencement of data collection To provide further protections to participants, a federal Certificate of Confidentiality will be sought. All procedures will follow guidelines as outlined in 45 CFR Part 46 Subpart D for research involving children, as well as those outlined in 45 CFR Part 46 Subpart C for research involving prisoner populations.

1. RISKS TO THE SUBJECTS

A. Human Subjects Involvement and Characteristics

Human subjects are being recruited for the proposed study to participate in a clinical trial evaluating an integrated treatment for substance use and PTSD (SUD/PTSD) for transition age youth. Specifically, 40 youth will be recruited to participate in this study.

Inclusion criteria are: (a) 18-25 years old; (b) meets diagnostic criteria for a substance use disorder; (c) meets criteria for full or subthreshold PTSD; (d) currently able to provide a urine drug screen that is negative for cocaine and non-prescribed methadone or opiates in the past 60 days (since we are not able to test for methadone or determine whether a positive test for opiates is from a prescribed or non-prescribed source, we will rely on patient self-reports to make final decisions about the methadone and opiate results); and (e) speaks English. Exclusion criteria are: (a) significant cognitive impairment or serious uncontrolled psychiartic problems (other than PTSD); (b) in recovery from pathological gambling or current pathological gambling diagnosis and desiring to stop or reduce gambling (because of potential concerns of similarity of prize reinforcers and gambling even though no increases in gambling have been reported; and (c) in a current domestic violence relationship. Youth who meet eligibility requirements and consent to study participation will complete three assessment interviews over 6 months (i.e., at baseline, 3-, and 6-months post-baseline). Youth will be randomized to either the integrated SUD/PTSD treatment (plus treatment as usual) or to treatment as usual alone.

Targeted enrollment is based on estimates from past studies completed by the research mentors with transition age youth. There will be no restrictions with regard to gender, race, or ethnic background. Individuals will, however, be required to speak and understand English in order to participate in the study.

B. Sources of Material

Participant assessments will include self-report measures, interviews (semi-structured and qualitative), urine drug screens, and breathalyzer tests. Participants will be assessed at three time points (i.e., at baseline and 3-, and 6-months post-baseline). All assessments will be collected in person by the Research Assistant or PI. Assessments will be scheduled at a time and location convenient for the participant. At each occasion, participants will provide self-reports of substance use, symptoms of PTSD and depression, HIV risk behaviors, and adaptive functioning as well as a biological measurement of substance use. In addition, interviews will be used at the baseline measurement to assess demographics, other Axis I disorders, and PTSD diagnosis. Finally, youth in the PE-CM condition will participate in a qualitative interview at 3 and 6 months post-baseline focused on their perceptions of acceptability of the treatment and research protocols. All therapy sessions and research visits will be audiotaped to ensure therapist adherence to the treatment protocol and the Research Assistant's adherence to the research protocol. To compensate for their time, participants will be paid $50 in giftcards for completing the initial assessments and $100 in checks or giftcards for completing each of the follow-up assessments. Participants in the treatment as usual condition will be paid $5 in checks or giftcards or small prizes per session for providing twice weekly urine and breathalyzer samples and completing brief self-report measures. Participants may also earn up to $45 for referrals who complete an intake ($15 each, up to 3 referrals).

C. Potential Risks

The risks that might be associated with this study include: 1) perceived coercion to participate; 2) potential embarrassment/distress due to sensitive assessment items; 3) potential distress if information obtained during the assessments were released to outside parties; and 4) potential distress due to participation in an exposure-based treatment for PTSD. As described next, several procedures will be used to protect against these risks.

2. ADEQUACY OF PROTECTION AGAINST RISKS

A. Recruitment and Informed Consent

Participants will be recruited from substance abuse treatment clinics or from ads. Patients who meet general eligibility requirements (i.e., age, presenting problem) will be asked if they are interested in learning more about a research study. It will be made clear to the potential participant that their eligibility for services is not contingent on their participation in the research study. A research assistant will follow up with any interested youth to complete a study screening assessment to determine initial study eligibility. If the youth is eligible, the research assistant will explain the study in more detail and, if the youth is interested in participating, an appointment will be scheduled for the youth to complete the informed consent procedure.

To ensure that consent is fully informed, the nature of the treatment, potential benefits and risks, the voluntary nature of participation, and the data collection procedures will be explained to the potential participant. It will be communicated that all therapy sessions and data collection visits will be audiotaped as part of the study. If the individual agrees to participate, written informed consent will be obtained. Both the Research Assistant and the consent form will make it clear that the individual's eligibility for services will not be affected by the decision to participate in the study.

All consent forms and procedures will be approved and monitored by the IRB at UConn Health. All research staff will receive the requisite training in human subject protections.

Incarceration: This is a minimal risk study that recruits non-prisoner patients from substance abuse treatment programs. However, a portion of the study patients are likely to be incarcerated during the study period due to illegal activities that are common in this population. If a patient is incarcerated during study participation, all study procedures are suspended except the evaluations. In the informed consent form, patients indicate whether or not they would like the evaluation questionnaires sent to them in prison. The mailing delivered to the incarcerated patient only contains the evaluation questionnaires and a cover letter indicating the questionnaires are follow-up to a study the patient participated in at UConn Health. A stamped and addressed return envelope is also provided with the questionnaires. If the patient completes and returns the questionnaires for Month 3 and 6, they will receive $25 in the form of a check. The patient will receive the check after their release from incarceration or they may designate a person to whom the check should be sent during their incarceration. The patient is notified in the informed consent form that their participation in this study while incarcerated will have no effect on their eligibility for parole. Approval for this aspect of the study will be obtained from OHRP before these procedures are implemented.

B. Protection against Risk

Coercion. Several strategies are embedded within the research protocol to reduce the risk of real or perceived coercion of potential participants. First, all research staff will complete an online Human Subjects Research Training course. This course discusses the importance of autonomy and informed consent in research.

To protect against coercion, it will be emphasized to the Research Assistant that s/he should under no circumstance attempt to influence the youth's participation, but rather provide information to potential participants and allow them to make their own decisions regarding participation. The Research Assistant will be trained to state clearly to potential participants that their access to services are in no way contingent upon their participation in the research study. Finally, the Research Assistant will make it clear to the participant that they may discontinue their participation in the research study at any time.

Participant Discomfort Due to Assessment. There is a possibility that some participants might experience distress when asked questions pertaining to trauma and trauma-related mental health symptoms. Many people assume that asking such questions produces substantial distress, particularly in research settings. However, our prior clinical research experience, as well as the empirical literature, indicates that this risk is minimal. Most individuals with traumatic event histories do not report significant distress and actually report obtaining positive benefits from their participation in studies using assessment instruments similar to the ones proposed (Cercone et al., 2009; Griffin et al., 2003; Newman et al., 1999; Zajac et al., 2010).

To minimize any possible embarrassment or distress associated with participation in the study: (a) the Research Assistant will be carefully chosen and trained by the Principal Investigator; (b) participants will be informed that they can discontinue participation at any time and that they do not have to answer any questions that they find objectionable; (c) study visits will be scheduled and conducted in ways that maintain participant privacy; and (d) the Research Assistant will be carefully supervised through weekly supervision meetings and auditing of audiotaped assessments by the Principal Investigator.

Confidentiality. All information obtained from participants will be confidentially maintained. Because of the sensitivity of some of the data (e.g., self-reports of criminal behavior), a Federal Certificate of Confidentiality will be obtained to render participant data immune from subpoena. In addition, the Research Assistant will receive training from the Principal Investigator on the importance of confidentiality and will have regular supervision meetings with the Principal Investigator to ensure strict compliance with the Human Subjects Protection plan.

Regarding data management and storage, interviews will be administered by either the Principal Investigator or a trained Research Assistant, who will enter data via laptop computers. Only participants' study identification codes will be inputted in the interview via REDCap, a secure online data collection system. The codes that link the name of the participant and the study ID will be kept confidential by the Principal Investigator in a secured cabinet. The interview is programmed to check data at the time of entry to ensure that values are within the

specified range and that items are not inappropriately skipped. The data will be imported directly into a password-protected SPSS data file. This file will only identify subjects by the study ID number. Audio files of the therapy sessions and the data collection visits will be used solely for research purposes. Files will be stored on encrypted hard drives or a secure server. Audio files will only be identified by numeric codes and will be destroyed at the end of the study. Only the therapists, Research Assistant, and investigators will hear the content of the audio recordings.

The only exceptions to confidentiality include situations involving potential abuse/neglect or risk of harm to self or others. Study cases will be supervised by Dr. Zajac, a clinical psychologist who has substantial experience successfully handling crises, or by therapists with advanced degrees who will be directly supervised by Dr. Zajac. Specifically, when a therapist learns of potential abuse/neglect of a child, the Department of Children and Families (DCF) is notified, and a DCF worker takes steps to keep the potential victim safe. If a study staff member has concerns about potential suicidal or homicidal ideation, Dr. Zajac will be contacted immediately. Dr. Zajac will ensure study staff members are well trained in assessing distress and suicidality (intent, plan, etc). If a participant is deemed at risk for suicide and the will not contract for safety, or has made a suicidal gesture or attempt, the participant will be assessed by local emergency department for possible inpatient hospitalization Dr. Zajac also will ensure all participating individuals and their families are well educated on how to access 24-hour emergency care (through 9-1-1 or going to the local Emergency Department).

Within the research context, the Research Assistant might hear indications of risk of harm to self or others or abuse/neglect through conversations with participants. If a Research Assistant is told that there is any risk of harm to the participant or others, s/he will immediately contact Dr. Zajac. Dr. Zajac will assess safety and provide instructions to the Research Assistant to address any risks. Dr. Zajac will conduct a comprehensive risk assessment with the participant. If there is any indication of a potential for harm, Dr. Zajac will take appropriate action (e.g., contacting the police or ensuring the participant is taken to the nearest emergency room). Routine monitoring of adverse events will also occur through weekly meetings between the Principal Investigator and the Research Assistant.

All research personnel collecting and manipulating data will have completed a Human Subjects Research Training course and will meet weekly with Dr. Zajac to ensure strict compliance with the IRB protocol. Only study personnel (Principal Investigator and research staff) will have access to data.

Distress Due To Participation in an Exposure-Based PTSD Treatment. Participants may experience temporary distress due to participation in Prolonged Exposure therapy for PTSD, which involves discussing a past traumatic event in detail. In past studies, Prolonged Exposure has been associated with participant reports of modest to moderate distress and, for some participants, temporary symptom exacerbation (e.g., Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002). However, these reports of distress and symptom exacerbation have been found to be transitory and not related to poor treatment outcomes (Foa et al., 2002). Further, decades of research have established the safety and efficacy of exposure-based treatments for PTSD (e.g. Foa et al., 1991, 1999, 2005) even for high-risk samples, including adolescents (Gilboa-Schechtman et al., 2010), war veterans (e.g., Nacasch et al., 2011), and adults with co-morbid substance use problems (e.g., Killeen, Back, & Brady, 2011; Mills et al., 2012), severe mental illness (Mueser et al., 2008), and borderline personality disorder (Feeney, Zoellner, & Foa, 2002). In addition, Dr. Zajac has received extensive training and has had over 5 years of experience conducting Prolonged Exposure therapy. She will provide intensive training and supervision to study therapists on all aspects of the treatment protocol, including how to teach participants techniques to cope effectively with trauma-related anxiety and how to assess and handle symptom exacerbation.

Despite substantial evidence for the safety of Prolonged Exposure therapy, every effort will be made to minimize any potential negative effects of this approach. Adaptations made during the development of the integrated SUD/PTSD protocol will follow recommendations made by Back et al. (2001) based on their use of Prolonged Exposure therapy with substance using populations. Specifically, substantial attention will be given to (a) providing participants with extensive psychoeducation about the functional relationship between substance use and PTSD; (b) an incremental rather than implosive approach to exposure, such that the participants identify and follow an exposure hierarchy, beginning with less anxiety-provoking exposure tasks and working up to more difficult tasks; (c) intensive training on and frequent review of the use of adaptive coping strategies with participants; and (d) careful monitoring of substance use following exposure sessions. These techniques are described in more detail below:

Assessment of Substance Use and Symptom Exacerbation

- Each session (i.e., two times per week), the therapist checks-in with the patient about substance use, including substance use following sessions and/or following exposure exercises, in two ways: first, through urine drug screens and breathalyzers and second, through the patient's self-report of use.

- Each week the therapist also checks in with the patient about symptoms of PTSD and depression using self-report measures during the weekly PE session. The therapist will also be doing a brief in-person check-in with the patient about PTSD symptoms during the second session of the week. This allows therapists to monitor symptom exacerbation.
- Standard Prolonged Exposure therapy includes between session phone calls to check in on the completion of patient homework assignments. During these calls, the therapist checks in about the completion of exposure exercises, encourages patients to complete any planned homework assignments that have not yet been completed, and checks in on the patient's response to the most recent session, including PTSD symptoms and substance use. In the current study, the patient will have an in-person meeting with the therapist between Prolonged Exposure sessions for the purposes of conducting the CM session (i.e., the second session of each week). This meeting will also include a check-in about homework assigned as part of Prolonged Exposure. Part of this conversation will also focus on PTSD symptoms and substance use. If the patient does not attend their second weekly session, the therapist will attempt to reach the patient by phone to conduct this check-in.

Preventive Measures

- Patients are educated about the connection between anxiety and substance use. They are also educated about the possibility that they may experience increased urges to use substances following an exposure session. The therapist and patient discuss strategies to cope with cravings in response to exposures. These may include the breathing retraining that is practiced in session 1 or coping techniques that the patient already uses (e.g., spending time with family members, exercise, etc). The patient is asked to make the therapist aware of any increased urges or symptoms in response to sessions or homework assignments.
- The therapy will be conducted by the PI of the study or by a mental health professional with an advanced degree who will be closely supervised by the PI of the study. The PI is a licensed clinical psychologist with extensive experience delivering Prolonged Exposure therapy and in managing psychiatric crisis situations.

Responses to Exacerbation of Substance Use and PTSD

- Any instances of substance use following exposure exercises are discussed, with the therapist and client working together to determine whether there are feasible alternative coping strategies for the client to use in place of the substances. If the client is unable to come up with effective coping strategies that can be used in place of the substance use and substances are being consistently used following or during exposure exercises, the therapist will decrease the intensity of the exposure sessions and homework exercises, as is standard in Prolonged Exposure therapy for patients who are overwhelmed by a treatment component. Alternatively, the therapist may choose to postpone further exposure exercises and work with the client on improving coping skills before resuming them.
- Some exacerbation in PTSD symptoms is expected in Prolonged Exposure treatment and does not indicate that Prolonged Exposure therapy should be discontinued. However, the Prolonged Exposure therapy protocol has built-in instructions for how to titrate the treatment to best match the patient's presentation. In the case of patients who are considered "overengaged" in exposure exercises or become overly emotionally distressed during or following exposure exercises, steps are taken to scale back the intensity of the exposures. These steps include (in the case of in vivo exposures), choosing exercises that are rated lower on the patient's In Vivo Hierarchy or (in the case of imaginal exposure), having the patient open his/her eyes during the exercise or write down the narrative instead of saying it aloud.

Serious Adverse Reactions

- Instances of exacerbation in PTSD symptoms or substance use, identified either during sessions or during phone calls, will trigger a more thorough assessment by the therapist. In these instances, the therapist will assess the patient's safety, specifically asking about any suicidal ideation. Of note, Prolonged Exposure therapy has not been linked to increased risk of active suicidal ideation in the scientific literature.
- Of note, patients who report serious uncontrolled mental health concerns are not eligible for this study. The Addiction Severity Index, which is used to assess this exclusion criterion, includes questions about serious suicidal thoughts and suicide attempts in the past 30 days. Patients answering affirmatively to these questions will be excluded from the study.
- In the unlikely event that a participant experiences suicidal ideation and is unable to contract for safety, the therapist will take steps to ensure that the patient receives a higher level of psychiatric care. When appropriate, the therapist will ensure that the patient is assessed at the nearest emergency room for admittance to an inpatient psychiatry facility.

Safety and Adverse Events. Risk of harm to self and others is directly assessed as part of treatment. The PI is a licensed clinical psychologist with substantial experience handling crisis situations, including suicidality and homicidality. Participants in the study who indicate any risk of harm will immediately be assessed and

referred for more intensive treatment if needed. Both expected and unanticipated adverse events will be continuously monitored by the Principal Investigator through weekly meetings.

Within the research context, assessment tools administered at each time point evaluate depressive symptoms (including suicidal ideation/risk of harm). The Research Assistant may also observe indicators of risk of harm to self or others or child abuse/neglect aside from the assessment instruments (e.g., through conversation with participants). The Research Assistant will not make independent decisions about these issues except in an acute emergency. S/he will be required to discuss the issue with Dr. Zajac as indicated above before any action is taken, unless a delay in action would clearly place the participant or another person in immediate danger. In these cases, the Research Assistant will contact the police or provide warning to the intended victim. Routine monitoring of adverse events also will occur through weekly meetings with the research team.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

The risks to youth participating in this project are minimal. Potential benefits to participants who receive the integrated SUD/PTSD treatment are substantial, including decreased symptomatology and substance use and improved adaptive functioning, though these cannot be guaranteed. In addition, the successful validation of clinically effective and cost-effective treatment approaches for comorbid SUD/PTSD among transition age youth would be of significant benefit to society.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Left untreated, comorbid SUDs and PTSD results in significant negative outcomes for justice system-involved transition age youth and extraordinary costs for individuals, communities, and society. Despite the significant consequences of these problems, research on integrated SUD/PTSD treatments for this population is limited. Therefore, the current application proposes to integrate and adapt two existing evidence-based treatments for SUDs and PTSD to meet the treatment needs of transition age youth and provide an initial test of feasibility, safety, and symptom reduction. This study represents the essential first step to the development of evidence-based practice for treating comorbid SUD/PTSD among high-risk transition age youth. The minimal risks to participants are reasonable given the importance of the knowledge to be gained.

5. DATA AND SAFETY MONITORING PLAN

The Principal Investigator will be responsible for monitoring the safety and efficacy of this trial, executing the NIDA-approved Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. The Principal Investigator will receive extensive consultation from her mentor, Dr. Petry, regarding these tasks. In particular, Dr. Petry has conducted a number of clinical research trials with populations with substance use disorders. The Principal Investigator will provide a summary of the DSM report to the study sponsors on an annual basis as part of the progress report. The DSM report will include the participants' socio-demographic characteristics, expected versus actual recruitment rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events, and any actions or changes with respect to the protocol. The DSM report will also include, when available, the results of any data analyses.

A. Participant Safety

Diligent safety monitoring will be conducted by the Principal Investigator throughout this study in compliance with the following required elements of the the IRB's continuing review process:

1. tracking of subject accrual (enrollment, drop-outs, demographics)
2. timely and appropriate reporting of informed consent process deficiencies, protocol deviations, privacy breaches, conflicts of interest, and/or changes in personnel
3. ongoing monitoring and appropriate reporting of adverse event activity
4. interim assessment of risk/benefit relationship in reference to adverse event occurrences, preliminary observations, and emerging information
5. timely and appropriate IRB submission of safety-related documents such as audit reports, sponsor progress reports, and other materials or communications that might impact the safe conduct of this study
6. active cooperation with the IRB and other applicable entities in the event of a random or for-cause internal or external audit

Participant Safety Relevant to Specific Application. Regarding the risk of harm to self or others, the nature of the population (transition age youth) and the inclusion criteria (symptoms of PTSD and substance use) entail

that specific adverse events, such as suicidal and homicidal ideation and attempts, are possible given the high-risk nature of the population under study. Regardless, both expected adverse events and unexpected adverse events will be monitored and addressed continuously throughout the course of the project.

Within the treatment context, risk of harm to self and others is directly assessed as part of the treatment. Participants in the study who indicate any risk of harm will immediately be assessed and referred to a higher level of care, if needed. Therapists and their supervisor, Dr. Zajac (who will be on-call 24 hours per day, 7 days per week for therapists) have extensive training in crisis management. Both expected and unanticipated adverse events will also be continuously monitored by the investigators through weekly meetings.

Participant safety is assessed routinely as part of the research context through assessment tools given at each time point to evaluate depressive symptoms (including risk of harm). At other times, researchers may also observe indications of risk of harm to self or others or child abuse/neglect aside from the assessment instruments (e.g., through conversation with participants). In these situations, the Research Assistant will consult with Dr. Zajac before deciding on a course of action unless there is an acute emergency and a delay in action would place the participant or another person in immediate danger. In these cases, the Research Assistant will contact the police or provide warning to the intended victim. Routine monitoring of adverse events will occur during weekly meetings of the research team.

For participants enrolled in the study, in any circumstances where the Research Assistant is concerned regarding suicidal or homicidal ideation or attempt, s/he will immediately contact the Principal Investigator, Dr. Zajac, who is a licensed clinical psychologist. Dr. Zajac will assess safety and provide instructions to the Research Assistant to address any risks. Dr. Zajac will conduct a comprehensive risk assessment with the participant. If there is any indication of a potential for harm, Dr. Zajac will take appropriate action (e.g., contacting the police or ensuring the youth is taken to the nearest emergency room). The Principal Investigator will ensure that the Research Assistant is well-trained in assessing distress and suicidality (ideation, intent, plan, etc). In circumstances where participants express suicidal ideation and are sincerely willing to contract for safety (i.e., will agree to keep her/himself safe), a plan will be made and carefully monitored. If a participant is deemed at-risk for suicide and will not contract for safety or has made a suicidal gesture or attempt, the participant will be assessed by a local emergency department for possible inpatient hospitalization. Dr. Zajac will also ensure that participants who present with risk for suicidal or homicidal ideation are well educated on how to access 24-hour emergency care (through 9-1-1 or going to the local Emergency Department).

B. Procedures for Monitoring Safety of Data

Regarding data management and storage, interviews will be administered by the PI or a trained Research Assistant, who will enter data via a laptop computer using REDCap, a secure online data entry platform. Only participants' study identification codes will be inputted in the interview. The codes that link the name of the participant and the study ID will be stored separately from the study data. The interview is programmed to check data at the time of entry to ensure that entered values are within the specified range and that items are not inappropriately skipped. In addition to these precautions, all personnel will have earned at least a bachelor's degree and have experience in conducting research. All research personnel collecting and manipulating data will have completed a Human Subjects Research Training course and will meet weekly with the Principal Investigator to ensure strict compliance with the DSM plan. Only study personnel (Principal Investigator and research staff) will have access to data. No data will be released to other agencies unless participants consent to release. Audiotapes of therapy and data collection sessions will be used solely for research purposes. Audio files will be stored on an encrypted hard drive at the research office, digital recordings will only be identified by numeric codes, and recordings will be destroyed at the end of the study. Only the Research Assistant, therapists, and investigators will hear the content of the audio recordings.

C. Adverse Events

The Principal Investigator, with consultation from her mentoring team, will be responsible for monitoring trial data and participant safety.

1. **Reporting of SAEs**. Participants who experience a significant psychiatric or medical problem requiring an overnight hospitalization at an acute care facility will be defined as having experienced an SAE, and these are our most common SAEs. Types of expected SAEs in this substance abusing population are as follows: (a) onset of clinically significant suicidal ideation, intent or action; (b) onset of clinically significant homicidal ideation, intent or action; (c) deterioration of mental status to an extent which renders the patient unable to care for self; or (d) deterioration of physical status renders need for inpatient medical treatment.

All SAEs (e.g., hospitalization, life threatening injury, death) are reported on an Adverse Events Monitoring Form and reviewed by the project manager and PI. The form collects detailed information about all adverse events, how they were handled, and their potential relationship to study participation with a sign-off by all appropriate supervisory personnel. Adverse events that are serious and unanticipated and probably, possibly, or definitely related or adverse events occurring with greater frequency than anticipated will be reported to the IRB per University policy within 48 hours of discovery.

In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an SAE, the participant will be monitored by the investigator via ongoing status assessment until 1) a resolution is reached i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected 2) the SAE is determined to be clearly unrelated to the study intervention, or 3) the SAE results in death. Outcome of SAEs will be periodically reported to NIDA and the UConn Health IRB per policies. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA.

We anticipate that unexpected and possibly study-related SAEs will be rare, because participants will be receiving primarily a psychosocial intervention. Research staff who conduct breath and urine sample testing as well as the baseline and follow-up interviews will most typically detect SAEs. All research staff has completed required institutional training on research with Human Subjects. Research staff are trained in adverse event reporting and understand that the responsibility is to document and report adverse events reported by study participants. At monthly research staff meetings, past month and study cumulative SAEs are reviewed.

2. Reporting of IRB actions to NIDA. The UConn Health IRB requires yearly reporting of all AEs (including those that are anticipated and unrelated), while any unanticipated and possibly related SAEs require reports within 48 hours. Any formal or non-routine IRB actions will be promptly reported to the NIDA Project Officer.

3. Report of changes or amendments to the protocol. The PI will provide timely reporting to the NIDA Project Officer of any major changes in the protocol, or its overall status including: protocol amendments; suspension or termination of subject recruitment or the protocol itself; changes in the informed consent or IRB approval status; and other problems or issues that could have a significant impact on participants.

4. DSM plan administration. The Principal Investigator will be responsible for monitoring the safety of this trial, executing the DSM plan, and complying with the reporting requirements. All DSM reports to NIDA will include a brief description of the trial, baseline sociodemographic characteristics, retention and disposition of study participants, Quality Assurance issues, regulatory issues, AEs and SAEs, and efficacy, as well as any actions or changes with respect to the protocol.

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