

STUDY #: NIDA-CTN-0017

**HIV AND HCV RISK REDUCTION INTERVENTIONS IN DRUG DETOXIFICATION
AND TREATMENT SETTINGS**

CTN Version Number: 7.6

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ASI-Lite	Addiction Severity Index-Lite
CAB	Common Assessment Battery
CDC	Center for Disease Control
C & E	Counseling and Education Intervention
CIDI-2	Composite International Diagnostic Interview Version 2.1
CRF	Case Report Form
CSAT	Center for Substance Abuse Treatment
CTN	Clinical Trials Network
CTP	Community Treatment Program
DMC	Data Management Center
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IDUs	Injection Drug Users
IRB	Institutional Review Board
LI	Lead Investigator
MAR	Missing at Random

MCAR	Missing Completely at Random
MMT	Methadone Maintenance Treatment
NIDA	National Institute on Drug Abuse
NKI	Nathan Kline Institute
PI	Principal Investigator
RBA	Risk Behavior Assessment
RBS-ACASI	Risk Behavior Survey-Audio CASI
RI	Role Induction
SAE	Serious Adverse Event
SEP	Syringe Exchange Program
SES	Socio-Economic Status
SOC	Stages of Change
SR	Services Received Questionnaire
TA	Therapeutic Alliance Intervention
TFB	Time Line Follow Back Assessment of Treatment Participation
WAI	Working Alliance Inventory

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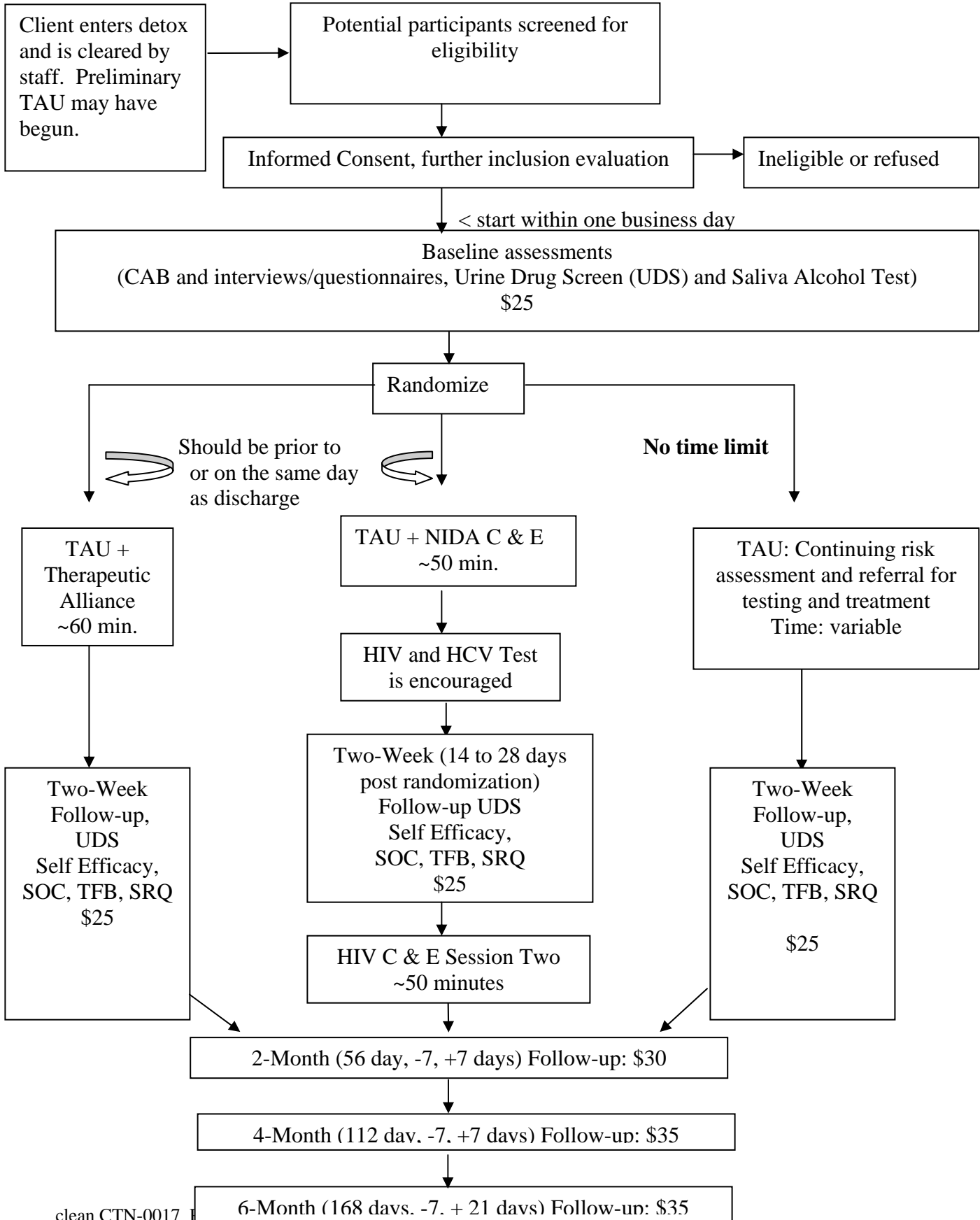
0.0 Study Synopsis and Schema

This study investigates the impact of two interventions on reducing HIV and HCV risk behaviors among injection drug users (IDUs). The NIDA Counseling and Education Intervention (C & E) uses testing and education to encourage IDUs to avoid using contaminated injection equipment that might transmit HIV or HCV, as well as to practice safe sex behaviors. The Therapeutic Alliance Intervention (TA) seeks to engage clients leaving detoxification and route them into outpatient drug treatment. This study proposes to assess the relative effectiveness of the C & E and TA Interventions compared to Treatment as Usual (TAU) regarding HIV risk reduction practices. The analyses will determine which interventions are most effective in reducing HIV-related risk behaviors over a six-month follow-up period. Eight residential detoxification centers from Community Treatment Programs (CTPs) participating in the Clinical Trials Network (CTN) will conduct the study. Each detoxification unit will sample approximately two clients per week over a period of approximately 52 weeks. Detoxification centers should serve a large and diverse population providing medical assistance and withdrawal management for clients who inject methamphetamines, amphetamines, cocaine or opiates.

Study participants include injection drug users who by definition are at risk for HIV and HCV infection or if infected, at risk for transmitting HIV and/or HCV. All participants must be 18 years of age or older. The goal is to recruit an average of sixteen participants per week across eight sites for a total of 808 randomized participants. Participants will be randomly assigned to one of three conditions, TAU + C & E, TAU + TA, or TAU alone, resulting in approximately 269 participants per condition. Participants will be assessed at baseline, while they are still in the detoxification center and re-assessed at 2 weeks, and 2, 4, and 6 months.

Linear and nonlinear mixed model analyses will assess whether frequency of risky injection behaviors decreases as a result of the interventions, whether treatment engagement is increased by the interventions and whether risky sexual behavior (having vaginal and/or anal sex without a condom) decreases as a result of the interventions.

Figure 1: Study Schema for NIDA-CTN-0017



1.0 Introduction

The association between AIDS and drug injection is well established. Through June 2001, injection drug users (IDUs) accounted for more than 40% of the 784,032 cases reported among persons aged 13 or older to the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention, 2000). Sharing syringes and injection paraphernalia, as well as unprotected sex, increases the risk of infection from HIV and other blood borne illnesses among drug users and their sexual partners (National Research Council, 1989; National Research Council & Institute of Medicine, 1995). HIV transmission, the etiological agent for AIDS; (Alcapes & Friedland, 1995; Barre-Sinoussi et al., 1983), has been linked to injection frequency (Marmor et al., 1987; Schoenbaum et al., 1989), injecting in shooting galleries (Chaisson et al., 1989; Vlahov et al., 1990), number of needle sharing partners (Choopanya et al., 1991; Nicolosi, Leite, Musicco, Molinari, & Lazzarin, 1992), frequency of needle sharing (Coutinho, 1990; Robertson, Skidmore, & Roberts, 1988), sharing cottons, cookers and rinse water (Koester, Booth, & Zhang, 1996) and injecting cocaine (Chaisson et al., 1989; Koblin, McCusker, Lewis, & Sullivan, 1990). IDUs play a critical role in the transmission of HIV to non-IDUs due to sex risk behaviors (Des Jarlais & Friedman, 1987; Friedland & Klein, 1987), including unprotected sex (Saxon, Calsyn, Whittaker, & Freeman, 1991; Watkins, Metzger, Woody, & McLellan, 1993), exchanging sex for drugs or money (Astemborski, Vlahov, Warren, Solomon, & Nelson, 1994; Kim, Marmor, Dublin, & Wolfe, 1993), and multiple sex partners (Bulterys et al., 1993; Wiebel, Chene, & Lampinen, 1988). IDUs are also at increased risk for HIV infection through sexual intercourse with other IDUs (Battjes, Pickens, Amsel, & Brown, 1990; Booth, Koester, Brewster, Weibel, & Fritz, 1991; Murphy, 1987).

Transmission of Hepatitis C virus (HCV), primarily through sharing drug preparation and injection equipment, is also a major public health concern. Sixty percent of HCV transmission is related to injection drug use (IDU) behavior and estimates of IDUs infected with HCV range from 50 to 95 percent (Alter, 1999; Garfein et al., 1998). This high rate among IDUs, even in locations where HIV prevalence is not high, may be partly due to the higher transmissibility of HCV (compared to HIV) which can be easily spread through the use of rinse water, spoons, and filters, even if drug users do not share needles (Coutinho, 1998; Crofts, Caruana, Kerger, & Bowden, 2000). Newer IDUs are also thought to be infected relatively early in their injection drug use careers (Centers for Disease Control and Prevention, 2002), contributing to the high rate of infection.

2.0 Study Rationale

Risk Reduction: Interventions and policy proposals to prevent HIV and HCV infection among IDUs have emphasized increased access to sterile syringes and, when necessary, the use of bleach to reduce transmission (National Research Council & Institute of Medicine, 1995; Needle & Coyle, 1997; School of Public Health- University of California Berkeley & Institute for Health Policy Studies- University of California San Francisco, 1993). Interventions have included media campaigns (Bortolotti, Stivanello, Dall'Armi, Rinaldi, & La Grasta, 1988; Power, Hartnoll, & Daviaud, 1988), street outreach (Booth & Wiebel, 1992; Colon, Robles, Freeman, & Matos, 1993; Watters et al., 1990), HIV testing and counseling (Calsyn, Saxon, & Freeman, 1992; Casadonte, Des Jarlais, Friedman, & Rotrosen, 1990; Skidmore, Robertson, & Roberts, 1989), syringe exchange programs (Des Jarlais et al., 1996; Watters, Estilo, & Clark, 1994) and substance abuse treatment (Ball, Lange, Myers, & Friedman, 1988; Hartgers, van den Hoek, Krijnen, & Coutinho, 1992; Sorenson & Copeland, 2000). Each of these approaches has demonstrated some degree of success in reducing HIV-related risk behaviors. For this protocol, one of the interventions to be tested is an updated version of the HIV Counseling and Education (C & E) Intervention model developed by NIDA for their Cooperative Agreement with out-of-treatment drug users (Coyle, 1993). The approach includes HIV pre-test counseling, optional (although strongly encouraged)

HIV testing, post-test counseling, and the provision of test results. This manual-driven model has been compared to more expensive and labor-intensive approaches (e.g., didactic education, group intervention, street outreach) and found to be as effective in reducing HIV risk behaviors (Booth, Kwiatkowski, & Stephens, 1998; Stephens, Kwiatkowski, & Booth, 2000). For example, in an evaluation of more than 3,700 IDUs from eight Cooperative Agreement sites, 34% of those who received the C & E Intervention reported not injecting at follow-up, compared to 37% who received enhanced interventions (Booth, Kwiatkowski, & Stephens, 1998). Similarly, the percent of IDUs reporting known use of a previously used syringe without disinfecting decreased by 17%, and sharing cotton, cooker or water decreased by 25% between the baseline assessment and the 6-month follow-up interview among those receiving the C & E Intervention. In a study of nearly 5,800 drug users, Stephens et al. (2000) reported a 25% reduction in the percent injecting drugs at follow-up and a frequency decrease of 28 times injecting in the past 30 days among participants in the C & E Intervention. While differences between the interventions were not statistically significant, there were significant differences from baseline to follow-up within each intervention on these measures, offering support for the less expensive and less demanding C & E Intervention. It should be noted that, for ethical reasons, the Cooperative Agreement did not include a “no” intervention control group. Everyone received at least the minimal C & E Intervention. For this protocol, we will update the intervention to include more recent information regarding safer injection practices and HCV prevention.

Stephens et al. (2000) assessed reductions in sex-related risk behaviors among Cooperative Agreement participants. They found that both those in the NIDA C & E Intervention and the more involved site-specific enhanced interventions reduced their risks by 18% from baseline to six-month follow-up. This included change in always using condoms and abstinence. Calsyn et al. (1992) also assessed an AIDS testing and counseling intervention and reported that participants increased their condom use from 12% to 28% over an 18 month period, while having multiple sex partners declined by 22% and 21% among men and women, respectively. Two studies of high-risk women found that condom use increased and anal sex decreased significantly following HIV testing and counseling interventions (Cohen et al., 1988; Corby, Barchi, Wolitski, Smith, & Martin, 1990). These investigations lend support to the C & E Intervention proposed in this protocol and its ability to reduce sex-related HCV/HIV risk behaviors.

Drug Treatment: Drug treatment is also an effective intervention to reduce needle use and the risk of HIV infection (National Research Council, 1989; Sorenson & Copeland, 2000). Consequently, the Federal Substance Abuse Prevention and Treatment Block Grant requires priority access for IDUs. Long-term drug treatment is of central importance in reducing drug use and associated risk behaviors for those who are drug dependent (Gerstein et al., 1994; R. L Hubbard, Craddock, Flynn, Anderson, & Etheridge, 1997; R. L. Hubbard et al., 1989; Sells & Simpson, 1976; Simpson, Joe, & Brown, 1997). However, despite enhanced access to publicly funded treatment, many IDUs (and drug users without priority access) rely primarily on detoxification services. In New York City, for example, 18% of the 8,386 clients seen in Central Intake sites between 1992 and 1994 were referred to detoxification (P. Kleinman, Millery, Breeder, Tesiny, & Millman, 1995). In this same time period, 45% of 44,169 clients served by the Target Cities project in Boston were treated in detoxification (Schwartz, Baker, Mulvey, & Plough, 1997). While detoxification could serve as a gateway to long-term treatment, only about one-in-five detox admissions leads to further treatment (McCusker, Bigelow, Luippold, Zorn, & Lewis, 1995). Strategies to enhance engagement in formal treatment following completion of detoxification are thus critically needed in order to reduce HIV and HCV risk among drug using patients. The TA between clients and counselors has been identified as an important factor in the retention of drug abuse clients in treatment. As the strength of the relationship between client and counselor has been demonstrated to predict treatment outcome across treatment modalities (Horvath & Symonds, 1991), process characteristics are beginning to

take center stage in treatment. Luborsky et al. (1985) observed that an early alliance between client and counselor in Methadone Maintenance Treatment (MMT) predicted better client outcomes, and similarly, Mohl et al. (1991) found low working alliance scores predicted early dropout. Therapeutic alliance scores were found to explain a significant amount of variance, over other demographic and cognitive variables, in accounting for length of stay in treatment (De Weert-Van Oene, Schippers, De Jong, & Schrijvers, 2001). Thus, an intervention that increases the therapeutic alliance between the counselor and client may be highly effective in motivating clients in detoxification to continue their treatment experience in outpatient care. The intervention we propose will use counselors who provide outpatient services to make appointments with the clients to enter further treatment before the client leaves detoxification. It is hypothesized that treatment entry following detoxification will be greater among clients receiving the therapeutic alliance intervention than the comparison condition and that clients who enter treatment after detoxification will reduce their sex and drug related HIV and HCV risk behaviors to a greater extent than those who do not enter treatment.

The concept of the TA has been well developed theoretically. It has been variously defined as the ability of the client and counselor to work together purposefully to achieve agreed upon goals (Greenson, 1971) and as the patient's experience with the therapist as a helpful agent in achieving the patient's goals (Luborsky, Crits-Christoph, Alexander, Margolis, & Cohen, 1983). It is comprised of cognitive, affective, and relational components. Although the concept of therapeutic alliance originated within the psychoanalytic literature, in the last quarter century, it has emerged as an overarching, transtheoretical concept (Safran & Muran, 2000). This trans-theoretical formulation was well explicated by Bordin (1979). He proposed that the TA is common to all forms of psychotherapeutic treatment, that it develops through participation of both client and therapist, and that it is composed of three core elements. These include the positive bond between client and therapist, agreement about the tasks of treatment and agreement about the goals or expectations of treatment. The TA Intervention in the current study is based upon this formulation and addresses each of these elements. Bordin postulated that the TA is both a condition of treatment, which facilitates change driven by specific treatment components, as well as a change agent in and of itself. Other theorists have concurred, describing the relationship between therapist and client as the primary means through which client change occurs (Waterhouse & Strupp, 1984).

Empirically, the role the therapeutic alliance in the process and outcome of psychotherapy, in general, and in drug treatment specifically, has been studied extensively. The research has consistently shown that the TA is a robust predictor of treatment outcome (Safran & Muran, 2000). This finding holds within drug treatment as well. For example, Woody et al. (1983) found that opiate addicts benefited from participation in psychotherapy in addition to standard drug counseling. As reported by Luborsky, Barber, Siqueland, McLellan & Woody (1997) they also found that the TA, as measured by the Helping Alliance Questionnaire (Luborsky, 1984), significantly predicted outcome for a combined sample of the three types of treatment offered, cognitive behavioral therapy, supportive-expressive therapy, and standard drug counseling.

Connors, Carroll, DiClemente, Longabaugh & Donovan (1997) found that ratings of the therapeutic alliance predicted treatment participation and drinking behavior during treatment, as well as 12 months post-treatment, for clients in the Project Match study of outpatient alcohol treatment. This finding held across all three treatment modalities studied: 12-step oriented treatment, motivational interviewing, and cognitive behavioral therapy. In this study, Connors et al. used the Working Alliance Inventory (WAI) (Horvath & Greenberg, 1986) to assess the TA. The WAI consists of three subscales: 1) the Goal Subscale measuring mutuality regarding the goals of treatment; 2) the Task Subscale

measuring agreement about the tasks of treatment and 3) the Bond Subscale measuring the bond between client and counselor. As discussed above, these are the core elements of the TA conceptualized by Bordin (1979) which have been incorporated into the TA Intervention in the proposed study.

Other studies have found that length of stay in drug treatment is significantly predictive of long-term outcome (Simpson, 1981) and that the quality of therapeutic relationship significantly influences length of stay (De Weert-Van Oene et al., 2001; Simpson, 1998). Recently, Joe et al. (2001) found that counseling rapport, as measured by counselor ratings of therapeutic involvement and relationships with patients, contributed explicitly to the prediction of outcome in MMT, independent of treatment retention.

Despite development of scales to measure TA and research investigating its role in treatment outcome, there has been relatively little work on interventions designed specifically to develop or enhance TA. In drug treatment, where initial drop out rates are high (Stark, 1992) and rates of transition from detox to ongoing treatment are low (B. Kleinman, Millery, Scimeca, & Polissar, 2002). Interventions based on the TA concept to increase initial retention are urgently needed.

One area of research in which interventions postulated to enhance the TA have been investigated is that of "role induction." Role induction interventions are essentially treatment preparation interventions designed to educate clients about what to expect in the treatment process, including "roles" of client and counselor, tasks, and goals of treatment. This focus on achieving understanding and agreement between client and counselor on treatment tasks and goals explicitly addresses two of the core components of the TA as described by Bordin (1979).

There is substantial evidence that use of role induction as a psychotherapy preparatory technique increases retention in outpatient mental health treatment (Walitzer, Dermen, & Connors, 1999). A number of studies have also shown role induction procedures to be effective in increasing attendance in substance abuse treatment. Stark and Kane (1985), the latter of whom is the author of the current TA Intervention, tested brief role induction interventions at the initial assessment for outpatient drug treatment with four groups: a general psychotherapy role induction (RI) strategy; a drug-treatment specific RI; an informational control; and an assessment as usual control group. The drug treatment specific RI intervention differed from the general psychotherapy RI intervention by emphasizing the relationship between drug abuse and other problems, the importance of being honest with the therapist about drug use, and denial and rationalizations associated with drug use. The general RI group focused on building the relationship with the therapist, being honest with the therapist and discussing troublesome thoughts and feelings. They found that participants in the two RI groups were significantly more likely to return for at least one treatment session than control participants (81% vs., 56%), and those who received the drug-treatment specific RI returned at an even greater rate (91%) than those who received the general RI (72%). Craigie and Ross (1980) conducted a role induction study with alcohol detoxification patients. They compared patients who participated in an alcohol treatment, videotaped role induction with control participants who watched a videotaped alcohol education group. RI participants were significantly more likely to leave detoxification treatment with a treatment referral and, to make an initial post- detox treatment contact.

Several, non-experimental studies have also shown RI interventions to increase treatment attendance. Keaney et al. (1995) found that use of a structured RI interview designed to increase clarity about the purpose and expectations of outpatient relapse prevention group significantly decreased dropout rates for problem drinkers relative to rates which occurred prior to the initiation of the RI interview. Verinis (1996) found that a sample of low SES minority alcoholic veterans who participated in a RI orientation

group had significantly better treatment attendance for the next 30 days than a similar sample of veterans who did not participate in the RI group. Recently, CODA, a community treatment program in Portland, Oregon, and a CTN CTP, adapted role induction interventions for use in post-detoxification treatment referral. In a non-published demonstration project, detox clients met with outpatient counselors and discussed the process of outpatient treatment, including developing a plan for attending. This intervention increased rates of attendance at first outpatient session from 25% to 72%.

3.0 Study Design

This study aims to test the effectiveness of two interventions for detoxification clients combined with TAU compared to TAU alone. The C & E is a risk reduction intervention, which uses educational materials to instruct injection drug users about safer injection and sexual practices and administers HIV and HCV tests to inform participants of their current serostatus. The second intervention, the TA facilitates treatment entry by means of establishing a therapeutic alliance between the patient and a counselor who can provide outpatient services. Participants in this condition will be encouraged to make an appointment.. Using techniques adapted from Role Induction (RI), the intervention is designed to develop rapport between the participant and counselor and facilitate further treatment.

Eligible clients in detoxification centers will be administered baseline assessments, then randomly assigned to one of three conditions: A) TAU plus the NIDA C & E Intervention; B) TAU plus the TA Intervention; or C) TAU only, consisting of normal clinic HIV/HCV risk reduction procedures and normal clinic procedures for linkage to continuing care. The TAU risk reduction intervention is the standard of HIV risk assessment screening and referral for testing that the clinic normally uses for clients coming through the detoxification center. If the client admits that she or he is already positive, they may be referred for testing to confirm this or referred to appropriate medical care, and will remain eligible for this study. The TAU linkage to continuing care procedure involves meeting with a treatment staff member who offers a referral to treatment and assists with making phone calls and arranging appointments upon the client’s request. These procedures are standards of care in most detoxification settings. Research participants in the two experimental conditions will also receive TAU. Whenever possible, the two experimental interventions, described in section 6.0, will take place on the same day as the baseline assessments, or at the latest, within the same day as discharge from the clinic. Every attempt will be made to follow all participants who have been randomized.

Figure 2: Schematic Diagram of the design and recruitment goals.

Counseling and Education Intervention N=269	Therapeutic Alliance N=269	Treatment as Usual N=270	Total n = 808
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4.0 Objectives

Primary Aim: The primary aim of this study is to evaluate the relative effectiveness of three interventions, TAU + C & E, TAU + TA, and TAU (normal detox clinic HIV procedures) on HIV/HCV risk behavior reduction following a stay in a detox center. The primary outcome variable for HIV/HCV risk behavior will be the cumulative sharing of needles/syringes without disinfecting, sharing water, cotton, cooker and sharing the drug solution in the previous 30 days. This variable is calculated on the basis of the following four items from the Risk Behavior Survey (RBS): 1) In the last 30 days, how many

times (# of injections) did you inject using works (needles/syringes) that you know had been used by someone else? ; 2) Of the times you injected after someone, how many times did you clean the works with full-strength bleach?; 3)How many times in the last 30 days did you use a cooker/cotton/rinse water that had been used by another injector? ; 4) How many times in the last 30 days did you fix with another person, then split the drug solution (through the use of the same cooker/spoon or through front or back loading? These items will be assessed at baseline and at 2, 4, and 6-month follow up assessments. The primary outcome variable is calculated by subtracting the response to item 2 from the response to item 1 and then adding the responses to items 3 and 4.

Secondary Aim #1: To evaluate the effectiveness of C & E and TA compared to TAU on outpatient treatment entry following discharge from the detoxification clinic. Data on initial treatment entry will be collected at the 2-week follow-up and at 2, 4 and 6-month follow-up visits. These treatment entry rates will be compared across the three study conditions. This variable will be assessed by self-report using the TFB.

Secondary Aim #2: To evaluate the effectiveness of C & E and TA compared to TAU on treatment retention over a 6-month follow-up period measured by the number of weeks patients attended outpatient drug treatment after discharge from the detoxification clinic by self-report using the TFB procedure.

Secondary Aim #3: To evaluate the effectiveness of C & E and TA compared to TAU on reducing the percent of those injecting and reducing the frequency of injecting in the past 30 days by self-report using the RBS-ACASI.

Secondary Aim #4: To evaluate the effectiveness of C & E and TA compared to TAU on reduction in sex risk behaviors related to HIV/HCV infection (unprotected vaginal or anal intercourse) over the 6 month follow up period utilizing self-report of whether participants used a condom 100% of the time vs. less than 100% or engaged in no vaginal or anal sex activities by self-report using the RBS-ACASI.

We expect that C & E, will have a greater impact on HIV/HCV risk behaviors than TA or TAU. Given that standard clinical practices (TAU) usually offer only a risk assessment and a referral for testing, we hypothesize that this intervention is not likely to be effective in reducing HIV/HCV risk behavior among the injecting population because there is typically no educational component on how to reduce risk, nor is there an effort to bridge the client into a treatment that could reduce their drug use. We hypothesize that, of participants in the TA group, those who enter treatment will be most likely to reduce HIV/HCV-related risk behaviors, and that more individuals enter treatment following the TA Intervention than the C & E intervention or TAU. The C & E intervention is more likely to reduce HIV/HCV-related risks due to the educational and demonstrative nature of addressing risk reduction to at-risk individuals. Since the C & E intervention has a sex risk education component, this intervention is more likely to reduce sex risks than either the TA Intervention or TAU. Each of the aims above is designed to evaluate the above hypotheses.

5.0 Study Population

Detoxification Centers: Eight residential detoxification centers will be included from Community Treatment Programs (CTPs) participating in the Clinical Trials Network (CTN). The sampling goal for each detoxification unit is approximately sixteen clients per week across eight sites over a period of one year.

Study participants will be injection drug users recruited during detoxification treatment, 18 years of age or older, eligible for outpatient services, have a recent history of injection drug use, and have not been previously consented for this study. Furthermore, participants will agree to a urine drug screen at each

visit, plan to remain in the area for the next 6 months, and agree to a detox records review to confirm eligibility.

Recruitment: The goal is to recruit an average of sixteen clients per week across all sites, with the total number of participants across all 8 sites expected to be 808 and not to exceed 820 participants randomly assigned to one of three conditions.

6.0 Study Intervention

Two interventions will be implemented to test the effectiveness of different approaches in reducing HIV and HCV risk behaviors and increasing rates of treatment entry and retention. The NIDA C & E intervention consists of an initial session with a follow-up session approximately two weeks later at which point the results of the HIV and HCV tests are provided (if the participant agreed to a blood draw). The TA Intervention consists of one session, with no follow-up session. The two-session approach is necessary for the C & E intervention but it is not necessary, nor theoretically relevant, for the TA Intervention. The TAU will vary by CTP, depending on standard HIV risk assessment and referral practices.

As noted, the interventions differ in length. In some designs, time differences between interventions are balanced with controlled attention (i.e., control group activities such as watching videos, or non-effective interventions) in order to keep the time of intervention from confounding the effect of the treatment. We have decided not to employ this technique as our aim is to determine which of these two experimental interventions is more effective and whether they are more effective than TAU.

6.1 NIDA Standard Counseling and Education (C & E) Intervention

The C & E intervention is a manualized individual-level prevention model developed by NIDA and a group of investigators from the Cooperative Agreement (Coyle, 1993). It consists of two education and counseling sessions that “structurally bracket – and encourage – confidential HIV antibody screening.” The decision to be tested is left up to the individual and the content of the intervention sessions is sufficiently flexible to accommodate those who decline to be tested, as well as those who test either seropositive or seronegative. At the conclusion of the initial counseling session participants are offered free HIV antibody testing; at the beginning of the second counseling session, approximately two weeks later, test results are reported (if they were tested). For this protocol, we will modify the intervention to include information about HCV as well as the offer of free HCV testing.

The intervention, as originally designed, stressed reducing needle and sex-related risk behaviors through using bleach to disinfect needles and syringes and condoms for safer sex. In 1993 and in 1997, however, CDC, CSAT and NIDA issued a joint HIV/AIDS Prevention Bulletin revising the earlier recommendation to strictly use bleach. Specifically, emphasis was placed on the importance of stopping or decreasing injection drug use through entering drug treatment, and for those who continue to inject, always using sterile injection equipment (i.e., a new syringe). Bleach was recommended only if a new unused syringe was unavailable. While NIDA’s C & E intervention included a discussion on the benefits of drug treatment, it did not address the use of new injection equipment. These changes will be incorporated into the revised C & E intervention. More specifically, the intervention will include the risk reduction hierarchy recommended by NIDA, CSAT and CDC in 1997 (Centers for Disease Control and Prevention, 1997). It recommends that drug injectors be counseled to do the following: 1) Stop using and injecting drugs; 2) Enter and complete substance abuse treatment, including relapse prevention; 3) Never reuse or “share” syringes, water, or drug preparation equipment; 4) Use only syringes obtained from a reliable source (e.g., pharmacies); 5) Use a new sterile syringe to prepare and inject drugs; 6) If possible, use

sterile water to prepare drugs, otherwise use clean water from a reliable source (e.g., tap water); 7) Use a new or disinfected container (“cooker”) and a new filter (“cotton”) to prepare drugs; 8) Clean the injection site prior to injection with an alcohol swab; 9) Safely dispose of syringes after one use; 10) If new, sterile syringes and other drug preparation and injection equipment are not available, then previously used equipment should be boiled or disinfected with bleach using the methods recommended in the April 1993 bulletin (Centers for Disease Control and Prevention, 1993). To further facilitate use of sterile syringes, in sites where syringe exchange programs (SEPs) exist, their locations, hours of operation and policies regarding needle exchange will be provided to participants assigned this intervention. In all sites, information will be provided regarding needle exchange programs, the purchase of syringes in pharmacies, if applicable, including locations, hours and cost, as well as local ordinances related to the sale of syringes. Because injectors may find themselves in a position where they do not have access to sterile equipment, sites may elect to include in the intervention demonstrations and rehearsals of needle cleaning, as well as condom use, to inform participants how to protect themselves from becoming infected in the event they continue using drugs and/or engage in risky sexual practices. CTPs uncomfortable with demonstrating and rehearsing needle cleaning will be asked to present the needle cleaning procedure recommended by CDC in 1993, but without an actual syringe. It will be emphasized, however, that the use of bleach is recommended only as a last resort.

Trained C & E Interventionists/phlebotomists (C & E Interventionists, if appropriate, may also serve as phlebotomists; if not appropriate, phlebotomist role will be a separate one) will provide this intervention. The phlebotomist will take a blood sample from each participant who consents to be tested for HIV and HCV. Samples will be sent to local laboratories for testing. Counseling sessions are succinct and delivered in a one-on-one private office setting. Informational cue cards guide the content of both intervention sessions and rehearsals of how to clean injection equipment and use condoms provide practical skill building. As part of the protocol, we will measure perceived self-efficacy to practice safe injection and sex behaviors. Referrals can be limited to the provision of written referrals, although sites with adequate resources can offer seropositive participants more active referral services for medical treatment.

The goals of the intervention include:

- Education about HIV and HCV and the behaviors that transmit them;
- The adoption of preventive behaviors – ideally, abstinence from drug use and adoption of monogamous or protected sex; or, at least reducing the frequency of drug use and the number of sex partners, avoiding shooting galleries, avoiding renting, borrowing, and sharing injection equipment (needles, syringes, cotton, cookers and rinse water) or the drug solution;
- Complementary prevention behaviors – entry into drug treatment (or remaining in treatment) is strongly encouraged, as is HIV and HCV antibody testing, partner notification, and family planning;
- The adoption of protective behaviors – specifically, the use of sterilization procedures for needles and syringes and the use of condoms or other protective means for sexual contact;
- The correct application of protective skills - specifically, correct needle sterilization techniques and use of condoms.

Because many IDUs engage in or have engaged in high-risk behaviors, the interval between the pretest and post-test counseling sessions – a period of approximately two weeks waiting for test results – is often a period of intense reflection. It is this intensity that adds strength to the C & E intervention. The theoretical bases for the intervention includes the Health Belief Model and fear arousal. According to the Health Belief Model, motivation to change behavior requires that individuals perceive their own vulnerability to risk, as well as their ability to protect against risk (Janz & Becker, 1984). The fear arousal theory maintains that fear messages function to motivate behavior change, when they are carefully linked to instruction about new behaviors that can be adopted (Sutton, 1982). Incorporating these theories, the first intervention session is designed to provide basic information about HIV and HCV infection. By focusing on risk behaviors associated with drug use and sex, the intervention is designed to show that commonplace activities, relatively safe only a few years ago, have become life-threatening practices in the era of the HIV and HCV epidemics. To address perceived vulnerability and fear, C & E Interventionists next focus on the preventive importance of eliminating injection drug use, or at least discontinuing sharing/renting/borrowing injection equipment, and the benefits of drug treatment and HIV and HCV antibody testing.

Social learning theory, which maintains that behaviors are learned through observation and copying, is also incorporated into the C & E intervention, combined with self-efficacy about the ability to practice new behaviors (Bandura, 1977). For this reason, in the first and second intervention sessions, counselors demonstrate how to use bleach and condoms correctly and ask participants to rehearse these behaviors until the participant demonstrates the necessary skills.

The content of the second intervention session is based primarily on whether the participant tested negative or positive to the HIV or HCV antibody tests, or declined to be tested. The second session repeats some of the educational materials from the first session, along with the rehearsal of correct bleach and condom use. This booster session is designed to clarify participants' understanding about risk reduction behaviors and increase competence and perceived self-efficacy about practicing new behaviors. Alternatives to high-risk behaviors are stressed, including drug treatment, discontinuation of injection drug use and sex without protection, elimination of sharing drug equipment or the drug solution and reduction in the number of sex partners. For participants who test seropositive, basic health care advice and a medical referral are provided, along with the importance of partner notification. For participants who become distressed by the results of their HIV or HCV tests, HCV/HIV tester/counselors will be trained to deal with such situations. Participants who become emotionally stressed will be encouraged to talk to the HIV tester/counselor about their feelings. In the event that any participant is assessed to be in need of extra support, appropriate referrals will be given. We offer a full range of assistance, including appropriate psychological and medical referrals. Participants identified in any phase of the research as suicidal, will be immediately referred and transported to appropriate crisis intervention and mental health services. Each site maintains a policy for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or other acutely distressed participants. Furthermore, evidence of emotional distress secondary to test results will be tracked as an SAE for this study.

To assist in promoting positive change, the C & E intervention model includes providing the materials and support necessary for the adoption and maintenance of safe behaviors. Participants are offered free bleach and condoms after both education sessions. In addition, literature about HIV and HCV transmission and the correct way to use hygiene materials is distributed. The literature also includes the names, phone numbers and addresses of social service agencies that can assist participants. If sites have the resources, counselors can make phone calls and provide transportation to assist with referrals for

participants who are seropositive. At both sessions, information about Syringe Exchange Programs (SEP), if available, and pharmacies will be provided.

6.2 Therapeutic Alliance (TA) Intervention

Counselors available to provide outpatient services will deliver the TA intervention. The single session intervention introduces clients to the process of counseling at the outpatient treatment center and begins the development of a positive treatment relationship with an outpatient treatment staff member. The counselor engages the client in a dialogue which focuses on developing the core components of the therapeutic alliance, agreement about the tasks of treatment, possible goals for treatment, and the partnership between client and counselor to attain those goals. The intervention addresses both content, that is, reaching a mutual understanding about treatment and process, developing a positive bond between client and counselor. Participants are encouraged to ask questions and discuss fears, expectations, and hopes about treatment. The counselor describes the treatment process, engaging clients in a dialogue regarding treatment goals and the shared tasks of both counselor and client. A collaborative, "team" approach and expectations of treatment success are emphasized. Lastly, the counselor describes common experiential elements of engaging in treatment, and frames these as part of recovery and treatment progress. The session concludes with the TA counselor and participant scheduling an outpatient treatment appointment if the participant agrees, or providing the participant with written information about scheduling or referrals. Outpatient treatment appointments, which occur after the TA session, are not part of the intervention itself and will follow standard treatment procedure at each site. The primary goal of this intervention is to reduce HIV/HCV risk behavior as mediated by post-detox treatment participation. A concomitant goal is to increase treatment entry and retention post-detoxification relative to standard detox discharge counseling and referral.

The TA intervention utilizes components of the RI intervention as delivered by the counselor who will be available to work with the client in outpatient treatment.. RI has been enhanced specifically to assist in the development of core components of the TA based on Bordin's (1979) conceptualization. It does so by addressing the tasks of treatment and the goals of treatment, as typically addressed in role induction, as well as explicitly facilitating the development of a collaborative and positive bond between counselor and participant, a process element which has usually been left implicit in role induction interventions conducted in previous studies. The current TA Intervention follows many of the recommendations made by Luborsky et al. (1997) regarding procedures for improving the TA and, consequently, outcomes, in substance abuse treatment, including strategies which increase "therapist alliance-facilitating behaviors" (Luborsky et al., 1997, p. 238). The intervention is thoroughly outlined, straightforward, and relatively simple to learn. It is one that will likely appeal to counselors, for the purpose of enhancing their alliance building therapy skills, as well as community treatment programs, for its simplicity and straightforward appeal.

7.0 Measures

The main outcomes of interest are the drug and sex-related HIV and HCV risk behaviors (from the RBS) that the participant engaged in during the 30 days prior to study entry and at each follow-up assessment point. These measures will be collected on all participants enrolled in the study, as defined by signing the study consent. Participants will be assessed using the full battery of instruments from the Common Assessment Battery(CAB), an alcohol test, along with the Self-Efficacy (SEF), Services Received (SRQ) and Stages of change (SOC) questionnaires and a Urine Drug Screen (UDS) after consenting. Participants will also be asked to provide locator information. Whenever possible, the CAB and associated interviews will be conducted immediately following consent, but no longer than one business day after consent. If the baseline assessments are not started within one business day of consent, the participant will be

administratively withdrawn from the study. A short interview will take place for all participants 14-28 days after randomization, during which they will be given the SOC and Self-Efficacy questionnaires, the TFB, the SRQ, and a UDS. Follow-up interviews, the ASI and questionnaires, and UDS, will be collected at 2 months (56 days), 4 months (112 days) and 6 months (168 days) after the randomization date. A 14 day window, defined as 7 days before and 7 days after the due date, will be available to complete the 2 and 4 month follow-up interviews and a 28 day window, defined as 7 days before and 21 days after the due date, will be available to complete the 6 month follow up interview. The locator information will be updated at the two-week, 2-, and 4-month follow-up visits. Time line follow-back techniques (Sobell & Sobell, 1996) will be used to collect information regarding treatment prior to the current visit.

7.1 Instrumentation

7.1.1 Common Assessment Battery (CAB)

A Demographic Questionnaire developed for use by the CTN assesses age, ethnicity/race, and gender. This will be administered at baseline.

The Composite International Diagnostic Interview Version 2.1-Substance Use Diagnosis (CIDI-2 (SUD module)) is a structured lay-interview for diagnosing psychiatric disorders with demonstrated reliability and validity (Kessler et al., 1994). This will be administered at baseline.

The Addiction Severity Index-Lite (ASI-Lite) for Baseline and Follow-up (ASI-F) (McLellan et al., 1992; McLellan, Luborsky, O'Brien, & Woody, 1980) is a comprehensive instrument, which assesses the drug and alcohol use behavior of respondents in seven major areas over the participant's lifetime and in the past 30 days. Composite scores are available for the Medical, Employment, Alcohol Use, Drug Use, Illegal Activity, Family/Social, and Psychiatric domains. This instrument has been used in many studies to assess substance-abusing clients and its reliability and validity are well established (McLellan et al., 1985) with extensive research and testing in drug and alcohol abusing populations. Modifications also continue to be made to improve the usability of this instrument across populations and assessment periods (Carise et al., 2001). This will be assessed at Baseline (ASI-Lite) and at the 2, 4, and 6-month follow-ups (ASI-F).

The Risk Behavior Survey (RBS), an abbreviated version of the Risk Behavior Assessment (RBA) developed by NIDA (1993) for a Cooperative Agreement, will be used to measure HIV and HCV risk behaviors in the areas of drug use and sex in the previous 30 days. This assessment will be collected using the Audio-CASI method (Needle et al., 1995; Weatherby et al., 1994). The computer-administered self-interview with audio (ACASI) is a computer-based interview. Using ACASI, participants are asked and they answer sensitive questions by themselves. Participants simultaneously read and hear the questions and provide answers without the interviewer. The self-conducted survey includes questions about using works (needle/syringe) previously used by another injector and not disinfected, sexual activities, health, sexually transmitted diseases, and HCV/HIV. During an interview, the participant's responses are entered into the computer and automatically saved. Once an interview is completed, ACASI creates Automated Interview Data Files (QAD files). These files contain all the information collected in the interviews, thus eliminating the data entry process. The QAD files are collected by NKI and added to the study database. The site will receive a printed confirmation of completion of the RBS bearing the ID# and date for each participant. Although many studies have reported adequate reliability and validity of self-report data with injection drug users using an interview-administered assessment (e.g. Booth, Crowley, & Zhang, 1996; Needle et al., 1995; Weatherby et al., 1994), use of ACASI has been found to minimize social desirability and encourage even more accurate reporting of HIV risk behaviors (Des Jarlais et al., 1999; Lessler,

Caspar, Penne, & Barker, 2000; Macalino, Celentano, Latkin, Strathdee, & Vlahov, 2002; Turner et al., 1998). Research has also shown that drug users are comfortable using computers for interviewing and possess the requisite skills to complete the interview with a touch screen and audio enhancement (Williams, Freeman, Bowen, & Saunders, 1998). Locally, two years experience with ACASI support these conclusions. The RBS ACASI will be administered at Baseline, 2-, 4-, and 6-month follow-up visits.

7.1.2 Additional Interviews/Questionnaires

To assess drug use, Urine Drug Screen test strips (UDS) for Amphetamines, Barbiturates, Benzodiazepines, Cocaine, Methamphetamine, Methadone, Morphine, Phencyclidine, Tricyclic Antidepressants and THC. The Urine Drug Screen will be performed at baseline, the 2-Week follow-up visit, and the 2-, 4-, and 6-month follow-up visits. Standard UDS test-cup kits will be supplied to each site.

A saliva test (ALCO Screen O2 (ST)) will be used for testing the presence of alcohol at Baseline only.

Timeline Follow-Back Assessment of Treatment Participation (TFB) modeled after Sobell & Sobell (1996) Timeline Followback Method assessing alcohol and drug use - will be used to determine alcohol and drug abuse treatment sessions received since the last study visit. The method uses a calendar on which the interviewer asks the respondent to indicate the days they attended substance abuse treatment. This will be administered at 2-week and, 2, 4, and 6-month follow-up visits.

Self-Efficacy (SEF) for engaging in safer drug and sex behaviors is measured using a modified version of the Cooperative Agreement “RBA Behaviors and Beliefs Trailer” developed by Rhodes (1998). It assesses the degree to which individuals feel confident that they can perform safer drug and sex behaviors when faced with risky situations. As such, it evaluates the effectiveness of the C & E intervention in teaching protective measures. This will be administered at baseline, 2-week and, 2, 4, and 6-month follow-up visits.

Stages of Change (SOC) for quitting drug use will be measured using a modification of the Motivation Scales, including Drug Use Problems, Desire for Help, and Treatment Readiness, from the data instruments developed by Simpson et al. for the Drug Abuse Treatment, Assessment, and Research Project (Simpson, Joe, Broome et al., 1997). The instrument, SOC, has excellent predictive validity relative to treatment entry (Booth, Kwiatkowski, Iguchi, Pinto, & John, 1998) and its test-retest reliability is 90%. It will serve as a measure of the TA Intervention’s ability to increase motivation for treatment. This will be administered at baseline, 2-week, 2-, 4-, and 6-month follow-up visits.

Services Received Questionnaire (SRQ) questionnaire measures the extent of TAU assessment for risk behaviors and referrals the participant remembers receiving during detoxification. This brief measure will be administered at baseline and at the 2-week follow-up.

Locator Form information typically includes contact information such as a residential street address, or an address of someone who knows where to contact the participant if they are homeless, and a phone number where they can be reached. Additional information includes the names and addresses of two or three individuals who likely would know their whereabouts, particularly relatives or close friends. This information will be obtained immediately following completion of the interviews. Locator information will be updated at the 2-week, and 2- and 4-month follow-up visits.

8.0 Study Procedures

8.1 Roles of the study

Consenting process:

- Identify potential participants
- Obtain informed consent
 -

Scheduling roles:

- Coordinate appointments for baseline
- Conduct randomization
- Coordinate follow-up assessments
- Set clinical appointments for interventions with C & E or TA therapists
- Assure participants are directed to their assigned intervention

Safety and protocol management:

- Review Adverse and Serious Adverse Events
- Crisis intervention consultation
- Supervise the work of the research assistant

Data collection-interviews:

- Administer CAB (back-up required)
- Administer protocol specific assessments (back-up required)

Data Entry:

- Enter data from CRFs
- Reconcile data errors
- Assist with data audits

Administer Interventions:

- Counseling and Education (back-up required)
 - Phlebotomy (back-up required)
- Therapeutic Alliance (back-up required)

Supervisory (need one for each intervention):

- Adherence/competency rating for each intervention
- Trained on administration of interventions (back-up to therapists)
- Retraining therapists on interventions if necessary

Study coordination, oversight:

- Supervision of RA (back-up to RA)

8.2 Identifying Participants-

This protocol may involve vulnerable populations (Pregnant women and fetuses, and Mentally/Cognitively Impaired). This protocol does not specifically recruit pregnant women and fetus, or the Mentally/Cognitively Impaired, however, they may enroll in this study with proper clearance from the site personnel. Because drug and drug detoxification centers include these two vulnerable populations, it

is essential for these subjects to be allowed to enroll in the research. Site clinical personnel are well qualified to determine the medical and emotional status of the clients, and will clear the client prior to obtaining informed consent. Secondly, the person obtaining informed consent will be well trained in determining that the potential participant has adequate understanding of the protocol. Understanding will also be evaluated using a Consent Quiz. Any potential participant requiring a proxy consent will not be enrolled. The study involves the comparison of two treatment modalities which are therapy sessions geared at education around high risk behaviors for contracting HIV/HCV among injections drug users, and the engagements of the client into therapy within the clinic. We do not anticipate these interventions will harm either of these populations.

A staff member in the detoxification unit will present a brief description of the study and offer the study Information Sheet which will describe the purpose of the study, how long it will take, and states that the participant will be compensated for their time, that there is no cost to the participant, and the usual services of the clinic are not affected by participation in this study. If the client expresses interest the client will proceed to the consenting process. Research personnel further explain the study to potential participants and continue to assess eligibility. If the potential participant expresses continued interest in the study, research personnel will begin the full study Informed Consent process. First the research personnel will review the study ICF with the potential participant and conduct the Consent Quiz. Prior to signing the study ICF, the potential participant must demonstrate an understanding of the protocol procedures, risks, and benefits with 100% correct responses on the consent quiz to continue with the screening process. Any item missed on the quiz will be reviewed and explained until it is understood. If an item is not understood after thorough explanation, the potential participant will not be admitted to the study. If at any time during the consent process it is determined that the potential participant is incompetent to provide informed consent, the participant will not be enrolled in the study. Consent by proxy is not allowed.

8.3 Determining Eligibility

Some sites routinely obtain injection drug use history and visually inspect track marks at intake to the detoxification unit. Other sites do not specifically obtain information regarding injection drug use. We have incorporated steps to determine eligibility in the study consent.

The Consent Form will authorize researchers to review intake records for injection drug use history and inspection of track marks if this information is routinely collected by the clinic at intake. If this information is not routinely collected, the Consent authorizes the research staff to ask about injection drug use in the last thirty days, and to inspect potential participants for signs of recent drug injection (i.e., “track marks”) or, if track marks are not visible, to ask the client to describe their injection practices. If, during the consent process, potential participants determined to be mentally or cognitively impaired to provide informed consent will not be enrolled in this study. Potential participants must meet *all* of the following eligibility criteria for study participation:

8.3.1 Study Inclusion Criteria

Participants must:

1. Present for services at a detoxification clinic

2. Be at least 18 years of age
3. Be cleared to be consented by detoxification clinic staff
4. Have both a. and b. of the following indicators of recent drug injection:
 - a. (Visible marks of recent injection) **OR** (has self-identified as an injector **AND** describes correct injection practices).
 - b. Self-report of injection of opiates, cocaine, amphetamine or methamphetamine in the previous 30 days
5. Have passed the consent quiz and has provided informed consent
6. Report planning to remain in the area for the next 6 months
7. Agree to provide locator information for subsequent follow-up contacts
8. Agree to be tested with a urine test at the time of each interview
9. Be sufficiently fluent in English to understand consent and assessments

8.3.2 Study Exclusion Criteria

Participants must not:

1. Be unable to provide informed consent
2. Be incompetent to provide informed consent
3. Require consent by proxy
4. Have a medical or psychiatric condition that would, in the opinion of the clinic staff, make participation in this study hazardous
5. Have pending legal action that would prohibit or interfere with participation in the next 6 months
6. Be **known to have a high likelihood of entering long term residential treatment immediately after discharge from detox. ("long term" is defined as longer than 4 weeks)**
7. Have previously consented to this study

If potential participant meets all inclusion criteria, and no exclusion criteria, the participant is determined to be eligible for the study and scheduled for the Baseline Assessment the same day of consent, or at most, the Baseline Assessments must start within the next business day after consent. The participant must still be in the detoxification center at the time of the Baseline Assessment.

8.4 Baseline Assessment

The interviewer will conduct the Baseline Assessment using the following instruments:

1. Urine Drug Screen (UDS)
2. Saliva Alcohol Test (ST)
3. Demographics Questionnaire (DEM)
4. Drug Use Screening Questionnaire (DUS)
5. Services Received Questionnaire (SRQ)
6. Addiction Severity Index -Lite (ASL)
7. Composite International Diagnostic Interview Version 2 (CIDI-2) (SUD)
8. HIV Risk Behavior Survey (RBS)-audio CASI
9. Stages of Change (SOC)
10. Self Efficacy (SEF)
11. Locator Form

8.5 Randomization

A computer-based, centrally administered, blocked randomization scheme provided by the Veteran's Administration Randomization System will be utilized to randomly assign participants to one of the three

conditions stratified by site/CTP. Blocked randomization guarantees that at no time during randomization will the imbalance in the participants assigned to each condition be large and that at certain points, the number of participants in each group will be equal. Personnel involved with the protocol will be blind to the block size and randomization scheme, which will be operationalized and administered by an external technician of the VA. The Study Site Coordinator or designee for each CTP will utilize the Randomization System via telephone to obtain the randomization assignment for each participant. Confirmation of the randomization assignment will be faxed to the SSC or designee. Records of randomization will be regularly reviewed by the local and Lead Node QA monitors.

8.6 Administration of Interventions

Upon completion of the Baseline assessments, the Study Site Coordinator, or designee, will contact the VA Randomization System to obtain information on what group the participant will be assigned.

If appropriate to group assignment, the Study Site Coordinator, or designee, will schedule the participant for an intervention with either the C & E Interventionist or the TA Therapist depending on the randomization assignment. Every attempt will be made to schedule the intervention the same day as the Baseline assessments. If this is not possible, the intervention should occur prior to or on the same day as the participant discharge from the detoxification.

8.6.1 Audio-Taping the Intervention Sessions

The C & E and TA interventions will be audio-taped and evaluated by an expert trainer to assure fidelity. Only members of the research team will review the audiotapes. The participant has the right to stop taping at any time during the session. The participant also has the right, at any point during participation, to request that the current and/or all exiting tapes be erased. Audiotapes will not be used for training or any other purpose and identification of tapes will be by code number only. Audiotapes reviewed by members of the research team will be held for a maximum of one year after the results of the study have been published, then the tapes will be erased.

The three groups and their intervention are as follows:

8.6.2 NIDA C & E Intervention

- The C & E interventionist administers the first part of the C & E intervention, and offers a free blood draw for HIV and HCV testing. If the participant agrees to the blood test, the C & E interventionist draws the blood, if trained, or the participant is referred to a phlebotomist. Each site will develop a local SOP regarding obtaining a Release of Information or other instructions so that test results are delivered directly to the research personnel, prior to informing the participant. Within Colorado, positive test results for HIV and HCV will be reported by the testing laboratory to the Colorado Department of Public Health and Environment as required by state law. Each site outside of Colorado must inform participants of the local regulations concerning reporting of positive HIV and HCV test results.
- A second session of the C & E intervention is given 14-28 days after randomization. The C & E Interventionist delivers part two of C & E intervention and provides test results (if applicable).
- If a participant declines the blood test during the first C & E session, but later requests a blood test, that participant will be referred for testing using the CTP's usual referral system.

8.6.3 Therapeutic Alliance Intervention

- Introduction to TA Counselor

- Counselor delivers TA Intervention. The session concludes with the TA counselor scheduling an outpatient treatment appointment for the participant if the participant agrees, or providing written information about scheduling or referrals.
- If at any time a participant requests a blood test, that participant will be referred for testing using the CTP's usual referral system.

8.6.4 Treatment as Usual

- Variable time depending on clinic, consisting of standard HIV risk assessment and possible referral for testing.
- Standard referral information for further treatment.
- If at any time a participant requests a blood test, that participant will be referred for testing using the CTP's usual referral system.

8.7 Two Week Follow-up Assessment

Participants in each of the three groups will be assessed 14 to 28 days post-randomization using the Self-Efficacy (SEF), Services Received (SRQ) and Stages of Change (SOC) questionnaires along with the Timeline Follow-back (TFB), and will provide a urine sample to be tested with the Urine Drug Screen (UDS). The window for this interview will be from the two-week due date to 14 days after this due date.

8.8 Two, Four, Six Month Follow-up Assessments

Every effort will be made to retain participants at follow-up intervals. The follow-up rate of previous studies conducted by the Lead Investigator is between 80-85% at six months. We have adapted many of the suggestions of Nurco (1992) and others for improving retention. Specific strategies that we will employ will be described in detail in the Operations Manual.

Site Research Staff will schedule the next follow-up appointment at the time of the current visit, whenever possible. Locator information will be used to remind participants of the next scheduled visit, and to track participants who have missed an appointment. A reminder letter will also be sent to the address indicated by the participant to assure delivery. The 2-month follow-up will be scheduled using a window of within 7 days before and 7 days after the follow-up due date. The following assessments and information will be collected from each participant.

1. Follow-up Addiction Severity Index (ASF)
2. Timeline Follow-back Assessment of Treatment Participation (TFB)
3. HIV Risk Behavior Survey (RBS) Audio CASI
4. Urine Drug Screen (UDS)
5. Stages of Change (SOC)
6. Self-Efficacy (SEF)
7. Locator Form

This same procedure will be used for the 4 and 6-month post-randomization follow-up sessions, except the Locator information will not be obtained at the 6-month follow-up. The window on the 4-month interview is also 14 days - 7 days prior to and 7 days after the due date. The window on the 6-month interview is 28 days - 7 days prior to the due date and 21 days following the due date.

8.9 Follow-Up Procedures

Attempts to obtain follow-up data will continue through the end of the 6-month window for every participant, unless the participant dies or withdraws consent. Locator information will be updated at each

study visit. Study staff will be trained on successful follow-up techniques to help assure a high follow-up response rate. Follow-up assessments will not be collect by phone.

8.10 HIV/HCV Testing and Counseling at Six Months

Following the six month interview, all participants will be offered a referral for HIV and HCV testing and counseling, including those in the TA and TAU conditions, and those in the C & E condition who declined testing when offered at the first C & E session. For ethical reasons, it is felt that this option should be made available.

8.11 Administrative Withdrawal

A participant may be administratively withdrawn from the study if imprisoned for a duration that extends beyond the 6th month follow-up timeframe, acquires a change in medical status that makes it unsafe for continued participation in the study, withdraws consent, is administratively terminated from treatment by the clinic for safety, or non-compliance reasons, or does not begin the Baseline Assessments within one business day of consent.

Participants who are administratively withdrawn from the study will continue receive TAU.

9.0 Statistical and Power Analysis

9.1 Objectives of Analysis

The primary goal of this study is to evaluate and compare effectiveness of the C & E and TA Interventions with TAU on HIV/HCV risk behavior reduction post-detoxification. Although both C & E and TA have empirical support from separate pilot studies and/or efficacy trials, their effectiveness in reducing risky behaviors has never been directly compared.

Specifically, regarding the primary goal of evaluating these interventions, it is hypothesized that:

Hypothesis 1a: *C & E will be more effective than TAU (post- discharge risk behavior counseling as usual) in reducing HIV/HCV injection risk behaviors.*

Hypothesis 1b: *TA will be more effective than TAU in reducing HIV/HCV injection risk behaviors (mediated by facilitating treatment entry)*

Hypothesis 1c: *C & E will be more effective than TA in reducing HIV/HCV injection risk behaviors.*

The primary outcome variable is the sum of all instances of sharing the following injection paraphernalia reported to have occurred in the past 30 days: needle/syringe, cotton/cooker/rinse water, and the drug solution. For example, in the past 30 days if a participant shared a needle 2 times, cotton/cooker/water 3 times, and the drug solution 1 time, the total is $2+3+1 = 6$.

Secondary aims of this study assess and compare the effectiveness of the C & E and TA Interventions with TAU on treatment entry, retention, and compliance, reducing drug use and the frequency of injecting and reducing sex risk behaviors related to HIV/HCV. Specifically, in evaluating these interventions' effectiveness relative to treatment, it is hypothesized that:

Hypothesis 2a: *More participants in the TA arm will enter outpatient treatment over the 6-month follow-up period compared to C & E and TAU.*

Hypothesis 2b: *Participants in the TA arm will stay longer in treatment and have more treatment visits than participants in C & E and TAU.*

The outcome variable for evaluating these secondary hypotheses related to treatment success (entry, retention, and compliance) is the number of weeks participants attended one or more treatment sessions (first attendance corresponds to treatment entry). Opportunities for treatment participation will likely vary somewhat by CTP (e.g. some might have resources to offer multiple sessions per week whereas others will not). Secondly, we are interested in how progression through stages of change may be differentially related to treatment success according to the intervention.

In assessing reduced drug use (measured by self-report and urinalysis) and reduced frequency of injecting (measured through self-report), it is hypothesized that:

Hypothesis 3a: *C & E will be more effective than TAU in reducing drug injection frequency and increasing abstinence.*

Hypothesis 3b: *TA will be more effective than TAU in reducing drug injection frequency and increasing abstinence (presumably mediated by facilitating treatment entry).*

Hypothesis 3c: *TA will be more effective than C & E in reducing drug injection frequency and increasing abstinence.*

The outcome variables for evaluating the above secondary hypotheses are use of any illicit drug and frequency of injecting drugs in the 30 days prior to interview.

In evaluating these interventions' effectiveness related to reduction in HCV/HIV sex risk behaviors, it is hypothesized that:

Hypothesis 4a: *Participants in the C & E intervention will demonstrate a greater decrease in risky sex behaviors than those in TAU.*

Hypothesis 4b: *Participants in the C & E intervention will demonstrate a greater decrease in risky sex behaviors than those in the TA.*

The outcome variable for evaluating these secondary hypotheses related to risky sex behaviors is whether participants always practiced safe sex, i.e. abstinence or 100% condom use, during the past 30 days.

Although our primary hypotheses are assessing overall differences between the interventions and TAU, the longitudinal design allows for the secondary evaluation of change over time and differential change over time between the three interventions or groups, i.e. differences between interventions in the time to achieve risk reduction and in the sustaining of those reductions. For example, C & E might cause earlier risk reduction which may or may not be sustained whereas risk reduction in the TA group might be delayed until participants enter treatment and begin working with their counselor.

9.2 Overview of Analysis

Testing of Distributional Assumptions. Empirical distributions of all variables will be visually inspected. Prior to performing analyses addressing the primary and secondary hypotheses, data will be screened for (1) entry errors, (2) outliers, (3) the extent and pattern of missingness. The underlying proposed statistical methods for each analysis will be examined, primarily through inspection of graphical displays, standardized residuals, and influence diagnostics. Where appropriate, transformations will be utilized to account for extreme values. Although a trial should not be unduly influenced by a single observation, deleting data violates the intent to treat principle and makes it difficult to generalize and interpret trial results. A sensitivity analysis assessing results of redoing the primary analysis while deleting each participant one at a time will be conducted. If results differ when outlying values are deleted, this will be reported as a secondary analysis and implications for the trial interpretation will be discussed.

Preliminary analyses will validate that our randomization scheme is successful, i.e. there are no baseline differences in drug use, risk variables, and demographics across the three intervention conditions and across CTPs. Although we expect that baseline differences will be accounted for by randomization, should differences remain we will adjust for them as appropriate. Sometimes randomization can fail, producing treatment groups which are not equivalent on all variables. If imbalances between groups are present, then it is possible to adjust trial results for these imbalances by co-varying those variables that are both correlated with the primary outcome variable and that differ by group. The following variables have been shown to be correlated with the primary outcome of interest and will be evaluated for inclusion in the primary analysis as covariates: gender, treatment entry, type of drug injected (e.g. opiates), and perceived self-efficacy to practice safer behaviors.

Missing Data and Attrition. All clients who provide informed consent, following initial screening, will be included in the study. Thus, we do not expect any deviation in the estimated number of clients to be recruited (i.e., 808). Missing data are a serious problem with no adequate statistical solutions. The problem with all of the statistical approaches to missing data is that they require assumptions about the reasons why the data are missing which are not testable. It is difficult to know how to handle missing data and whether or not it threatens trial validity because the true causes of missing data are unknown. The best solution is to prevent it and Section 8.8 outlines procedures designed to minimize the likelihood that data will be missing. Missing data will be managed in a variety of ways and sensitivity analyses will be performed to determine the effects of missing data on the inferences regarding the outcome of the primary hypotheses. The pattern of participant dropout will be examined to ensure a reasonably equal distribution of participants lost to follow-up across a variety of baseline measures including clinic site, injection and sexual risk behaviors, and demographic variables. Primary analyses on the intent-to-treat sample will evaluate results utilizing various strategies for handling missing data. The linear and nonlinear mixed effects models proposed in Section 9.3 employ maximum likelihood techniques of parameter estimation that can utilize participants with incomplete data, avoiding the potential bias caused by listwise deletion. These techniques are robust under conditions of missing completely at random (MCAR) and missing at random (MAR) and therefore, the comparisons of experimental groups will not be biased as long as missing data is ignorable (Laird, 1988). To allow for the possibility of non-ignorable dropout, pattern-mixture models will be evaluated (Little, 1993). Secondarily, analyses of participants who complete the study will be conducted and compared with the principal intent-to-treat results. The follow-up rate of previous studies conducted by the Lead Investigator is between 80-85% at six months.

9.3 Analytic Strategy

Each outcome variable can be assessed with the same design: three interventions or groups (C & E + TAU, TA+TAU, TAU alone) by n clinics (here, estimated 8) over four times (baseline, 2, 4, and 6

months). Depending on the type of outcome variable (continuous, or dichotomous), linear and nonlinear mixed effect models will be utilized specifying participants, clinics, and any interactions with clinic as random effects. These are hierarchical generalized linear models. A two-tailed alpha level of 0.05 will be used to evaluate the significance of the apriori planned comparisons for the three primary hypotheses (Hypotheses 1a, 1b, 1c) comparing the primary outcome which involves summing all instances of sharing injection paraphernalia in the past 30 days across conditions. Two-tailed tests are proposed in order to detect differences between conditions in either direction. Differences in treatment arms on secondary endpoints will be examined in terms of their support for the primary endpoint, but will not be used as independent tests of the treatment effect.

Linear Mixed Model Analyses. For continuous outcomes such as the primary outcome variable, frequency of risky injection behaviors mixed model analysis of variance (ANOVA) will be used with the fixed effects being three groups by four times, the random effects being 8 clinics and 101 participants per clinic on average and any interactions involving clinics. A general model for each continuous outcome variable Y (that can be expanded to incorporate covariate(s) such as treatment entry) is:

$$Y_{ijkm} = \mu + g_i + \tau_j + (g\tau)_{ij} + c_k + (gc)_{ik} + S_{m(ik)} + e_{ijkm}$$

i = 1-3 groups/interventions: CE, TA, TAU
j = 1-4 times: baseline, 2, 4, 6 months
k = 1- 8 clinics
m = 1-101 participants per clinic

where participant, clinic, and clinic by group interaction effects, $S_{m(ik)}$, c_k , and $(gc)_{ik}$ are assumed to be independently normally distributed with means 0 and variances σ^2_S , σ^2_C , and σ^2_{gc} , respectively. The responses Y_{ijkm} are assumed to be normally distributed, conditional on these participant, clinic, and clinic by group interaction effects. Pilot data suggest that several of our outcome variables including the frequency of risky injection behaviors are sufficiently skewed that the above assumptions will be better met on the logarithmic scale. Standard software for implementing mixed model analyses such as SAS PROC MIXED (SAS Institute Inc., 1999) will be used.

Survival Analyses. Survival analysis will be used to assess differences in the intervention groups for time to first treatment entry in the six months of follow-up. Participants who have not entered treatment by the end of the six month follow-up or who are lost to follow-up will be censored at the end of their six month window from their date of randomization into the study. If the necessary assumptions are reasonably satisfied, proportional hazards regressions will be conducted with clinic (CTP) and/or intervention group as potential stratifying variables.

Logistic Mixed Model Analyses. For dichotomous outcomes such as “safe sex” (abstinence or 100% condom use) in the past 30 days, mixed model logistic regression will be used with the fixed effects being three groups by four times, the random effects being 8 clinics and 101 participants per clinic on average and any interactions involving clinics. A general model for each dichotomous outcome variable Y (that can be expanded to incorporate covariate(s)) is:

$$Y_{ijkm} = \begin{cases} 1 & \text{if present} \\ 0 & \text{if absent} \end{cases} \sim B \left[n = 1, \Pi_{ijkm} = \frac{e^{\mu + g_i + \tau_j + (g\tau)_{ij} + c_k + (gc)_{ik} + S_{m(ik)}}}{1 + e^{\mu + g_i + \tau_j + (g\tau)_{ij} + c_k + (gc)_{ik} + S_{m(ik)}}} \right] \text{ or}$$

$$\text{logit}(\Pi_{ijkm}) = \mu + g_i + \tau_j + (g\tau)_{ij} + c_k + (gc)_{ik} + S_{m(ik)}$$

i = 1-3 groups/interventions: CE, TA, TAU

j = 1-4 times: baseline, 2, 4, 6 months
k = 1- 8 clinics
m = 1-101 participants per clinic

where participant, clinic, and clinic by group interaction effects, $s_{m(ik)}$, c_k , and $(gc)_{ik}$, are assumed to be independently normally distributed with means 0 and variances σ^2_s , σ^2_c , and σ^2_{gc} , respectively. The responses Y_{ijkm} are assumed to be binomially distributed with parameter Π_{ijkm} , conditional on these participant, clinic, and clinic by group interaction effects. Software for implementing nonlinear mixed model analyses such as SAS PROC NLMIXED (SAS Institute Inc., 1999) will be used.

Power Analyses. Power analyses were conducted to detect differences between any two of the three conditions at a point in time using an alpha level of .05. Raudenbush and Liu (2000) discuss sample size requirements to provide adequate power for assessing treatment differences when clinics and the group by clinic interaction are specified as random effects. Based on their methodology, we computed power for a medium effect size 0.50 (Cohen, 1988) and medium to large variability of group differences, 0.10 to 0.15, after standardization with respect to the variability between participants (Raudenbush & Liu, 2000). Eight clinics with 101 participants each on average provide power ranging between 0.80 and 0.90 for detecting differences between any two groups.

Power analyses were also conducted via the methods of Raudenbush and Liu (2000) to detect variability of group differences from clinic to clinic (i.e. the random group by clinic interaction). Eight clinics with 101 participants each on average provide power ranging between 0.77 and 0.89 for detecting medium to large variability of group differences, 0.10 to 0.15. (See Table 1 for comparison of power relative to variability of group differences based on methods described by Raudenbush and Liu).

Table 1. Power estimates for different effect sizes.

Effect Size	Variability of group differences standardized with respect to variability between patients	Power for detecting differences between any two groups	Power for detecting variability of group differences from clinic to clinic (i.e. Group*Clinic)
Small: 0.2	0.05	0.30	0.32
	0.10	0.22	0.58
	0.15	0.18	0.74
Medium: 0.5	0.05	0.94	0.32
	0.10	0.84	0.58
	0.15	0.74	0.74
Large: 0.8	0.05	0.99	0.32
	0.10	0.99	0.58
	0.15	0.98	0.74

A medium effect size was chosen because it is within the range that has been considered to be clinically meaningful in similar behavioral intervention studies attempting to reduce one or more potentially harmful behaviors (Johnson, Carey, Marsh, Levin, & Scott-Sheldon, 2003). Given that previous studies have shown a correlation between reductions in risky needle behaviors and reductions in rates of HIV seroconversion, meaningful change can occur with proportionate changes in behavior (Sorenson & Copeland, 2000). To aid in standardization across different measures and different studies, Cohen (1988) has ascribed labels of "small", "medium", and "large" to different effect sizes, which in CTN-0017 refer to standardized differences between any two treatment groups (e.g. C & E+TAU and TAU). We are requiring at least a medium effect size before reporting that any one group (e.g. C & E+TAU) demonstrates a significant improvement in risk reduction over another group (e.g. TAU).

The sample size and power estimates here are conservative since the actual analyses will involve pooling variance estimates from all three groups and will utilize repeated measurements over all four times.

Interim Analysis. Guidelines for terminating the trial because of overwhelming evidence that one or more of the treatment conditions (e.g. C & E+TAU) is either substantially better or worse than another (e.g. TAU) are provided in the following interim analysis plan, which will be implemented once 50% of the participants have completed the 6 month assessment. This interim analysis will only be executed should recruitment into the protocol fall below the targeted rate of an average of 2 per week per site. Given the expected recruitment rate, it will take approximately 13 months to collect all data for 50% of participants to be used in the interim analysis. However, with that recruitment rate, all participants would be randomized by 12 months, which is before the necessary data would be collected for the interim analysis, rendering it useless.

Both C & E+TAU and TA+TAU are expected to improve HIV/HCV risk behaviors but may have different impact at different time points in the study, i.e. a treatment by time interaction is expected. One possibility would be that C & E+TAU could possibly have a larger initial reduction in risk behaviors and TA+TAU have a slower perhaps more sustained reduction. Consequently, collecting data for the full time period (6 months) is ideal to discern the pattern in reduction for each treatment. Consequently, it is necessary to have data on each participant up through the 6 month assessment for the interim analysis.

Once 50% of the participants have completed their 6 month assessment (or exceeded the eligibility window for completing it), mixed model analysis of variance will be used to assess differences in the primary outcome variable, cumulative instances of sharing injection paraphernalia in the past 30 days. Ideally, the statistical model used in interim analyses is the same as that proposed to evaluate the primary hypotheses at the end of a trial. Section 9.3 specifies a general model for the primary outcome as:

$$Y_{ijkm} = \mu + g_i + \tau_j + (g\tau)_{ij} + c_k + (gc)_{ik} + s_{m(i,k)} + e_{ijkm}$$

i = 1-3 groups/interventions: CE, TA, TAU
j = 1-4 times: baseline, 2, 4, 6 months
k = 1- 8 clinics
m = 1-101 participants per clinic

where time and group are fixed effects and the random participant, clinic, and clinic by group interaction effects, $s_{m(i,k)}$, c_k , and $(gc)_{ik}$, are assumed to be independently normally distributed with means 0 and variances σ_s^2 , σ_c^2 , and σ_{gc}^2 , respectively. The responses Y_{ijkm} are assumed to be normally distributed, conditional on these participant, clinic, and clinic by group interaction effects. It is likely that a variable number of participants will be available from each clinic at the time of the interim analysis (50% of participants completing their 6 month assessment). For example, CTPs that begin recruiting early in the protocol might contribute many more participants to the interim analysis than those who begin later. Consequently, if we are unable to estimate the clinic effect and/or the group by clinic interaction at the time of the interim analysis, they will be removed from the interim model. Rather than addressing the proposed final statistical model, Pocock (1996) states that the initial interim analysis should be simple: "Indeed, interim analyses need only contain crude treatment comparisons on major end-points unless the results approach statistical significance, in which case some allowance for key prognostic factors may be worthwhile."

Accordingly, how the trial has progressed up to the point of the interim analysis must be carefully considered in interpreting the interim analysis results and in the conclusions that can be drawn from the interim analysis, for example: the number of sites contributing data, the number of participants per site, the characteristics of those participants, interviewer consistency or drift, etc. Before interim analysis results are considered compelling, it will have to be assessed whether the data obtained prior to the interim analysis are not sufficiently biased in some way that would invalidate the sample.

The group sequential procedure advocated by O'Brien and Fleming (1979) was chosen. This test requires large differences between groups at the interim point before achieving significance, i.e. exceeding the larger critical value obtained after adjusting for multiple looks at the data. However, O'Brien/Fleming is attractive in requiring a smaller increase in final sample size (provided the trial continues to completion) in comparison with other popular procedures (e.g., Pocock, 1977) and because the critical value used at the final test is approximately the same as that used if a single test were done (without interim analysis). For the i th analysis of K total analyses, their stopping rule compares the statistic Z_i with $Z^* \sqrt{K/i}$, where Z^* is determined so as to achieve the desired significance level. Table 2.3 in Jennison and Turnbull (2000) shows that $Z^* = 1.977$ for an overall alpha level of .05 with $K = 2$ analyses ($i = 1$ at interim and $i = 2$ at final). To maintain the 80-90% power specified in the CTN-0017 protocol, a sample increase of one participant per site is necessary, resulting in 808 total participants. The critical value Z^* at the interim point is 2.7959, providing a nominal alpha level of $\alpha_1 = 0.005$ (for the interim look) and the nominal alpha level corresponding to $Z^* = 1.977$ for the final analysis is $\alpha_2 = 0.048$.

Should an interim analysis be necessary (i.e. the recruitment rate is slower than the expected 2 participants per week), then the Lead Node statistician and data manager will work with the objective party who will perform the interim analysis as soon as 404 randomized participants have completed their 6 month assessment (or exceeded the eligibility period for completing the assessment). The planning for the analysis will occur well before the data have been obtained for the 404th randomized participant. This planning will include data cleaning procedures. It will also include the writing of SAS code to perform file creation, special analyses to aid in the interpretation of the results of the interim analysis, as well as the test statistic on which the formal interim analysis will be based as described above.

10.0 Participant Compensation

Participants will be offered cash or gift certificates to local merchants in the following amounts: \$25 for the Baseline Assessments and interviews, \$25 for the two-week interim interview, \$30 for the 2-month follow-up interview, \$35 for the 4- and 6- month interviews, and \$5 for returning the reminder letter at the 2-week, 2-month, 4-month, and 6-month follow-up visits, as compensation for their time.

11.0 Training and Fidelity

The following plans and manuals will set the standard operating procedures and provide guidelines for the training, implementation, adherence/competency, data management procedures, and quality assurance and safety monitoring of the study:

- Training Plan;
- Therapeutic Alliance Training Manual including Rating Measures and Guidelines for Adherence/Competency Monitoring;
- C & E Intervention Training Manual, including Rating Measures and Guidelines for Adherence/Competency Monitoring;
- Operations Manual;
- Data Management Plan
- Data Safety and Quality Assurance Plan.

The Rocky Mountain Node will provide one centralized training for all study staff, including but not limited to Site Coordinators, RA/Interviewers, C & E Interventionists, TA Interventionists, Intervention Supervisors, Node Implementation Coordinators, and Node QA monitors. Phlebotomy training will be the responsibility of the site. Local QA monitoring site visits will be conducted on a regular basis to monitor record keeping and prevent protocol violations and data errors. Intervention fidelity for both interventions will be closely monitored by intervention supervisors and Lead Node experts through the use of audiotapes to ensure consistency and quality of intervention delivery. Lead Node experts will regularly assess inter-rater agreement among Supervisors.

12.0 Regulatory and Reporting Requirements

12.1 IRB Approval

Prior to initiating the study, the investigator at each site will obtain written IRB approval to conduct the study. Should changes to the protocol be necessary, protocol amendments will be submitted in writing to the IRB by the investigator for approval prior to and/or during implementation. The IRB will also approve all advertising materials used for participant recruitment and any educational and prevention materials provided to the participant. A protocol summary, Consent form, and consent quiz, will be provided by the Lead Node.

12.2 Informed Consent

The consenting process for study participation is described below.

The Informed Consent Form (ICF) will be presented to the potential participant in a private, quiet room. Individuals may read the consent or have it read to them. They will be encouraged to ask questions about the study procedures, risks involved, benefits and confidentiality. A study specific true/false quiz will be administered to the participant to further insure and document understanding of study components and procedures. Participants must score 100% to be eligible for the study. Any item missed on the quiz will be reviewed and explained until it is understood. If the person explaining the consent determines that the potential participant is not competent to provide informed consent, the consent process will stop. The ICF may be obtained at a later time when it is determined the potential participant could provide informed consent. Once the potential participant has passed the quiz, they will then be asked to sign the ICF. No study procedure will be performed prior to the ICF being signed by the participant. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice or penalty. All participants will be provided a copy of the ICF.

All participants will sign the site HIPAA compliance forms to authorize collection of data for research purposes including Name and Phone number, Demographic information, Diagnoses, History and/or Physical, Testing for or infections with HIV, Survey and Questionnaires concerning risk behaviors, services received, and self-efficacy, and psychological interviews including drug use, abuse and dependence, psychiatric and medical history, and social and economic situations. This information will be shared with Nathan Kline Institute (Data Management), the CTN Regional Research and Training Center, Rocky Mountain Region (Data management and analysis, and quality assurance). Locally, research data also may be shared with Signal Behavioral Health Network, The Alcohol and Drug Abuse Division (ADAD) of the Colorado Department of Health, Biopharmaceutical Research Consultants, Inc., and the National Institute on Drug Abuse, for evaluation of this research project. CTN Sites outside of the Rocky Mountain Region should list local agencies that might have access to data in their local HIPAA compliance documents. Participants may request access to their research data by contacting Robert Booth, Ph.D., or the director of the clinic as listed in the consent form.

12.3 Clinical Monitoring

Lead node and NIDA Monitors will conduct a site initiation visit prior to the beginning of the study. At this visit they will assure that there is proper study-related documentation and assist in any training that is required. All sites will allow representatives of the Lead Node Lead Investigator (LI), local node QA monitors, and NIDA to audit all CRFs and corresponding source documents for each participant at mutually convenient times during and after the study. These monitoring visits will allow the LI and study staff to evaluate the progress of the study, collect data for fidelity measures, and inform the PI and study staff of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement with source documentation. Additionally, monitors will verify that participants' consent to participate was properly obtained and documented, confirm that those entered into the study met all inclusion and exclusion criteria, review primary and secondary outcome measures, and assure that all essential documentation required by Good Clinical Practices was appropriately filed. Prior to leaving the study site, study monitors will conduct an exit interview with the Site Director and/or Study Site Coordinator to review and clarify preliminary findings. Reports of local QA monitor visits will be sent to the Lead Node and NIDA within 21 days of the visit. The Lead Node QA monitor and the RMR DSMQA committee will review all reports for issues or concerns involving validity of data and participant safety. The Lead Node QA monitor will conduct regular conference calls with the participating node QA

monitors for discussion of issues and resolution. At the conclusion of the study, the LI will advise on the disposition and storage of study records.

12.3.1 Monitoring for Trial Safety

Known Adverse Events Relating to the Underlying Clinical Condition: Exclusion criteria are designed to minimize the psychiatric and medical risks to the participants such as those who are acutely suicidal or require medication intervention. There is, however, some risk that discussing sensitive topics, especially drug use and risks and consequences of HIV and HCV infection, will cause distress in some participants. Participants may become emotionally fatigued or upset. These risks are applicable to all study participants, regardless of assignment, yet they do not exceed those that are a normal part of any clinical interview or treatment session. The use of individual assessment procedures (such as those included in the baseline and follow-up interviews) has not been shown to be either harmful or directly helpful to psychiatric/substance abusing participants. All research interviewers and research counselors are trained to assess for level of distress and to be attentive to the participant's needs. Appropriate breaks will be given, and if necessary, additional support will be provided at the end of the interview or session.

In general, the risks associated with trials employing behavioral interventions are presumed minimal relative to those evaluating pharmacologic interventions. However, the population for this study is a vulnerable population at higher risk because of the nature of the information being provided, especially during the C & E intervention. This would not apply to those in the TA or TAU arms. All adverse events reported by the participant are recorded on the AE log. All adverse events determined to be study related are recorded on the AE log, and entered into the AE CRF. In addition, this study population may present with adverse events which are characterized by acute emotional distress leading to ER or urgent care center visit or urgent phone call to MH professional, relapse to substance use requiring hospitalization, drug overdose, or suicidality with a plan. Therefore, for this study, we add to the list of standard Serious Adverse Events (SAEs), suicidality with a plan, recent suicide attempt after entering study, and homicidal ideation with a plan. Confirmation of a participant who is actively suicidal, for instance, would be considered an SAE and thus needs to be monitored, recorded and if necessary, provided appropriate assistance. All SAEs, including the above listed study-defined SAEs, are recorded on the Adverse Event Log, AE CRF, SAE form, SAE Summary Report, and tracked to resolution or through the last follow-up contact.

Partner Notification: In states with mandatory reporting of HIV and/or HCV positive results to local health departments, such as in Colorado, state or county health officials will attempt to contact those found to be infected, unless a prior agreement is arranged with the local state authorities. The purpose of this contact is to ascertain with whom the infected individual has been having sex and/or injecting drugs. Although individuals are not required by law to reveal any information along these lines, such a contact may cause distress and anxiety. Each site will follow their state's mandatory reporting and partner notification guidelines.

Each study site maintains a referral policy for persons who are found to be emotionally distressed. Participants found to be in emotional distress will be encouraged to talk to the detox or clinic counselors about their feelings, or referred for support following clinic policy. In the event that any participant is assessed to be in need of extra support during the active treatment phase or at any follow-up, appropriate referrals will be given. Each site maintains a well-established protocol for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or other acutely distressed participants. Participants identified in any phase of the research as imminently suicidal will be immediately referred to appropriate crisis intervention and mental health services. The CTP Study

Site Coordinator or designee will be available 24 hours a day for consultation about untoward reactions or severe symptoms, including suicidality. Participants can be evaluated at any time should that prove necessary.

Probing for Suicidality and Harmful Emotional Distress: Using regular clinic procedures, detoxification center staff will clear the client prior to being screened or recruited to participate in this protocol. The potential participant should not be actively suicidal or suffering acute mental illness at the time of intervention and baseline assessment. Furthermore, the psychiatric status section of the Addiction Severity Index-Lite, administered by the RA/Interviewer at Baseline and at the 2-, 4-, and 6- month follow-up, contains questions on depression, anxiety, suicidal ideation and past attempts. It is important to assess the degree to which positive responses on the ASI-Lite to questions of depression, anxiety, suicidality and hostility toward others indicates that the participant or others are in imminent harm at baseline and follow-up interviews. To protect participant safety, it is important for the interviewer to establish baseline information with the use of probing questions to positive responses to questions on the Psychiatric Status and Family/Social Status sections of the ASI-Lite during baseline and all Follow-up sessions. Probes should be used that will assess the degree of imminent harm to the participant or the harm the participant may pose to others, regardless of condition.

For Suicidal Ideation With a Plan:

Does the participant have a plan to commit suicide?

- a) Does the participant have a method in mind (i.e., pills, gun, hanging etc.)?
- b) Does the participant have a time frame in mind?
- c) Has the participant attempted suicide previously?

If yes to a and b, it is a protocol-defined SAE, if no, it is an AE.

For Suicidal or Homicidal Ideation With a Plan

1. Does the participant's symptomatology put him/her or others in imminent harm? Does the participant do things that are dangerous to self or others? This should be behavior that puts someone at immediate harm, not a chronic condition that may eventually harm health (e.g., smoking 4 packs of cigarettes a day).

If yes, it is a protocol-defined SAE. If no, it is an AE.

2. Does the participant plan to harm someone else such as a specific neighbor or a family member? If yes,

- a) Does the participant have a method in mind?
- b) Does the participant have a time in mind?

If yes to a. and b., it is a protocol-defined SAE. If no, it is an AE.

These probes should be used as a part of the ASI-Lite and ASI-Follow-up interviews, Family/Social, and Psychiatric sections. The interviewer should use open-ended probes to begin to assess these features. For instance, if a participant mentions that he or she has thought about suicide, the interviewer should say, "Tell me more about that," Or otherwise probe for more information. If the participant reveals that he or she is serious about his or her suicidality, then the interviewer will follow with specific questions that ascertain the seriousness of the risk. Once serious risk is confirmed, or strongly suspected, the interviewer will alert the Study Coordinator while the participant is still in the interview office. The Study Coordinator must then make an assessment and if positive, the clinic's protocol for handling a severely disturbed client will be immediately implemented.

Assessment, Reporting and Monitoring of Adverse Events (Fig. 3):

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial. Stable chronic conditions, such as drug use, which are present prior to clinical trial entry and do not worsen, are not considered AEs. All AEs reported at each study visit are recorded on the AE log and described in more detail in a visit progress note. Adverse events are categorized as serious or non-serious, and as related or not related to the study. All non-serious AEs determined to be study related are recorded on the AE log and the AE CRF and described in a progress note. An AE is categorized as related to the study if the participant reports it occurred at least in part as a response to being involved with the study. Examples of potential adverse events that may be related to this study include but are not limited to:

1. Relationship discord
2. Increased or acute emotional distress
3. Increase in substance use
4. Violation of confidentiality
5. Homicidal or aggressive ideation with no plan or intended target
6. Suicidal ideation with NO plan

Study related adverse events are recorded on the AE log, **and** entered into the AE CRF, described in a progress note, reviewed weekly by the site study coordinator or designee, and tracked to resolution.

At each study visit, the participant may spontaneously report an adverse event, or may report an event in response to the question, “How have you been feeling since the last time I saw you?” Participants are advised to observe any signs of severe symptoms of Substance Use Disorder, relationship discord, or depression and to discuss this with study staff. Study staff are trained to refer such situations to clinical staff, who then follow their clinic’s policy for managing clients in crisis. Following or during each study visit, the RA/interviewer, other research personnel, or interventionist record the occurrence of AEs discovered during study visits (or study intervention sessions) on a progress note and the AE log. Interventionists who may be continuing clinical care **AFTER** the study intervention sessions are not asked to record AEs reported during their clinical care. AEs occurring between study visits, that are reported by the participant, will be recorded at the next study visit. The CTP site study coordinator or designee determines if the AE is serious or not, and also if it is study related. If unsure of this determination, the CTP site study coordinator consults with the local node investigator, or if needed the LI, before a final determination is made. The local node investigator and the LI will be qualified and trained to make these determinations.

Serious adverse events (SAEs) are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, congenital anomaly or birth defect, or any event requiring intervention to prevent any of the previously listed serious events. For the purposes of this study, the following events are added to the standard SAE list above, and are also defined as Study-related Serious Adverse Events:

1. Suicide ideation with a plan
2. Suicide attempt since the last study visit
3. Homicidal Ideation with a plan

For the purposes of this study, hospitalization for normal childbirth, and admission to a hospital for elective surgery, pre-scheduled diagnostic tests or drug abuse are NOT reported as SAEs.

Study related SAEs or death: Any SAE, and subsequent additional information, which is determined to be study-related and occurs during the course of study requires expedited reporting. The SAE must be reported by telephone and followed by a FAX of the SAE form within 24 hours to the following: The

Lead Investigator, RMN DSMQA chairperson, and the NIDA-CCTN Medical office. All deaths, whether study related or not, are reported to the same entities within 24 hours. The initial notification may include just the AE CRF and SAE form (which may not be complete). The Lead Investigator or designee (RMN DSMQA) is responsible for reviewing the AE CRF and SAE form, submitting additional queries or requests to the CTP, and completing the SAE summary report. Within two weeks, updated information about the event should be completed on the AE CRF, SAE form, and a SAE summary report generated, signed by the local study PI and LI, as indicated on the forms, and submitted to the NIDA medical office. Additional close out information may be obtained after the initial two weeks. The AE CRF, SAE form, and SAE summary reported should be completed with update information as received and sent to the local PI, LI, and NIDA medical office. Local nodes must also report SAEs in accordance with local node IRB regulations. In the event of occurrence of a study related SAE that may negatively impact continuation of the study, all nodes will be immediately informed, and report to local IRBs following local IRB reporting requirements. Failure to comply with reporting requirements can result in serious negative consequences, including criminal and or civil liabilities.

In Summary:

Any SAE determined to be study related or a death must be reported within 24-hours by telephone and FAX to:

Lead Investigator:

Robert E. Booth, Ph.D. (303) 315-0960 (office)
Division of Substance Dependence (303) 316-7697 (fax)
Department of Psychiatry
University of Colorado School of Medicine
1741 Vine Street
Denver, CO 80206

Laetitia Thompson, Ph.D. (303) 315-2511
Chairperson, RMN DSMQA (303) 315-2527 (fax)
Department of Psychiatry
University of Colorado School of Medicine
4200 E. Ninth Avenue
Denver, CO 80220

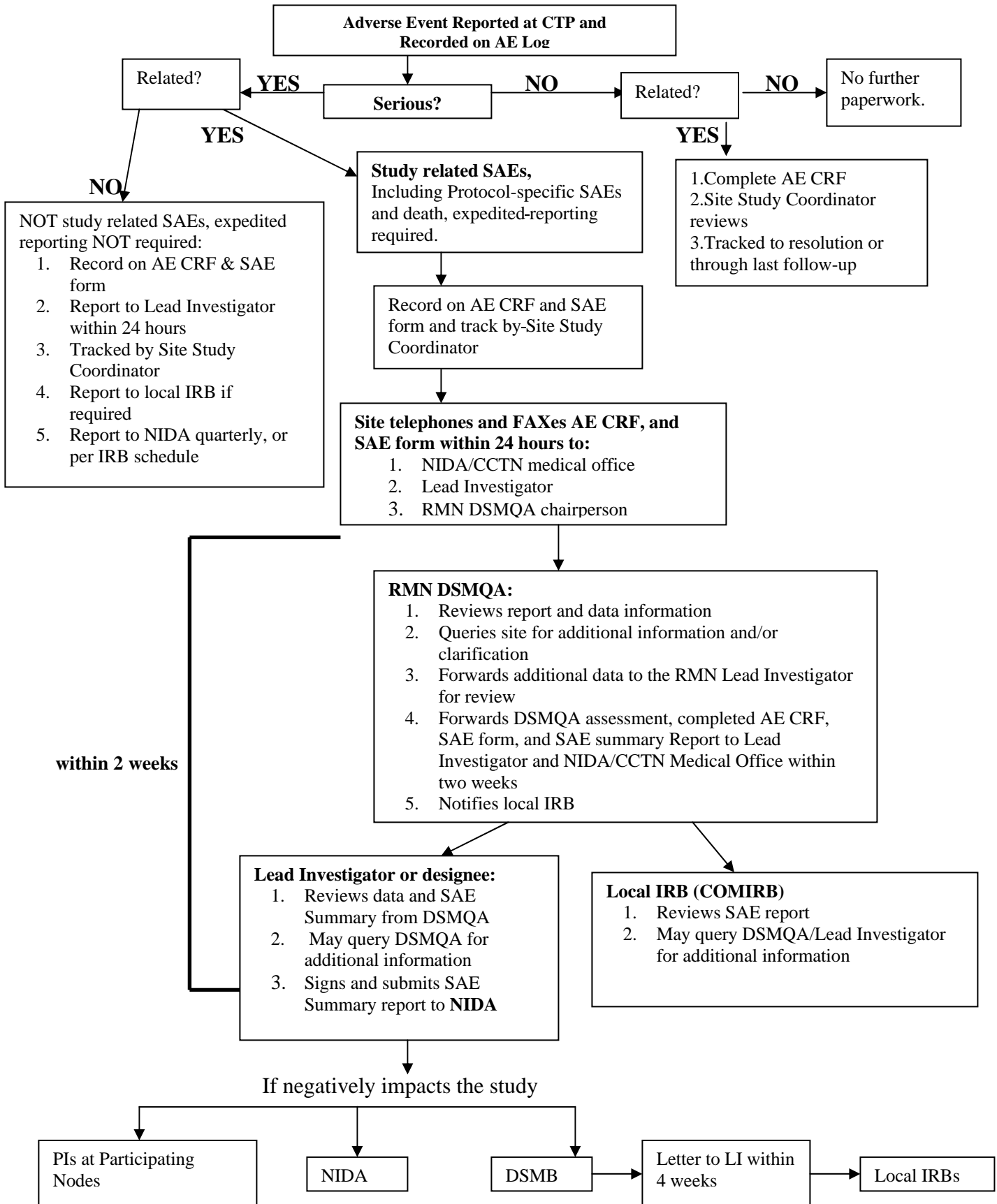
NIDA/CCTN Medical Monitor (301) 443-6697
Division of Treatment Research and Development (301) 443-2317 (fax)
National Institute on Drug Abuse
6001 Executive Blvd.
Bethesda, MD 20892

Local Node PI
Local IRB, as required.

Non-Study related SAEs: SAEs and additional subsequent information determined to not be study related should be recorded on the AE CRF and an SAE form, and reported to the Lead Investigator within 24 hours via Fax of the SAE form, tracked to resolution or through the end of the study, reported to local IRBs per local requirements, and reported to NIDA on a Quarterly basis or in accordance with local IRB reporting frequency. Study investigators have the responsibility of reporting all SAEs to NIDA and to the

Lead Node investigator. For the purposes of this study, hospitalization for normal childbirth, and admission to a hospital for elective surgery, pre-scheduled diagnostic tests or drug abuse are NOT reported as SAEs.

Fig. 3 Procedures for Reporting AEs and SAEs



12.3.2 Data Safety Monitoring Boards

Rocky Mountain Data Safety Monitoring and Quality Assurance Committee: This committee meets monthly to review the data of enrolled participants, to advise on implementation of the protocol, to examine safety data, review QA monitoring report summaries, and to make recommendations for a discontinuation of study for an individual participant based on adverse experience or to recommend early termination of the trial because of safety issues.

NIDA Data Safety Monitoring Board: Meets on a regular basis to review the data of enrolled participants, to advise on implementation of the protocol, to examine safety data, and to make recommendations for a discontinuation of the study for an individual participant based on adverse experience or to recommend early termination of the trial because of safety issues.

13.0 Confidentiality

13.1 Confidentiality of Data

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

13.2 Confidentiality of Patient Records

By signing this protocol the investigator agrees that within local regulatory restrictions and ethical considerations, sponsor, sponsor's representative, NIDA, or any regulatory agency may consult and/or copy study documents in order to verify case report data.

13.3 Certificate of Confidentiality

The Rocky Mountain Node, as the lead node for this protocol, holds a Certificate of Confidentiality from the National Institute on Drug Abuse, protecting research data from forced disclosure that would identify study participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The Certificate will be distributed to each research site.

14.0 Signature Page

This page documents the agreement among the NIDA-CTN, the Protocol Lead Investigator, and the participating investigators to conduct the trial in compliance with the protocol and all necessary regulatory authorities. This is the last page of the protocol so the title, version and page will appear as a header or footer. This page will require updating as protocol versions or investigators change.

The signatures of the Sponsor and the Lead Investigator indicate acceptance of the protocol version distributed to participating sites. The signature of the Node Principal Investigator indicates acceptance for site (CTP) and node participation.

Investigator statements: This is recommended text for non-IND studies. This text will be replaced with the 1572 text for studies under an Investigational New Drug application (IND). *(This text mimics the 1572 statements, with the exception that FDA 21CFRs references have been deleted or replaced with the Common Rule [45CFR46 Subpart A].)*

Participating Investigators are defined as:

- (a) Lead Investigator: The LI is responsible to NIDA for overall study performance. The LI resides in a Node, which is referred to as the Lead Node.
- (b) Node Principal Investigator: The Node PI has overall responsibility for the conduct of studies within his/her Node (there are currently 17) to NIDA.
- (c) Protocol Principal Investigator: The Protocol Principal Investigator is the person responsible to the site IRB for the conduct of the study. This individual is responsible for and will "personally supervise" the conduct of the study. This person will sign the 1572 form if the study is under an IND.
- (d) Investigator(s): All those individuals who will have responsibility for study-related decisions or subject safety. The Lead Investigator should designate the roles for required signatures. The Node Principal Investigator or Protocol Principal Investigator is responsible for identifying those investigators who will fill those roles and are required to sign at each Node. The Node Principal Investigator or Protocol Principal Investigator may also designate additional staff. If the study is under an IND, these individuals will be listed under section 6 of the 1572. The term "Sub-Investigator," as used by the FDA form 1572, may be substituted by the Lead Investigator for the term "Investigator."

Signature Page(s)

SPONSOR

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

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

LEAD INVESTIGATOR

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

Name/Signature Date

NODE PRINCIPAL INVESTIGATOR

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

Name/Signature Date

INVESTIGATOR (S)

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

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

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

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

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

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

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

Protocol Principal Investigator Name/Signature

Date

Investigator #1

Name/Signature

Date

Investigator #2

Name/Signature

Date

(Add additional lines / pages for further other Investigators)

15.0 References

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