# NIDA CTN Protocol 0032

# HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.

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# 1.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ACASI | Audio Computer-Assisted Self-Interview |
| CCC | Clinical Coordinating Center (EMMES) |
| CCTN | Center for Clinical Trials Network |
| CoC | Certificate of Confidentiality |
| CLIA | Clinical Laboratory Improvement Amendments of 1988 |
| CRF | Case Report Form |
| CSAT | Center for Substance Abuse Treatment |
| CTN | Clinical Trials Network |
| CTP | Community Treatment Program |
| DSC | Data and Statistics Center (Duke Clinical Research Institute (DCRI)) |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| FWA | Federal-Wide Assurance |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| ICH | International Conference of Harmonization |
| IRB | Institutional Review Board |
| ITT | Intent to Treat |
| LI | Lead Investigator |
| NIDA | National Institute on Drug Abuse |
| NIH | National Institutes of Health |
| PI | Principal Investigator |
| PV | Protocol Violation |
| QA | Quality Assurance |
| RA | Research Assistant |
| RESPECT-2 | HIV Prevention Counseling |
| SAE | Serious Adverse Event |
| SUD | Substance Use Disorders |
| STI | Sexually Transmitted Infections |
| STD | Sexually Transmitted Disease |
| TAU | Treatment-as-Usual |

# 2.0 STUDY SYNOPSIS

**Study Objectives:** According to estimates from the nation's new HIV incidence surveillance system, there were approximately 56,300 new cases of HIV/AIDS diagnosed in the United States in 2006 and this number is believed to have been roughly stable since the early 2000s. Moreover, among the more than one million people living with HIV in the U.S., approximately one-fourth do not know they are infected. Identifying these individuals is among the biggest challenges for HIV prevention in the United States. Early diagnosis of such individuals, combined with prevention counseling and provision of health care, could decrease the spread of HIV and improve the survival of HIV-infected persons.

The recent introduction of rapid HIV testing offers a critical public health screening approach for facilitating earlier diagnoses of HIV infection. Despite the recent focus on increasing the delivery of HIV testing in a diversity of medical and non-medical settings; there have been no wide-scale attempts to move HIV rapid testing with or without counseling into drug abuse treatment programs. Recent studies have shown that fewer than half of U.S. drug treatment programs are currently offering HIV testing on-site to their drug treatment patients (Brown Jr. et al., 2006; Oser, Tindall, & Leukefeld, 2007; Pollack, D'Aunno, & Lamar, 2006; Strauss, Des Jarlais, Astone, & Vassilev, 2003). This is clearly a missed opportunity: both injection and non-injection drug abuse continue to be important risk factors for HIV infection, with substance users at increased risk for HIV infection compared with the general population (Colfax & Shoptaw, 2005; Kral et al., 2003; Santibanez et al., 2006; Strathdee & Sherman, 2003).

In response to changes in testing and in an effort to increase HIV testing rates, in September, 2006 the Centers for Disease Control and Prevention (CDC) released new testing guidelines making it a priority to bring HIV rapid testing into outpatient medical care settings (Branson et al., 2006). The CDC is currently working on developing HIV testing guidelines for non-medical care settings. (The majority of drug abuse treatment programs in the United States would be defined as non-medical care settings.) A major policy shift in the new CDC testing guidelines is that prevention counseling should not be required with HIV testing or as part of HIV screening programs in health care settings. This recommendation is a major departure from the long-standing recommendation that HIV testing should be accompanied by HIV risk reduction counseling. In their current work on the guidelines for providing HIV testing to adults in non-medical care settings, the CDC is considering what the role of counseling will be in these new guidelines (B. Branson, personal communication, October 12, 2007).

Despite the current and forthcoming CDC recommendations, little is also known about whether offering testing in the absence of counseling influences acceptance of testing and receipt of test results. How testing influences HIV sexual risk behaviors in the absence of counseling also remains to be determined. Therefore, the overall goal of this study is to evaluate the more effective strategy (referral, onsite rapid testing, onsite rapid testing + counseling) to (1) increase HIV testing acceptance and receipt of results and (2) decrease HIV sexual risk behaviors. Our target population is individuals receiving drug abuse treatment within community-based drug abuse treatment programs in the United States. This study has the unique opportunity to provide policy-relevant information that can be used in the new HIV testing guidelines both for medical and non-medical care settings.

**Study Design:** This is a randomized controlled clinical trial in which individuals receiving drug abuse treatment will be recruited to participate in a multi-center HIV testing and counseling study. We will assess the relative effectiveness of three HIV testing strategies on increasing

receipt of test results: (1) on-site HIV rapid testing with brief, participant-tailored prevention counseling, (2) on-site HIV rapid testing with information only, and (3) referral for off-site HIV testing. The study will also assess the effectiveness of the three testing strategies in reducing HIV sexual risk behaviors. Because the study will be conducted among drug abuse treatment clients, drug use (including injection drug risk behavior) will be a secondary outcome. Participants will complete a baseline assessment to report their demographics, HIV testing history and sexual and drug-using risk behaviors, and will be randomized to one of three testing groups. At one month post-randomization, participants will complete a follow-up assessment to determine whether or not they received their HIV testing results. At six months post-randomization, participants will complete a follow-up assessment to assess any changes in their HIV sexual and drug use risk behaviors (see Figure 1).

**NIDA Clinical Trials Network:** This study will be carried out through the NIDA-funded National Drug Abuse Treatment Clinical Trials Network (CTN). The CTN is a consortium of NIDA, treatment researchers and community-based drug abuse treatment providers (CTPs) who cooperatively test efficacious treatment and HIV intervention options with patients in community level clinical practice. The CTN framework consists of Nodes (Regional Research and Training Centers - RRTCs linked with three to ten or more Community-based Treatment programs - CTPs), a Clinical Coordinating Center, and a Data and Statistical Center. A full description of the CTN is available at http://www.nida.nih.gov/ CTN/about.html.

**Study Population:** 1,272 individuals receiving drug abuse treatment from approximately 12 CTPs throughout the United States will be enrolled. We will recruit approximately 106 participants from each CTP.

**Eligibility Criteria:** There are minimal eligibility criteria for CTP participation and minimal eligibility criteria for patient participation at the CTPs:

**Site eligibility:** CTPs are eligible if a particular treatment service program to be considered for participation is not currently providing on-site HIV testing at the time of site selection (we will define “currently” as the past 30 days). All types of treatment programs (including outpatient methadone maintenance, outpatient counseling, residential, and partial hospitalization or intensive outpatient) are eligible. More than one treatment program may participate from one CTP.

In an effort to determine the potential eligibility of CTPs, our study team conducted a survey of all CTN CTPs in February – March 2007. We received results from 105/132 CTPs and found that 39% (n=41) had no on-site testing at any of their programs[1] and another 18% (n=19) of CTPs did not have on-site testing in some of their treatment programs. In total, 57% of CTPs (n=60) had at least some programs that did not offer on-site HIV testing. In April – May, 2007, we conducted a second survey with 8 CTPs that did not have on-site HIV testing and examined the HIV testing behaviors of all their patients who visited their site over a 7 day period. Among the 2,303 patients surveyed, 78% had not been HIV tested in the past 12 months and would therefore be eligible for this protocol.

**Participant eligibility**: Participants are NOT required to accept HIV testing; they may refuse testing and enroll; this allows us to determine the acceptance of testing in the study arms.

[1] Many CTPs have more than one treatment program as part of their CTP. For example, CTPs may offer different levels of services including in-patient, out-patient, methadone, etc and/or they may have different locations for their services.

Participants must: (1) be seeking or currently receiving drug (including alcohol) abuse treatment services at the participating CTP, (2) be at least 18 years old, (3) report being HIV-negative or status unknown, (4) report no receipt of results from HIV test initiated within last 12 months, (5) be able and willing to provide informed consent; (6) be able to communicate in English, (7) be able to provide locator information, and (8) be willing to sign a release form that will allow us to abstract HIV testing records to corroborate self-report of testing, receipt of results and HIV status at follow up.

**Interventions**: Participants will be randomized to one of three groups, with each group consisting of an **offer** for one of the three different HIV testing strategies. *Participants randomized to the two on-site testing groups will be offered testing, but need not accept in order to participate in the study. Likewise, participants randomized to the referral group will be offered a passive referral for off-site testing, but need not accept the referral in order to participate in the study.* The following groups are detailed further in section 6.0.

**Group 1: HIV testing and brief, prevention counseling**

Participants will be offered an oral fluid HIV rapid test (via oral swab) and brief prevention counseling that addresses both risk reduction and motivation to be HIV tested based on an evidence-based counseling approach (Project RESPECT-2 counseling). Prior to receiving testing, study participants must first provide consent for HIV testing. Consent for testing will be obtained through a second consent form required of all participants who wish to proceed with the HIV test.

**Group 2: HIV testing and information only**

Participants will be offered an oral fluid HIV rapid test (via oral swab). Prior to receiving testing, study participants must first provide consent for HIV testing. Again, consent for testing will be obtained through a second consent form required of all participants who wish to proceed with the HIV test. Participants will receive rapid HIV testing and test results after signing the consent to be tested.

In both Groups 1 and 2, participants who test reactive (preliminary positive) will be counseled on the sexual risk behaviors associated with transmission of HIV and the acquisition of STDs, as is current clinical practice with those testing HIV positive (Branson et al., 2006). In addition, the importance of receiving ongoing HIV primary medical care and referral to care and case management services will be included (Walensky, Weinstein, Smith, Freedberg, & Paltiel, 2005). All participants testing invalid or reactive on the rapid test (via oral fluid) will be offered a second, more specific, rapid whole blood test (via fingerstick) and confirmatory testing, and study staff will work to ensure that the confirmatory test is conducted and the result given to the participant.

**Group 3: Referral for HIV testing**

Participants randomized to group 3 will receive a referral list for HIV community-testing agencies. Each CTP site will have previously prepared an extensive referral list of testing sites in the surrounding geographic area. By virtue of their status as patients in the CTPs, they will receive whatever HIV testing and HIV education referrals the CTPs normally provide to their patients. This is the standard of care at CTPs that do not provide on-site testing.

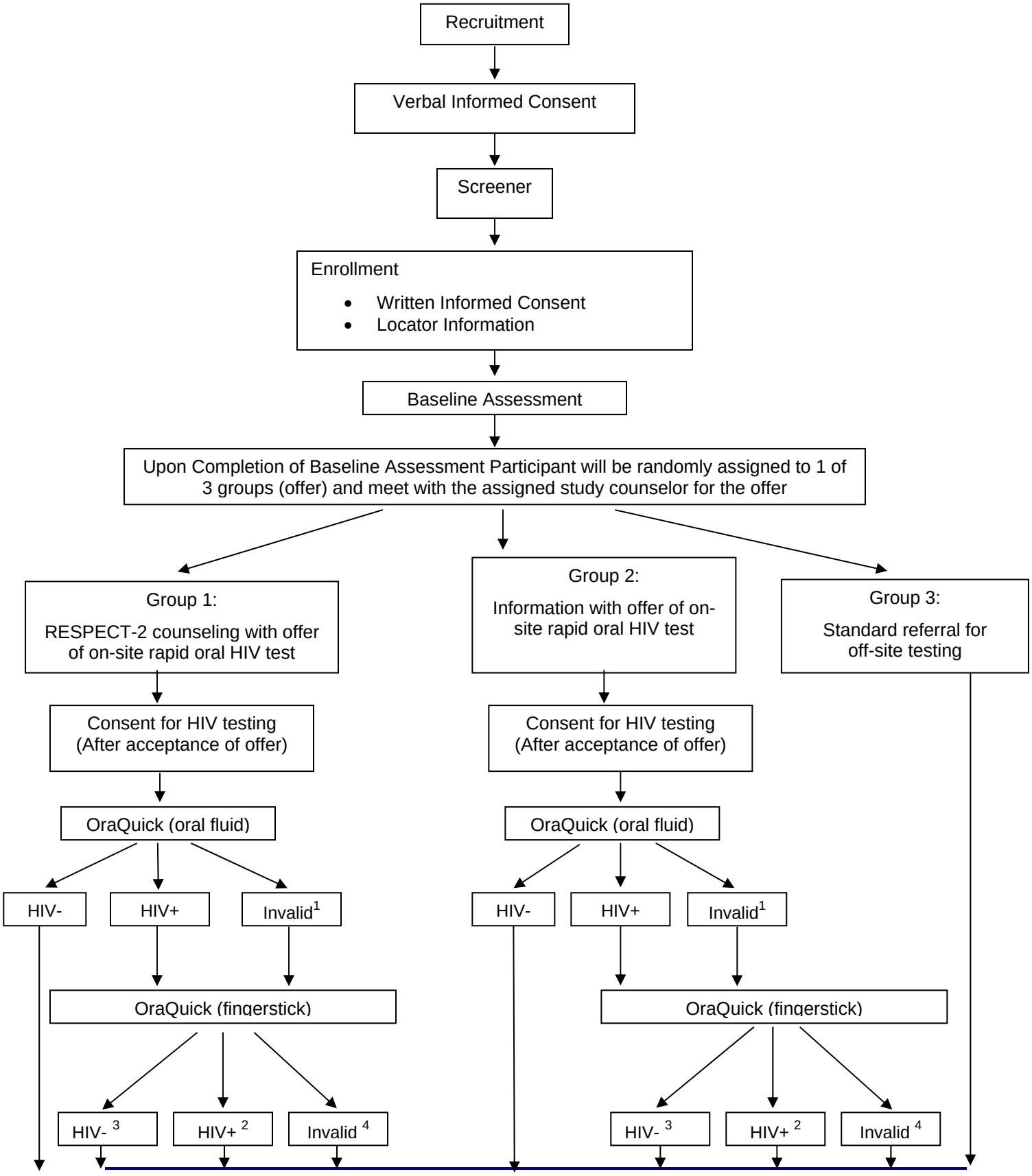
**Safety Assessment**: All participants will provide informed consent prior to their involvement in the protocol. Additionally, all participants in treatment groups 1 and 2 who wish to participate in the HIV rapid test will provide a second consent in order to proceed with HIV testing. There will

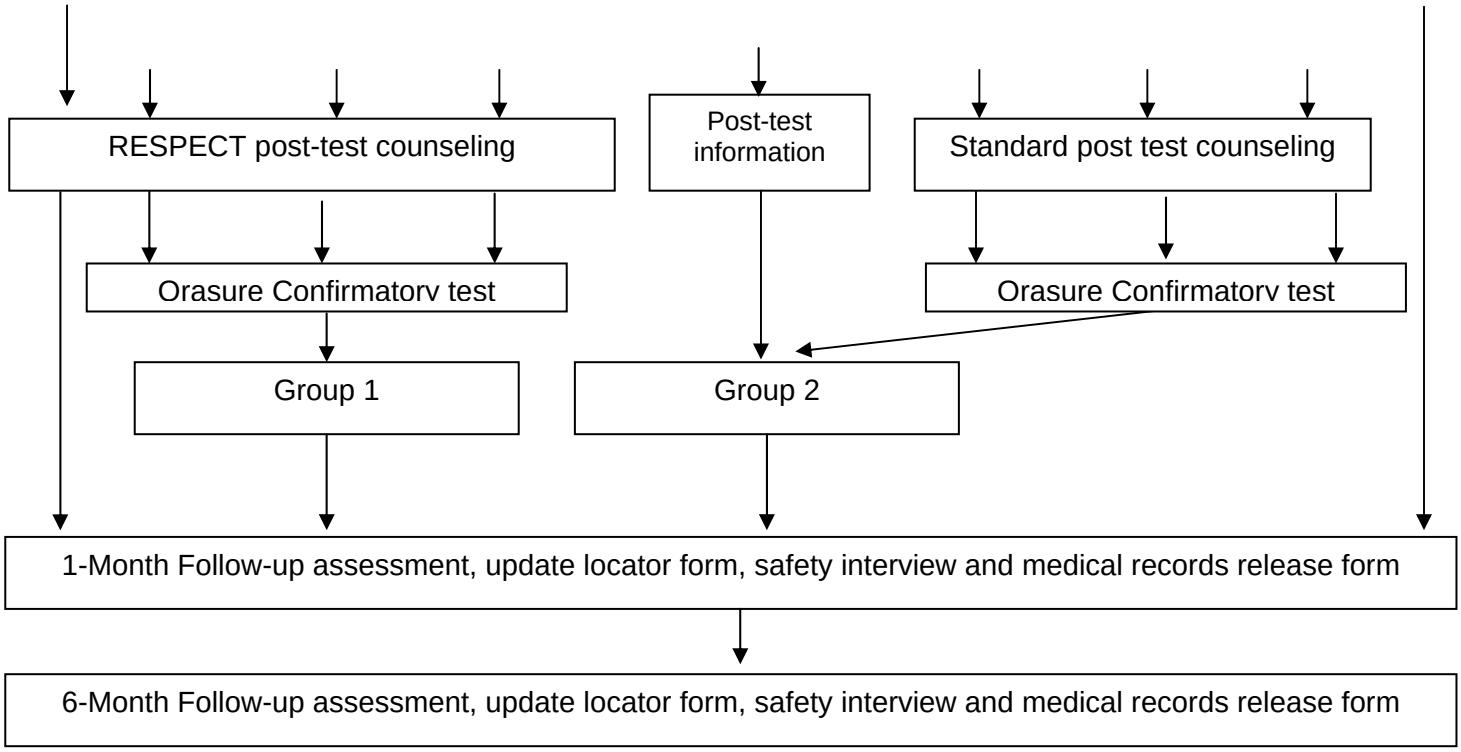
be ongoing monitoring of adverse events. Adverse events will be collected at each research visit.

**Outcomes**: There are two primary outcomes for this study. The first primary outcome is self-reported receipt of HIV test results at one month follow-up. The second primary outcome is self-reported sexual risk behavior, which will be measured at baseline and six months post-randomization as the self-reported number of unprotected sex acts (vaginal or anal sex without a condom).

**Analysis**: The primary outcome variables will be analyzed using logistic regression for the binary outcome, receipt of testing (Y/N), and ANCOVA for the continuous outcome, number of sexual risk behaviors. All analyses will be performed under intent-to-treat (ITT) criteria.

**Regulatory Issues**: The trial will be conducted in compliance with protocol, International Conference of Harmonization (ICH) guidelines for Good Clinical Practice (GCP), and applicable federal, state, and local regulatory requirements.


Recruitment
Verbal Informed Consent
Screener
Enrollment
Written Informed Consent
Locator Information
Baseline Assessment
Upon Completion of Baseline Assessment Participant will be randomly assigned to 1 of 3 groups (offer) and meet with the assigned study counselor for the offer
Group 1:
RESPECT-2 counseling with offer of on-site rapid oral HIV test
Group 2:
Information with offer of on-site rapid oral HIV test
Group 3:
Standard referral for off-site testing
Consent for HIV testing (After acceptance of offer)
Consent for HIV testing (After acceptance of offer)
OraQuick (oral fluid)
OraQuick (oral fluid)
HIV-
HIV+
Invalid[1]
HIV-
HIV+
Invalid[1]
OraQuick (fingerstick)
OraQuick (fingerstick)
HIV- [3]
HIV+ [2]
Invalid [4]
HIV- [3]
HIV+ [2]
Invalid [4]




[1]***Note:*** *Participants with invalid initial oral fluid rapid test results will be tested via oral fluid rapid test a 2nd time.*

[2]***Note:*** *Participants with reactive oral fluid and fingerstick will receive additional counseling message, "You are most likely HIV positive, but you still need a confirmatory oral fluid test." Additionally, individuals in both Groups 1 and 2 will receive RESPECT-2 post-test counseling.*

[3]***Note:*** *Participants with reactive oral fluid and non-reactive fingerstick will receive additional counseling message, "The oral fluid was most likely a false-positive, but you still need a confirmatory oral fluid test."*

[4]***Note:*** *Participants with reactive oral fluid and invalid fingerstick will be tested with the fingerstick a 2nd time and referred off site for additional confirmatory testing.*

# 3.0 BACKGROUND AND SIGNIFICANCE

## 3.1 HIV Rapid Testing and Counseling within Drug Abuse Treatment Programs

The overall goal of this study is to evaluate the more effective strategy to (1) increase receipt of HIV test results and (2) decrease sexual risk behaviors that lead to HIV transmission and acquisition among individuals receiving drug treatment within community-based drug abuse treatment programs in the United States.

In this section, we first provide the scientific and public health rationale for focusing on HIV testing and counseling with persons at moderate and high risk for HIV. Second, we discuss the need for expanding HIV testing and counseling in drug treatment settings including the results of recent surveys conducted in the CTN in preparation for this study. We then describe the HIV rapid test and our selection of the oral fluid test. This is followed by a presentation of the brief prevention counseling that will accompany the HIV testing in the first group. Finally, we provide the rationale and scientific evidence for our three proposed testing groups and present our research questions and planned comparisons.

## 3.2 Scientific and Public Health Rationale for Expanding Screening and Counseling for HIV in the U.S.:

There are two major reasons for expanding screening and counseling for HIV in the United States.

**Reason #1: HIV testing can save lives and is cost effective**

There are a sizeable numbers of individuals in the United States who do not know their HIV status (Glynn & Rhodes, 2005). HIV is often discovered at an advanced stage, often in the course of medical care and often when individuals have already progressed to AIDS; CDC researchers report that 40% of individuals diagnosed with HIV between 1994 and 1999 received an AIDS diagnosis within one year of being diagnosed with HIV (Neal & Fleming, 2002). Notably, this 40% is consistent over time and is reported in CDC's annual HIV/AIDS surveillance reports. Results from CDC's 2004-2005 National HIV Behavioral Surveillance study conducted with 2,261 men who have sex with men recruited in Baltimore, Los Angeles, Miami, New York City and San Francisco indicate that 48% of the 450 men who tested positive in that study were unaware of their HIV infection (Sifakis et al., 2005). Recent data from a pooled cross-sectional analysis of the 2000-2005 National Health Interview Survey showed that less than one-fourth of respondents who reported engaging in HIV risk behaviors had reported having an HIV test in the past year (Ostermann et al., 2007).

Early detection of HIV is important because knowledge of positive serostatus increases the likelihood that these individuals will obtain recommended medical care, resulting in improved quality of life for this population (*Institute of Medicine,* 2004; Bozzette, 2005). An earlier diagnosis may also facilitate more rapid access to antiretroviral therapy which is associated with the suppression of viral replication, decreased morbidity and mortality, and may result in decreased HIV transmission risk due to reductions in sexual risk behavior and decreased viral load (Holmberg, Palella, Lichtenstein, & Havlir, 2004).

Recent studies suggest that the value of extending HIV screening to moderate and high risk populations in outpatient settings would be similar to the value of routine screening for other common chronic diseases such as diabetes, hypertension and breast cancer (Paltiel et al., 2005; Paltiel et al., 2006; Sanders et al., 2005). Paltiel and colleagues (2005) estimate that with widespread routine screening of HIV, there would be substantial benefits for HIV-infected patients. When screening high risk populations (defined as those populations who have a 3.0% prevalence, or greater, of undiagnosed HIV infection), the average CD4 count at HIV diagnosis would increase because of earlier diagnosis (from 154 to 210 cells per cubic millimeter), and there would be a decrease in the proportion of HIV-positive persons that are diagnosed at the time of an opportunistic infection. Both studies estimate that the effects of screening would extend survival by 1.5 years for the average HIV-infected patient.

These analyses showed that offering routine HIV testing and counseling with moderate and high-risk populations also would be cost effective in terms of quality-adjusted life-years gained[2] (Paltiel et al., 2005; Sanders et al., 2005). The CDC recommends the routine use of screening for populations with HIV prevalence rates that are 1% or greater. In these populations, Sanders et al. (2005) estimate the incremental cost-effectiveness ratio of one time screening to be $41,736 per quality-adjusted life-year. This figure considers only the benefit to the identified patient (not the possible benefit to sexual partners as a result of potential decreased HIV transmission risk) and is based on a one-time screening program increasing life expectancy by 3.92 days, or 2.92 quality-adjusted days, at a cost of $333 relative to current practice. Paltiel et al. (2005) estimate the incremental cost-effectiveness ratio of one-time screening to be $38,000 per quality-adjusted life-year gained; notably, both of these estimates are less than the usual threshold for cost-effective care, which is $50,000 per quality-adjusted life year gained. Screening is even more cost-effective for high-risk populations (HIV prevalence > 3.0%). The effect of reducing the annual rate of HIV transmission (see discussion below) dramatically increases the cost-effectiveness of screening. Sanders et al. (2005) estimated that one-time screening in a population with a 1% prevalence of HIV infection would reduce the annual rate of transmission by 20%. When taking into account the costs and benefits of one-time screening to sexual partners, the cost of screening would be reduced from an incremental cost effectiveness ratio of $41,736 to $15,078 per quality-adjusted life year gained.

**<u>Reason #2</u>: Knowledge of one's serostatus and risk reduction counseling reduce sexual risk behaviors**

Previous studies have shown that the majority of persons who learn that they are HIV-positive will reduce their sexual risk behaviors, resulting in reduced transmissions to others (DiFranceisco, Pinkerton, Dyaltlov, & Swain, 2005; Marks, Crepaz, Senterfitt, & Janssen, 2005; Weinhardt, Carey, Johnson, & Bickham, 1999). A recent meta-analysis of 11 independent studies reported a 68% reduction in high-risk behavior (unprotected anal or vaginal intercourse with uninfected partners) among HIV-positive persons who were aware of their HIV status compared with HIV-positive persons who were not aware of their HIV status (Marks et al., 2005). Marks and colleagues (2006) estimated that more than half of new sexually transmitted HIV infections in the U.S. stem from the 25% of the infected persons in the U.S. who are unaware of their seropositive status (i.e., 250,000 persons). Taking into account that 80% of new HIV diagnoses each year are among people who become infected through sexual exposure and CDC's previous estimate that there are 40,000 new cases each year (32,000

[2] Notably, cost-effectiveness changes based on the prevalence of disease in a particular population or setting.

related to sexual transmission), their estimates show that the majority of new cases related to sexual transmission, or about 17,280 cases, may be from those who are unaware of their infection status. In fact, the HIV transmission rate is estimated to be 6.9% (17,280/250,000) among those who are unaware of their HIV-positive status, compared with an estimated 2% (14,720/750,000) among those who are aware of the HIV-positive serostatus. Therefore, the HIV transmission rate for the unaware group was 3.5 times that of the aware group after adjusting for population size differences between groups (Marks et al., 2006).

In addition, among HIV-negative cohorts, counseling interventions based on behavioral theory have been shown to be effective in reducing STD incidence and risk behaviors associated with acquisition of HIV (The NIMH Multisite HIV prevention Trial Group, 1998; DiClemente et al., 2004; Kamb et al., 1998; Latkin, Sherman, & Knowlton, 2003). These interventions have ranged from brief individual counseling that accompanies HIV testing (Kamb et al., 1998) to group sessions with multiple interventions (The NIMH Multisite HIV Prevention Trial Group, 1998; DiClemente et al., 2004; Latkin et al., 2003) and have been conducted with various high risk population groups. In meta-analyses, such interventions reduce risk behavior by 23-26% (Johnson et al., 2002; Johnson, Hedges, & Diaz, 2003; Marks et al., 2005). At the same time, some research shows a lack of effect of HIV counseling and testing on HIV risk behavior, among HIV-negative individuals, as compared to untested individuals (Weinhardt et al.,1999).

## 3.3 Provision of HIV testing in Drug Abuse Treatment Programs in the U.S.

To date, there have been few widespread efforts to encourage the roll out of HIV testing and counseling in drug treatment programs in the U.S. There have been some efforts by SAMSHA; for example, SAMSHA's Rapid HIV Testing Initiative purchased rapid HIV test kits and provided access to training for some community-based service providers, and SAMSHA encouraged local public health departments to increase the delivery of HIV testing in drug treatment programs. Yet these efforts did not have research-quality planned evaluation components and there are no published studies on the evaluation of these efforts.

Despite HIV prevalence rates ranging from over 1% and as high as 28% in drug abuse treatment clinics (Lehman, Allen, Green, & Onorato, 1994; Murrill et al., 2001; Prevots et al., 1996; Sorensen, Masson & Perlman, 2002) and the well-established link between substance use, sex risk behaviors and HIV, less than one-half of drug treatment programs in the U.S. currently offer HIV testing and counseling. Brown Jr. and colleagues conducted a study focusing on the characteristics of community treatment providers (CTPs) in the CTN. Their findings showed that less than half (48.5%) of CTPs (n = 269) made HIV testing available either in the CTP or through referral or outsourcing (Brown Jr. et al., In Press). Strauss and colleagues (2003) had similar findings when they conducted a national telephone survey of residential drug abuse treatment units in 2001. Their findings showed that 48.6% of the residential drug treatment units made HIV testing available to their patients on-site. In a recent study conducted by the NIDA-funded Criminal Justice Drug Abuse Treatment Studies, Oser, Tindall and Leukefeld (Oser et al., 2007) found that 51.4% of treatment programs that self-report serving criminal justice involved clients (n = 217) offered HIV testing to their patients.

Pollack and colleagues (2006) conducted an analysis of data from the National Drug Abuse Treatment System Survey (NDATSS) to assess the extent to which outpatient substance abuse treatment programs were providing HIV prevention services. Specifically, they examined trends

in the number of Outpatient Substance Abuse Treatment (OSAT) units that report that they provided HIV testing for their clients; they examined the provision of services between 1995 and 2000. That paper also explored HIV outreach and counseling services. Their findings show that a large proportion of OSAT units reported providing HIV testing and this proportion increased from 1995 to 2000 (66% to 86%). This report was surprising and seemed to contradict other reports on the provision of HIV testing services in drug treatment programs (Brown Jr. et al., 2006). We contacted the authors and they clarified that their analysis did not explore whether these HIV testing services were provided directly or provided off-site. The authors also clarified that they did not explore the proportion of clients who actually received these services. The authors graciously agreed to conduct further analyses to further examine the HIV testing practices at outpatient drug treatment programs in their nationally-representative data set (NDATSS). Specifically, the authors:

- Examined the percent of clients who actually receive HIV testing (on-site or off-site) at these OSAT facilities.
- Examined the proportion of OSAT units (weighted by caseload) who provided *at least some HIV test on-site* prior to each survey wave. The authors operationalized this by including only those units which reported at least 1% of clients tested. Some OSAT units report that they provide testing, yet report no clients actually tested.
- Third, the authors included data for the NDATSS 2005/06 wave.

Table 1 shows the main results.

**Table 1**
HIV Counseling in the National Drug Abuse Treatment Systems Survey

| | **1995 (wave 4) [95% CI] (N=568)** | **2000 (wave 5) [95% CI] (N=501)** | ***2005 (wave 6) [95% CI] (N=500)*** |
|---|---|---|---|
| Percentage of clients who receive *off-site* HIV tests | 10.3% [7.6, 13.0] | 7.4% [4.6, 10.2] | *9.1% [4.4, 13.8]* |
| Percentage of clients who receive *on-site* HIV tests | 16.5 [12.2, 20.8] | 14.2 [10.4, 17.8] | *13.8 [10.3, 17.3]* |
| *Percentage of* units*, weighted by caseload, which provide at least some on-site HIV testing.* | *34.9 [28.2, 41.6]* | *42.6 [32.1, 53.1]* | *41.2 [32.0, 50.3]* |

The above table shows that fewer than half of outpatient drug treatment programs provided on-site HIV testing services and this has held constant since 2000. Furthermore, very few drug treatment participants (less than one-fifth) report receiving HIV testing while in drug abuse treatment and this has also held relatively constant since 1995.

In preparation for this study (between February and March of 2007), our study team conducted a brief survey of CTN CTPs' provision of on-site HIV testing. We sent the survey to 132 CTPs and achieved an 80% response rate (n=105 CTPs). A total of 269 treatment programs are represented within the 105 CTPs, including 97 outpatient counseling, 49 outpatient methadone

(or other narcotic replacement), 58 partial hospitalization or intensive outpatient and 65 residential services. CTPs were asked which (if any) of their adult treatment programs offered on-site HIV testing in the past 30 days. A large proportion (41/105 or 39%) of CTPs indicated no provision of on-site HIV testing during the past 30 days within any of their programs. An additional 18% of CTPs indicated that some of their programs did not provide on-site HIV testing. In total, 57% of CTPs or 60 CTPs would have at least one program eligible for this study.

Independent of whether testing is offered at sites or not, it is reasonable to ask whether there is a need for more testing options among substance users in treatment. Recent studies have demonstrated high rates of reported testing among some substance-using populations (Heimer, Grau, Curtin, Khoshnood, & Singer, 2007). Our study team sought to document the recent HIV testing experiences of drug users at CTN CTPs. We selected eight CTPs that identified themselves as not currently offering on-site HIV testing within all of their adult programs (as gathered in our brief survey described in the paragraph above) to participate in a brief information collection activity. CTPs were located in the following cities: Cape Girardeau, Missouri; Greensburg, Pennsylvania; Pittsburgh, Pennsylvania; Tucson, Arizona; Sante Fe, New Mexico, Kannapolis, North Carolina; Portland, Oregon; and Columbia, South Carolina. Information was collected from all adult clients who accessed services in outpatient counseling, assessment only[3], intensive outpatient or partial hospitalization, outpatient methadone or narcotic replacement, and residential programs within a seven calendar day information collecting period. Information was collected from only those treatment programs that do not currently offer on-site HIV testing, because only these programs would be eligible for this study. CTPs selected a seven consecutive calendar day period (one week) within April or May of 2007 that was most convenient for them to collect the information. Clients were asked if they had ever been tested for HIV; if ever tested, how long ago they were last tested and if they received the results of their last HIV test.

Information was collected from a total of 2,303 patients from eight CTPs. Results include information from seven outpatient drug free settings, three residential settings, two methadone settings, and two assessment only settings. As shown in Table 2, results indicate that 83% (ranging from 73% to 88%) of clients surveyed had not been tested for HIV within the past six months and therefore would potentially qualify for our proposed study. Additionally, the results indicate that the majority of participants (78%) have not been tested in the past 12 months (58% to 83% of study participants) and therefore would potentially qualify for our proposed study.

[3] The assessment period is part of the intake process where drug abuse treatment participants are assessed for their drug treatment needs.

**Table 2**
**CTN CTP clients reporting having not been tested within the past 6 months and 12 months**

| CTP | Number Surveyed | Percent of valid responses that had not been tested within the given timeframe | | | |
|---|---|---|---|---|---|
| | | % **not** tested within past **6** months | % **not** tested within past **12** months | # of valid responses | # missing or refused to answer |
| 1 | 780 | 85% | 83% | 757 | 23 |
| 2 | 101 | 78% | 70% | 99 | 2 |
| 3 | 101 | 81% | 74% | 94 | 7 |
| 4 | 459 | 81% | 76% | 436 | 23 |
| 5 | 138 | 73% | 58% | 134 | 4 |
| 6 | 152 | 76% | 72% | 145 | 7 |
| 7 | 442 | 88% | 83% | 413 | 29 |
| 8 | 130 | 78% | 72% | 125 | 5 |

As shown in table 3, notably, a sizeable number of CTP participants reported never having been HIV tested (41% ranging from 21% to 48% in the eight CTPs surveyed). Across CTPs, approximately 11% (ranging from 4% - 17%) of clients did not receive their HIV test results when tested. Although methadone programs are commonly believed to offer more medical services than drug free programs, a high proportion of clients (78%) surveyed in the methadone sites had not been tested for HIV within the past six months.

**Table 3**
**CTN CTP clients' HIV testing history**

| CTP | Percent of valid responses that had ever been tested | | | Percent of those that had ever been tested (valid responses only) that received their test results | | |
|---|---|---|---|---|---|---|
| | % ever tested | # of valid responses | # missing or refused to answer | % that received their results | # of valid responses | # missing or refused to answer |
| 1 | 52% | 763 | 17 | 89% | 393 | 4 |
| 2 | 70% | 100 | 1 | 88% | 69 | 1 |
| 3 | 55% | 100 | 1 | 85% | 54 | 1 |
| 4 | 58% | 440 | 19 | 85% | 252 | 3 |
| 5 | 79% | 135 | 3 | 83% | 106 | 0 |
| 6 | 72% | 146 | 6 | 89% | 104 | 1 |
| 7 | 58% | 424 | 18 | 94% | 243 | 3 |
| 8 | 75% | 126 | 4 | 96% | 90 | 4 |

**Scientific Basis for Selecting Rapid HIV testing and Project RESPECT Counseling:** The conventional method for HIV testing most often used since the advent of HIV testing and counseling in the U.S. involves pre-test counseling, drawing of blood through venipuncture, the sending of a serum specimen to a laboratory for screening with enzyme-linked immunoassay (EIA), and confirmation of repeatedly reactive EIA results with Western Blot or immunofluorescence assay. This process requires that a person return to a testing site approximately two weeks after the initial test to obtain test results and post-test counseling. However, clients often do not return for test results and may be less likely to accept testing if that return visit is required (Sullivan, Lansky, Drake, & HITS-2000 Investigators, 2004).

**Rapid testing:** The advent of the rapid HIV test permits a fast, simple, less invasive, and cost effective method to determine HIV serostatus (Bulterys et al., 2004; Greenwald, Burstein, Pincus, & Branson, 2006; Kassler, Dillon, Haley, Jones, & Goldman, 1997; Kendrick et al., 2005). Rapid HIV screening tests provide results in 20 minutes; if negative, the result is considered conclusive; if positive, follow-up confirmatory testing is required. Although rapid testing has been available for more than a decade, these tests were not widely used because the 1989 US Public Health Service guidelines required confirmatory testing before clients could receive any positive HIV test results (Hutchinson, Branson, Kim, & Farnham, 2006). This recommendation was revised in 1998 to encourage the provision of positive results before confirmatory results were available to increase the number of persons who learn their HIV test results (Centers for Disease Control and Prevention, 1998a). The rapid HIV test using whole blood from a fingerstick was approved for use by the FDA in 2002 (*FDA news,* 2002) and the use of oral fluid was approved in 2004 (*FDA news,* 2004).

The rapid HIV test has many advantages for reaching hard to access, high risk populations and is now the preferred method of testing for many providers and clients (Bulterys et al., 2004; Greenwald et al., 2006; Kassler et al., 1997; Kendrick et al., 2005). It (1) only requires blood from a fingerstick or oral fluid from a swab; (2) can be completed in 20 minutes which allows

testing and result notification to occur on the same visit; (3) does not require extensive sophisticated laboratory facilities or highly trained lab personnel and can be performed in office-based or mobile field settings without the requirement of having a doctor, nurse, or phlebotomist. A recent published meta-analysis of the effectiveness of alternative HIV counseling and testing methods to increase knowledge of HIV status demonstrated that rapid HIV testing led to substantial increases in receipt of HIV test results. In a review of seventeen studies with over 20,000 clients, rapid testing clients were approximately twice as likely to receive HIV testing results compared with conventional HIV testing and counseling clients (Hutchinson et al., 2006). Overall, the rate of false-positive test results was less than 1%. Studies have also shown that rapid HIV testing has facilitated the entry of newly identified HIV-infected patients into health care (Kendrick et al., 2005).

Due to the ease of specimen collection for both participants and staff, we propose to use a rapid HIV test, such as the OraQuick oral fluid rapid test. Oral fluid collection is viewed as a less-invasive testing method and has demonstrated high acceptability in preliminary studies with various risk groups, including drug users (McCoy, Comerford, Metsch, & Comerford, 2006; Pugatch D. L. et al., 2001; Pugatch D. et al., 2001), with results available in approximately 20 minutes (Spielberg et al., 2005). In contrast to the rapid blood test, oral fluid collection does not require a fingerstick or venipuncture, which causes some jurisdictions to require phlebotomy training in order to perform the rapid blood test. Despite initial concerns about unacceptably high false positive rates using the OraQuick oral fluid test, follow-up studies have demonstrated excellent sensitivity and specificity (>99%), when compared to EIA testing (Delaney et al., 2006; Wesolowski et al., 2006). Recently, in New York City (NYC), and previously in both San Francisco (SF) and New York City, there has been a reported increase in the expected number of false-positive oral fluid tests (Centers for Disease Control and Prevention (CDC), 2008). In response to the increase in false-positive results, both NYC and SF have been using a rapid OraQuick whole blood fingerstick test after any oral fluid test that is “reactive” or preliminarily positive since 2005. This immediate follow-up rapid test allows the counselor to guide the participant or client as to the likelihood of the reactive oral fluid test being a “true” or “false” reactive test. All clients receive confirmatory follow-up testing with a Western blot. This strategy, used in both NYC and SF, mitigates the potential adverse effects of false-positive results on both patients and clinic personnel (Centers for Disease Control and Prevention (CDC), 2008). This strategy also allows for the immediate and prompt detection of false-positive oral fluid tests and avoids instances in which clients leave the testing site with an oral fluid test result only (Centers for Disease Control and Prevention (CDC), 2008). Thus, counselors can provide more accurate test result information while minimizing the number of fingerstick tests that must be performed.

In response to the recent data on false positive oral fluid tests from NYC that was published on June 20, 2008 in MMWR (Centers for Disease Control and Prevention (CDC), 2008), we consulted with Dr. Bernard Branson, Associate Director for Laboratory Diagnostics in the Division of HIV/AIDS Prevention at the CDC and chief architect for CDC’s activities surrounding new technologies for HIV testing, including rapid HIV tests and tests for HIV incidence (B. Branson, personal communication, June 24, 2008), Dr. Rochelle Walensky, Associate Professor of Medicine at Harvard Medical School (R. Walensky, personal communication, July 1, 2008), and other HIV testing technology experts to review our HIV testing algorithm (refer to Figure 1). All agreed that the SF/NYC practice of immediately following a reactive oral fluid test with an OraQuick whole blood fingerstick test should be adopted for the study. Additionally, as our original strategy outlines, all reactive rapid tests will be followed by a confirmatory Western blot.

These participants will be re-swabbed and their oral fluid sent to laboratories for processing. Results will be available in approximately one week. This test is comparable to the traditional Western Blot in terms of sensitivity and specificity (Gallo et al., 1997).

**HIV counseling:** In the proposed protocol, rapid testing will be offered in two of the groups. In one group, it will be accompanied by information only, per the new CDC guidelines, and in a second group it will be accompanied by brief prevention counseling using the Project RESPECT-2 single visit counseling intervention (hereafter, RESPECT). RESPECT is a brief, client centered, individually administered prevention intervention of interactive counseling based on behavioral science theory and theoretical constructs (e.g., theory of reasoned action, social cognitive theory, self-efficacy and attitudes) that has been conducted on a mass basis in fast-paced, public health settings (e.g., STD clinics) in which time and resources are often strained (Kamb et al., 1998). Using counseling strategies that are similar to motivational interviewing and include both cognitive and action-oriented strategies, RESPECT seeks to increase knowledge, motivate behavior change and teach safer sex and drug use skills to persons at risk for HIV. In addition, this counseling intervention seeks to motivate persons to obtain HIV testing. RESPECT was tested and shown to be efficacious (Kamb et al., 1998) in reducing STD incidence and increasing condom use in STD clinics that included some drug users. Specifically, at 6 month follow-up, 30% fewer participants in the two session intervention compared with the didactic information only session had new STDs and at 12 month follow-up, 20% fewer participants in the two session intervention compared with the didactic information only session had new STDs. RESPECT counseling is the standard counseling approach recommended by the CDC if counseling is to be performed in the setting of HIV testing.

In the era of rapid testing, the two-visit pre- and post-test counseling sessions become obsolete, because test results can be delivered in one visit. In a trial to adapt RESPECT to the rapid testing era, the RESPECT two session counseling intervention was used with rapid testing (pre- and post-testing delivered in one visit) and compared with traditional HIV testing and the two session RESPECT intervention (delivered in two visits); the results showed that rapid testing participants were more likely to receive their HIV test results (Metcalf et al., 2005). Overall, there were no differences in rates of subsequent STDs between the two RESPECT arms (delivered at one visit vs. two visits). In light of these findings, and the advent of rapid testing that allows participants to be tested and receive their results in one visit, we propose to implement rapid testing combined with RESPECT delivered in two sessions, pre-and post-testing, during a single visit.

## 3.4 Need for Current Initiative and Research Questions:

Widely expanded access to routine HIV testing is now being promoted by the CDC and local health departments throughout the United States (Beckwith et al., 2005). Currently, the national effort in this area is to determine the best strategies for establishing HIV testing in both medical and non-medical settings to increase HIV testing throughout the U.S. population.[4] The CDC is currently working on developing HIV testing guidelines for non-medical care settings. The majority of drug abuse treatment programs in the United States would be defined as a non-

[4] *Opportunities for Improving HIV Diagnosis, Prevention and Access to Care in the U.S.* November 29 – 30, 2006. High level meeting (sponsored by numerous federal agencies) focusing on implementing new CDC guidelines regarding HIV testing. http://kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=1937

medical care setting. This study has the unique opportunity to provide policy-relevant information that can be used in the new HIV testing guidelines for both medical and non-medical care settings.

Rapid HIV testing is now the preferred method of testing because it ensures that people who are tested will receive their results. There has been little research conducted on the implementation of HIV rapid testing in drug abuse treatment programs (see letter of support from Dr. Bernard Branson of the CDC in Appendix 1). The effect of offering rapid, on-site, point of care (e.g., results available on-site in real time) HIV testing in drug abuse treatment centers has not been determined.

This study presents an ideal opportunity to provide relevant data that can be used to inform public health officials, drug abuse treatment programs, and policymakers on the more effective HIV testing strategy to implement in drug treatment settings throughout the United States. Using the extensive network of treatment sites afforded by the CTN, we will be able to answer key scientific questions directly relevant to public health:

**What is the effect of offering HIV rapid testing on-site at drug abuse treatment programs?**

We will answer two related but distinct questions:

- What is the effect of offering on-site rapid testing (in conjunction with counseling or not) on HIV testing rates compared with referral?
- What is the effect of offering on-site rapid testing in conjunction with counseling on HIV testing rates compared with rapid testing only (no counseling)?

Two of the three study groups offer HIV testing on-site in drug abuse treatment programs and one group offers a referral to HIV testing in the community. Referral to HIV testing in the community is the standard of care for drug abuse treatment programs that do not offer on-site testing. In settings other than drug abuse treatment centers, the convenience of having a test available on-site has been shown to be a positive factor in the decision to be HIV tested (Spielberg et al., 2003; Lopez-Quintero, Shtarkshall, & Neumark, 2005; Spielberg et al., 2005). Convenience may increase the likelihood that people accept testing, but it is not the only factor in the decision. Even when presented with an immediate opportunity to be tested, people often decline (Liddicoat, Losina, Kang, Freedberg, & Walensky, 2006; Wilson & Jaccard, 1996). It is possible that offering on-site, point of care testing will not increase testing substantially, due to a number of reasons. Clients may not perceive themselves to be at risk. Clients may be unprepared to receive results in real time. Previously tested patients may not be prepared to test. It is also possible that drug abuse treatment clients will reject convenient, on-site testing because of fears that counselors and other facility staff will become aware of the HIV test results. Studies have found that barriers to accepting testing include a concern about the stigma associated with testing positive for HIV and the desire to maintain anonymity (Awad, Sagrestano, Kittleson, & Sarvela, 2004; Hutchinson, Corbie-Smith, Thomas, Mohanan, & del Rio, 2004; Kalichman, Kelly, Hunter, Murphy, & Tyler, 1993; Myers, Orr, Locker, & Jackson, 1993; Spielberg et al., 2003). Investigation of the acceptability and effectiveness of providing HIV testing at community drug abuse treatment facilities will help inform the community's response to this important public health concern.

Previous studies have shown that integrative models providing primary care within drug treatment facilities versus referrals for such care have been efficacious in increasing utilization of care for hypertension, tuberculosis exposure, STDs and HIV (Umbricht-Schneiter, Ginn,

Pabst & Bigelow, 1994). While not evaluated in randomized trials, other integrative approaches that have established HIV prevention and clinical services at drug treatment facilities have shown promise in their ability to engage drug users in on-site services (Rothman et al., 2007). However, we have not found scientific literature illustrating that such models are efficacious in increasing HIV test acceptance or receipt of results. To our knowledge, the relative efficacy of integrative vs. distributive health services delivery models with respect to HIV testing and drug treatment has not been evaluated in a randomized controlled study.

**What is the effect of rapid HIV testing coupled with counseling on HIV testing and sexual risk behaviors?** Our design includes two groups that will be offered HIV testing onsite; one group is offered HIV testing with brief prevention counseling (RESPECT) and the other group is offered HIV testing with information only (following the new CDC recommendations for HIV testing, which does not require pre-test counseling or post-test counseling for those who test HIV-negative). A major barrier that has been identified in the roll out of rapid HIV testing is the requirement to complete HIV counseling. Some of the reasons for counseling being identified as a barrier include the additional time that it will take to do counseling and current staff potentially being uncomfortable or lacking the training to conduct the counseling. In addition, outside of STI clinics, where counseling has been shown to reduce STI risk among HIV-negative patients (Kamb et al., 1998), it remains to be determined whether HIV counseling in conjunction with HIV testing, reduces sexual risk behaviors among HIV-negatives. In their revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings, CDC authors wrote, “The benefit of providing prevention counseling in conjunction with HIV testing is less clear. HIV counseling with testing has been demonstrated to be an effective intervention for HIV-infected participants, who increased their safer behaviors and decreased their sexual risk behaviors; HIV counseling and testing as implemented in the studies had little effect on HIV-negative participants.” In this quote, the CDC authors are citing a published meta-analysis that examined 27 published studies that assessed HIV sexual risk behavior before and after HIV counseling and testing (Weinhardt et al., 1999). This analysis showed that while HIV-positive participants reduced unprotected sexual intercourse and increased condom use more than HIV-negative and untested participants, HIV-negative participants did not modify their behavior more than untested participants.

On the other hand, the CDC authors do recognize in their recommendations that among HIV-negative cohorts, counseling interventions based on behavioral theory have also been shown to be effective in reducing STD incidence and risk behaviors associated with acquisition of HIV. A recent meta-analysis of U.S. based HIV behavioral interventions reported on 18 behavioral interventions that met stringent “best evidence” criteria and were shown to significantly reduce both sexual risk and substance use (Lyles et al., 2007). A meta-analytic review of interventions for Black and Latino STD patients found significant reductions in sexual risk behavior (OR .57, 95% CI .40-.82) and STD incidence (OR .20, 95% CI .05-.73) (Crepaz et al., 2007). Additionally, in CTN 0019, a trial of a HIV safer sex skills building group intervention for women in methadone maintenance or drug free outpatient treatment, significant reductions in unprotected (vaginal or anal) sex occasions were obtained (Tross, 2007). In mixed-effect analysis, treating baseline unprotected sexual occasions as a covariate, model predicted means were: (1) Safer Skills Building Group: 17.3 unprotected sexual occasions (3-month follow-up) and 13.9 (6-month follow-up); as compared to (2) HIV Education (Control): 15 (3 month follow-up), and 24 (6-month follow-up). At 3-month follow-up, unprotected sexual occasions decreased in both conditions. However, at 6-month follow-up, this decline was maintained only

in the safer skills building group condition; in the control condition, unprotected sexual occasions rose.

The question of how counseling fits into the roll out of HIV rapid testing is a critical issue because counseling has been a cornerstone of drug treatment service delivery (Rounsaville, Carrol & Back, 2004). The role of counseling is also being considered by CDC in their development of the HIV testing guidelines for non-medical care settings (B. Branson, personal communication, October 12, 2007). Numerous individual and small group interventions with drug users have been shown to be efficacious in reducing high risk injection and sexual risk behaviors (Sterk et al., 2003; Latkin et al., 2003; Wechsberg, Lam, Zule, & Bobashev, 2004). By virtue of drug counseling occurring at drug treatment programs, it is possible that HIV prevention counseling may be more easily integrated into drug treatment centers compared with other test sites, such as the ER or STD clinics.

However, not wanting to participate in prevention counseling has been suggested as a possible reason that people avoid HIV testing. Speilberg and colleagues (2003, 2005) conducted a study of persons' preferences for alternatives to traditional HIV counseling and testing. She offered participants the choice of selecting traditional HIV testing with standard counseling, rapid testing with standard counseling, oral fluid testing with standard counseling, and traditional testing with choice of written materials or standard counseling. This study enrolled 7,014 participants from a needle exchange site and two bathhouses. Her results suggested that clients preferred the oral fluid test and written pretest materials compared to traditional counseling and testing. In her needle exchange site (n=3,874), acceptance of each of the three alternative testing strategies was significantly higher than the acceptance of traditional testing with 8.7% accepting traditional testing with standard counseling (Spielberg et al., 2005), 11.9% accepting traditional testing with counseling options, 14.1% accepting rapid testing, and 19.5% accepting oral fluid testing. It should be noted, however, that only 61% of clients at the needle exchange who agreed to accept HIV testing, actually completed the testing. Completion of testing correlated with shorter estimated wait times at both sites, which depended on the testing strategy and the number of clients who accepted testing during a given session. While there were discrepancies between the acceptance of HIV rapid testing and actual testing in this study, we believe that we will not encounter such discrepancies in our study. This is due to our drug treatment study population, the majority of which should not be in withdrawal and, therefore, be more willing to wait to receive testing and counseling and because we should have shorter wait times due to fewer participants testing at a given time in our study sites.

It is possible that offering counseling as part of rapid testing in drug abuse treatment centers reduces acceptance of testing; some participants may not want to discuss their sexual risk behaviors and may therefore decline the offer of HIV testing (Simmons, Monroe & Flannigan, 2004). It is also possible that while persons who receive counseling reduce their sexual risk behavior, a lower rate of test acceptance among persons who are offered counseling could offset this advantage at the population level, if in fact rapid testing alone reduces sexual risk behavior to some degree. By comparing, in an intent-to-treat analysis, rates of test acceptance and sexual risk behavior change in the group randomized to testing only versus the testing plus counseling group, we will determine the extent to which the offer imbedded within the context of counseling changes acceptance of testing and sexual risk behavior.

**Summary**: We need randomized controlled studies to inform the dissemination and implementation of rapid testing strategies. The proposed study will provide timely and relevant data to inform the national guidelines for how HIV testing should be delivered in drug abuse treatment programs. We will determine the extent to which offering rapid testing changes testing rates compared to referral, and whether the offer imbedded within counseling changes acceptance. Furthermore, we will determine whether offering counseling in conjunction with HIV testing reduces sexual risk behavior.

# 4.0 STUDY AIMS AND HYPOTHESES

**HIV Testing Primary and Secondary Outcomes**

The HIV testing primary outcome is self-reported receipt of HIV test results. This will be measured at one month post-randomization for all participants. We recognize that there are three potential HIV testing behaviors that could be evaluated in this study: acceptance of HIV testing, completion of HIV testing, and receipt of HIV testing results. Acceptance of testing refers to whether or not a participant would accept the offer of an HIV test. Completion of testing refers to whether or not a participant completes the HIV test. Receipt of HIV test results refers to whether or not a participant self-reports having received the results of the HIV test. We have selected the third behavior as the primary outcome because this is the behavior that has been associated with decreased HIV transmission (Marks et al., 2005; Marks et al., 2006) and improved quality of life for persons living with HIV. In other words, HIV-positive persons who learn their HIV status are more likely to reduce their sexual risk behaviors and to link themselves with HIV primary care. In this study, self-reported receipt of HIV test results encompasses the fact that participants will have accepted testing and completed testing in order to receive their results.

Secondary outcomes for HIV testing include validated receipt of test results. This will be measured at one and six month's post-randomization as whether or not participants' medical records indicate their receipt of results. The medical record would either be housed within research study records at the CTP (in the case of participants assigned to groups 1 or 2) or at a community HIV testing program (in the case of participants assigned to group 3 who are referred to HIV testing in the community). *We recognize that there may be some difficulty in obtaining records for participants who receive HIV testing in the community and therefore we are using the validated receipt of HIV test results as a secondary outcome.* Additional secondary outcomes for HIV testing are described in the statistical analysis section.

**Sexual Risk Behavior Primary and Secondary Outcomes**

The sexual risk behavior primary outcome is self-reported sexual risk behavior, which will be measured at baseline and six months post-randomization as the self-reported number of unprotected sex acts (vaginal or anal sex without a condom). Primary aims and hypotheses are outlined in section 4.1. Secondary analyses for sexual risk behaviors and drug use are described in the statistical analysis section.

## 4.1 Primary Aims and Hypotheses

**Primary Research Questions:**

Among persons who attend drug abuse treatment and report being HIV-negative or not knowing their status.

1) What is the more effective HIV testing strategy to increase receipt of HIV test results?
2) What is the more effective HIV testing strategy to decrease sexual risk behaviors?

**Primary Study Aims and Hypotheses:**

HIV Testing:

**Aim 1a:** To evaluate the effectiveness of offering on-site HIV rapid testing on receipt of HIV test results (measured via self-report) among clients in substance use treatment centers.

**H1a:** The self-reported HIV test result receipt rate in Groups 1+2 (offer of on-site HIV rapid testing) will differ from the self-reported rate of HIV test result receipt in Group 3 (offer of a referral for off-site HIV testing) at one month post-randomization.

**Aim 1b:** To evaluate the effectiveness of offering counseling as part of rapid testing procedures on receipt of HIV test results (measured via self-report) among clients in substance use treatment centers.

**H1b:** The self-reported HIV test result receipt rate in Group 1 (offer of on-site HIV rapid testing with brief prevention counseling) will differ from the rate of self-reported HIV test result receipt in Group 2 (offer of on-site HIV rapid testing with information only) at one month post-randomization.

Sexual Risk Behavior:

**Aim 2a:** To evaluate the effectiveness of offering brief prevention counseling with rapid testing on sexual risk behavior (anal or vaginal sex without a condom) among substance use treatment clients.

**H2a:** The number of risky sex acts in Group 1 (offer of on-site HIV rapid testing with brief prevention counseling) will differ from the number of risky sex acts in Group 2 (offer of on-site HIV rapid testing with information only) at six months post-randomization.

# 5.0 STUDY DESIGN AND ACTIVITIES

## 5.1 Overview of Study Design

This study will use a prospective, randomized, controlled design to assess the effectiveness of HIV testing strategies in increasing receipt of HIV testing results and reducing risky sexual behaviors. The target population is HIV-negative or status unknown individuals who have not received results of an HIV test initiated within last 12 months and who are currently receiving drug treatment within CTPs. We are using the criterion of not having received results of an HIV test initiated within the past 12 months (which encompasses not having been tested) because the new CDC guidelines recommend that all high risk persons be screened at least on an annual basis and because receipt of results is the behavior that has been associated with decreased HIV transmission (Marks et al., 2005; Marks et al., 2006) and improved quality of life for persons living with HIV.

CTPs are eligible if they are currently not providing on-site HIV testing at the time of site selection (we will define current as the past 30 days). There are several reasons for including only sites that are not currently providing on-site testing. We do not foresee these sites being willing to have their participants randomized to one of the three study arms, because testing is already being offered. One purpose of the study is to learn about feasibility parameters related to CTPs adopting and sustaining on-site testing through a controlled trial. If we were to include sites that already offer on-site testing, it would not be possible to evaluate the on-site testing strategy in a randomized manner. It is also likely that programs which currently offer on-site HIV testing would have higher percentages of patients at these programs that have recently been tested and thus this would diminish the effects of the potential study.

Individuals receiving drug abuse treatment at CTPs will be recruited from the treatment setting and screened for study eligibility. Specific eligibility criteria and recruitment procedures are outlined in section 5.3 of this protocol.

Individuals who screen as eligible will complete written informed consent procedures and will be enrolled and asked to complete a baseline assessment using audio computer-assisted self interview (ACASI). The baseline ACASI will elicit demographic information as well as detailed information on HIV testing behaviors, sexual risk behaviors, and drug-using risk behaviors (see description of measures in section 5.4.3). To minimize participant and staff burden, the instrument will take no more than 45 minutes to complete. Upon completion of the baseline ACASI, participants will be randomized to one of the three study groups:

- Group 1 – Participants will be offered on-site rapid HIV testing with brief prevention counseling (described further in section 6.1)
- Group 2 – Participants will be offered on-site rapid HIV testing with information only (described further in section 6.2)
- Group 3 – Participants will be given a referral for off-site HIV testing

At 1-month post-randomization, all participants will complete a follow-up assessment to determine whether or not they completed HIV testing and to assess their recent sexual risk behavior. At 6-months post-randomization, participants will complete a follow-up assessment to measure changes in their sexual risk and drug-using behaviors.

The proposed randomized trial incorporates elements of both an efficacy and an effectiveness trial, although we use the term "effectiveness" in this protocol. We follow the "hybrid model" that was put forth by Carroll and Rounsaville (2003) as a model to link efficacy and effectiveness in drug abuse treatment. Our study follows an efficacy approach as it includes scientifically rigorous design features that protect internal validity. These features include (1) random assignment of patients to treatment conditions; (2) blind assessment of outcomes; (3) intention to treat analysis; (4) use of objective outcome measures; (5) monitoring of treatments to assess intervention fidelity; (6) specialized training of all research and intervention staff; and (7) rigorous quality assurance. However, our approach also incorporates components of an effectiveness trial because we are 1) testing our intervention approaches in real world community-based drug abuse treatment settings, 2) using actual treatment staff to deliver the interventions, and 3) are allowing community-based treatment programs flexibility in how they set up staffing for this trial, reflecting adaptability and flexibility needed in a "real world" setting. On this last item, for example, CTPs can either use a full-time counselor (100% FTE) to deliver the interventions or they can split this time among several counselors. Additionally, our control conditions are more consistent with an effectiveness approach because they represent current HIV testing practices in drug treatment (referral arm) or they represent the omission of counseling (testing/information only arm) as suggested in the new CDC guidelines for offering HIV testing in medical care settings and as is being considered by CDC as they develop the new guidelines for rolling out HIV testing in non-medical care settings (B. Branson, personal communication, October 12, 2007). The Project RESPECT / rapid testing intervention, our counseling intervention approach, has been previously tested in an efficacy trial but it has not been tested in drug treatment programs. Therefore, this hybrid approach is appropriate for this trial.

## 5.2 Number of Sites and Participants

A target of approximately 1,272 participants from approximately 12 CTPs will be recruited, for approximately 106 participants at each participating CTP. Participants will be enrolled at an average of 8 participants per site per week. In addition, efforts will be made to recruit a sample of study participants that reflects the proportion of minorities and gender in the drug abuse treatment sites in which we are recruiting.

## 5.3 CTP, Counselor, and Participant Eligibility

### 5.3.1 CTP Eligibility

The study will be conducted in approximately 12 CTPs within one or more programs which have not offered on-site HIV testing in the previous 30 days and have no plans to do so for the duration of the study. We will aim to select those CTPs which can recruit approximately 106 members of the target population each over the recruitment period, and which have adequate space to accommodate study staff and activities. As a rule of thumb, in order to be confident that adequate recruitment numbers will be met, the clinic will need to provide services to at least three times the number of clients meeting inclusion criteria. Therefore, clinics participating in CTN0032 must typically serve at least 318 unduplicated clients within the recruitment timeframe. If multiple clinics within the same agency are located on the same property, it will be possible for the combined populations of multiple clinics within the same agency to participate in

the trial. In that case, the combined number of clients served should be at least 318 within the recruitment timeframe. Site selection will be guided by the goal of obtaining diversity in geographic region, primary drug of abuse, race/ethnicity and gender. The study can be conducted in programs that provide any of the following drug abuse treatment modalities: outpatient, partial hospitalization/intensive outpatient, narcotic replacement, and residential services. Type of clinic will be coded for the purposes of describing the sample and providing opportunities for potential secondary analyses.

In order to determine the number of sites that might meet the selection criterion of having sufficient client load for recruitment, we conducted a survey of CTPs that do not currently offer onsite HIV testing in the treatment units where they might host CTN0032. In October 2007, CTPs were asked to provide information about their number of new intakes and the total number of unduplicated clients (both new intakes and on-going clients) over the duration of time that we anticipated allotting for recruitment. A total of 39 CTPs representing 14 Nodes completed the survey.

CTPs were invited to provide responses for the treatment unit where they would most likely host CTN0032 and for other treatment units where they might host CTN0032. CTPs provided responses for a total of 93 treatment units. Some treatment units are located on the same property; it may be feasible to combine these units and use the same study staff for combined units. When some of the treatment units that are located on the same property are combined, the total number of sites is 85. Of the 85 sites, 36 served at least 318 unduplicated clients over a 4-month time period.

### 5.3.2 Counselor Eligibility

Counseling procedures will be conducted by appropriate, designated CTP staff members that are willing to participate in the trial. All participating CTP staff will undergo training in study procedures, including safety and informed consent procedures. To increase the validity of the study with regard to its implementation in a “real world” setting, the educational background, credentials, and experience of the staff implementing the study groups may vary across CTPs. However, all study procedures will be standardized. Designated CTP staff will obtain informed consent, and offer referral, rapid testing, and counseling, as appropriate, to participants.

We will conduct a brief survey of counselors prior to launching the trial (randomizing study participants) and repeated after the intervention is completed to garner basic information about counselors’ demographics, level of experience with HIV testing and prevention counseling, and attitudes and beliefs about HIV testing. Because it is the counselor’s role in the study to provide each of the three study interventions and, in most cases, to administer and process the HIV rapid tests, the study team wants to be able to describe counselor characteristics.

### 5.3.3 Participant Eligibility and Recruitment

Participant must:

1) Be seeking or currently receiving drug (including alcohol) abuse treatment services at the participating CTP,
2) Be at least 18 years old,
3) Report being HIV-negative or HIV status unknown,

4) Not have received results of an HIV test initiated within the past 12 months,
5) Be able and willing to provide informed consent,
6) Be able to communicate in English,
7) Be able and willing to provide locator information, and
8) Be willing to sign a release form that will allow us to abstract HIV testing records to corroborate self-report of testing, receipt of results and HIV status at follow-up.

Recruiters will attempt to approach all clients accessing services. CTPs will be asked to permit recruitment to occur during new intakes as well as during treatment sessions for on-going clients. For the latter, recruitment will occur before, after, or between treatment services, while clients are taking breaks, and wherever clients gather onsite. In October of 2007, we conducted a pilot test within two CTPs that are comparable to CTPs that will participate in CTN 0032 to assess the feasibility of approaching all clients accessing services. We used a brief, scripted approach in which we informed clients that we would like to tell them about an opportunity to participate in health-related research at the CTP and asked them if they would be interested in spending 5-10 minutes to hear more about the opportunity. A combined total of 51 clients accessed services during the time periods selected for the recruitment pilot and all 51 clients (100%) were approached by recruiters. All 51 clients (100%) listened to the entire recruitment script and 46 clients (90%) responded that they would be interested in hearing more about a health-related study.

In order to assess how representative the study sample is of the population of clients receiving services at participating CTPs, CTPs will provide summary information about the clients who access services at the CTP during the 4 month study recruitment period. Summary information will include the number of unduplicated clients accessing services, frequencies of client gender and race/ethnicity, and the mean and median client age. The information will be compared to the description of the sample of clients enrolled in the study. The information will also be compared to the number of clients that were screened during the recruitment period. Summary information of clients participating in the screening will also be compared to characteristics of participants enrolled in the study.

Recruiters will use a script to introduce the study to potential participants. Prior to screening individuals to determine their eligibility to participate, the research staff will briefly explain the study purpose, procedures, potential risks and benefits and voluntary nature of participation. Individuals who are not interested in hearing more about the study will be noted in the recruiters' ledger as a simple tally mark under an appropriate heading such as "declined" or "already enrolled" so that the number of approached individuals during the selected recruitment time slot can be calculated. Interested clients will be screened for eligibility and, if eligible, scheduled for the informed consent process. Screening may be conducted by the recruiter who initially approached the client or by a screener who is waiting for interested clients in a nearby screening area. If the interested client and recruiter or screener does not have time to conduct the screening process immediately after the study is introduced, the recruiter will make a tally mark on the recruiters' ledger under the heading "postponed screening." Study staff will employ active and passive strategies to follow-up with clients who wish to complete postponed study activities. All clients participating in the screening will be compensated for their time and effort. Interested clients will be screened for eligibility and, if eligible, scheduled for the informed consent process.

## 5.4 Measures and Assessments

Table 4 presents a schedule for study activities and assessments. Study assessments will be conducted at three points in time: 1) screening and baseline visit, 2) 1-month post-randomization follow-up visit, and 3) 6-month post-randomization follow-up visit. Participants will be informed and assured that data collected from research assessments will be kept confidential and not be shared with treatment staff.

### 5.4.1 Screening Assessment/Interview

The screening assessment/interview will take place after the individual has provided verbal informed consent for screening. The assessment will be brief and consist of the following steps: 1) obtain basic demographic information and 2) determine eligibility on the HIV testing and/or HIV status criterion. Eligible individuals will be free to enroll in the study after providing written informed consent. Individuals who screen as ineligible will be compensated for their time and effort and informed that they are ineligible to participate due to their not meeting one of several eligibility criteria. They will not be informed of the specific criterion that rendered them ineligible.

### 5.4.2 Basic Releases and Locator Information Form:

Locator Information Form: Participants will complete a locator information form which will be used to contact them to remind them of follow-up visits and to locate participants who cannot be found. When completing this form, participants will be required to provide their names, addresses, and telephone numbers and contact information for at least two friends or family members. Locator information will be updated at the one-month and 6-month follow-up visits.

Medical Record Release Forms: Participants will complete these forms (as applicable) in order to grant permission to study staff to review their medical records, including HIV testing records and HIV primary care records. The purpose of medical records review is to corroborate participants' self-report of HIV testing, HIV diagnosis, utilization of HIV primary care and progression of disease

### 5.4.3 Baseline and Follow-up Assessment Battery

Individuals who screen as eligible will complete written informed consent procedures and will be enrolled and asked to complete a baseline assessment using ACASI. The ACASI assessment will be used to minimize underreporting of risk activities. Participants using ACASI report significantly higher levels of risk behavior, including sexual risk and drug use, than those interviewed face-to-face by staff (Des Jarlais et al., 1999; Metzger et al., 2000; Perlis, Des Jarlais, Friedman, Arasteh, & Turner, 2004; Turner et al., 1998). The ACASI system displays each assessment question on a computer monitor while simultaneously playing an audio recording of the question through headphones. Study participants will enter responses to questions directly on the computer. In order to minimize potential social desirability bias in participants' reporting sexual and drug-use risk behaviors, ACASI responses are used for research purposes only; CTP staff not involved in the study conduct will not have access to participant research data.

Our experience is that ACASI is well accepted, including among individuals having low formal education levels (Metzger et al., 2000; Mizuno et al., 2007), who find it fairly easy to self-

administer questionnaires using ACASI when a brief tutorial session on how to use the technology is embedded in the survey process and precedes questionnaire administration.

Several levels of ACASI pre-testing will occur prior to commencement of study recruitment. The Innovative Clinical Research Solutions group at the Nathan Kline Institute who are developing the ACASI follows rigorous systems testing and quality control requirements before an ACASI application is released for use. Four levels of systems development testing or pre-testing will be conducted. The first level of testing is that the application programmers who write the program code are required to fully test the application. The second level is that NKI has a Certified Quality Control Specialist who spends full time testing NKI software. The specialist will completely test all ACASI applications. The third level of testing is that several members of the CTN 0032 protocol team will completely test all ACASI applications. The fourth level is that actual clients within community treatment programs will test the applications. It is anticipated that the ACASI will be tested by 8-10 CTP clients. Institutional Review Board (IRB) approval will be obtained prior to conducting this level of testing and we will compensate the clients for their time and effort. This comprehensive approach to ACASI testing will ensure that all ACASI applications are functioning accurately, are easy to use and are understood.

Primary and secondary outcomes have been outlined in sections 2.0 and 4.0. Participants will be compensated for their time and effort dedicated to completing each of the baseline and follow-up assessments. The following measures will be collected at baseline and follow-ups. Information will be collected through ACASI.

**Receipt of HIV Test Results, Acceptance of Testing and Completion of Testing:**

To evaluate the primary outcome of receipt of HIV test results, we will use self-report data collected via ACASI at the one-month follow-up visit. This measure will be a dichotomous (yes/no) variable. At the one-month post-randomization follow-up visit, completion of testing as a secondary outcome will also be collected via ACASI. This outcome will be assessed as a dichotomous (Yes/No) variable. Those participants in Groups 1 and 2 who are unable to complete their on-site HIV test, but who self-report having completed an HIV test off-site within one month of randomization, will be counted as “Yes” on the receipt of HIV test outcome. As described below, we will also look to corroborate these self-reports by checking the medical records at these off-site testing venues.

To ensure equivalence across those participants receiving a negative result and those receiving a preliminary positive result the HIV testing primary outcome is receipt of any test result. Monitoring will occur for those participants receiving preliminary positive results to examine whether they receive confirmatory test results.

We will also collect information from the CTP HIV testing log (in Groups 1 and 2 in which the acceptance of testing and receipt of results will typically occur during the baseline visit), and data abstracted from the medical records of off-site HIV testing venues for those participants who self-report off-site testing. All participants who self-report (at one month follow-up visits) engaging in off-site testing will be asked to identify (by name) the off-site venue attended as well as identify the type of venue (i.e. STD clinic, drug treatment program, HIV counseling and testing site, etc.). Off site testing sites may or may not utilize oral and/or rapid testing methods and therefore we intend to code off-site testing according to testing mode (e.g. rapid vs. non-rapid and oral swab, blood from finger or blood from arm). Their self-reported information will be corroborated by medical record data abstracted from the identified off-site testing venues. Information release forms specific to these sites will be obtained; willingness to release such

information will be a study requirement. Medical record abstraction will occur after a given participant completes the release form on or after the 1-month follow-up visit.

At one-month follow-up, participants who have not been HIV tested will also be asked a series of questions on their reasons for not getting tested. The questions will elucidate (1) individual factors of refusal such as fear of results, apathy, not being ready to test, and risk perception (2) system factors such as named HIV reporting, concerns about confidentiality, location of test site, wait time to test or receive results, provider/counselor discrimination, access to treatment if HIV-positive, (3) testing factors such as type of testing method preferred, concerns about test accuracy, and wait time for results, and (4) counseling factors such as resistance to counseling, and dislike of face-to-face counseling.

**Sexual Risk Behaviors/Unprotected Sex:**

We will use self-report data to evaluate the primary outcome concerning HIV sexual risk behavior. Despite numerous studies having measured self-reported condom use, there is still no agreed upon "gold standard" method for assessing condom use (Noar, Cole, & Carlyle, 2006). Noar and colleagues conducted a systematic review of 56 studies published in 53 articles in peer-reviewed journals between 1989 and 2003 to review measures of self-reported condom use within correlational studies of sexual risk behavior and evaluated them on the basis of suggestions from the methodological literature. Based on their review, and in an effort to improve future measures of self-reported condom use, Noar et al. (2006) synthesized several recommendations for measuring condom use. With respect to the type of measure, they recommend using frequency, proportion, last time and count measures. They recommend that questions specific to sexual partners (e.g., main sexual partner vs. casual sexual partner) be asked. Because condom use varies with different types of sex, questions should be specific to the type of sexual acts (e.g., vaginal, anal or oral sex) being studied. In the absence of a gold standard method for assessing sexual risk behavior and condom use and in light of recommendations from the literature summarized by Noar et al. (2006), we propose the following measures of sexual risk behavior:

Global sex behaviors: Our sexual risk behavior outcomes (and therefore our measures) focus on vaginal and anal rather than oral sex behavior because vaginal and anal sex are far riskier behaviors for contracting HIV (Vittinghoff et al., 1999). We will adapt ACASI questions used in prior studies that correlate with HIV seroconversion and are well-accepted by participants (Koblin et al., 2006). Questions will include total number of sex partners in prior 6 months; total number of vaginal sex partners and anal sex partners; total number of unprotected vaginal and total number of anal sex partners and total acts of unprotected vaginal and anal sex; and total number of unprotected vaginal/anal acts with HIV-positive, negative, and unknown serostatus partners.

Episode-level sex and substance use behaviors Questions are based on a well-tolerated ACASI grid format successfully implemented in previous studies (Koblin et al., 2003; Colfax et al., 2004). We will ask participants about their most recent vaginal or anal sex episode in the last 6 months with their most recent non-primary sex partner, as well as the most recent episode with their primary partner, if they have one (as in prior studies, a primary partner will be defined as "someone you live with or have seen a lot, and to whom you have a special emotional commitment)." Participants will answer questions to describe the characteristics of their most recent non-primary partner, including gender, location of meeting, relationship status with partner, time known, time since first sex encounter, HIV serostatus, age, and enumeration of sexual acts (anal/vaginal, protected/unprotected) with this partner during the most recent

vaginal or anal sex episode. For each episode, we will ask whether substances were used, types used, and the quantities used (i.e., number of drinks for alcohol). We have found these episode-specific measures allow us to efficiently obtain detailed data over extended time periods using ACASI without over-burdening participants, and without requiring more extensive, person-to-person interview techniques such as time-line follow back assessments, often used in studies with heavier substance users (Maisto, Sobell, Cooper, & Sobell, 1982).

**Utilization of HIV Primary Health Care:**

We will measure utilization of HIV primary health care for those study participants whose HIV test results are reactive (positive). This will not be a study outcome as we will not have sufficient numbers of persons who test HIV-positive in the study to analyze these data. Instead, we will describe what happens to participants who test HIV-positive. Because we will be actively following participants over a 6-month period, we will be able to document whether they visited the provider. We will seek to document whether they are receiving regular HIV care as defined by the HIV adult and adolescent treatment guidelines (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006). These guidelines state that HIV-positive adults and adolescents should be seen at least quarterly to have their CD4 and viral load monitored. At both the one and 6-month follow-up visits, we will record health-seeking behavior since receipt of HIV test results. Participants who indicate that they have not used HIV primary care services since receiving their test results will be asked a few brief questions to elicit reasons for not obtaining such care. We will also abstract information from participants' medical records (at their HIV primary care clinics) to validate their reported use of health services and to record their CD4 and viral load. Information release forms specific to these primary HIV health care centers will be obtained. Result of primary care use will be presented as % participants testing positive who reported obtaining any primary care (and % for whom any visit could be verified by medical record), and % who reported at least two primary care visits (and % for whom both visits could be verified).

Covariates: We have attempted to restrict the number of other variables that we will examine to limit the length of the assessments and to conserve statistical power. We provide a rationale for each of these measures below.

Self Efficacy for Safer Sex Behaviors: As part of a meta-analysis to quantify the relationship between psychosocial variables and self-reported condom use, Sheeran, Abraham, & Orbell (1999) investigated the correlation between self-efficacy for condom use (confidence in one's ability to use condoms during sex) and condom use in 25 studies. The average correlation was positive and of medium magnitude (r+ = 0.25), indicating that self-efficacy for condom use is a reliable predictor of condom use. In addition, improving one's self-efficacy to use condoms is an important behavioral secondary outcome of the RESPECT prevention counseling intervention (Kamb et al., 1998). We will use the 28-item *Condom Use Self-Efficacy Scale, CUSES*, (Brafford & Beck, 1991; Brien, Thombs, Mahoney, & Wallnau, 1994) to measure self-efficacy for the mechanics of putting a condom on oneself or the partner, use of a condom with a partner's approval, ability to persuade a partner to use a condom, and ability to use condoms while under the influence. Responses will be measured on a 5-point ordinal scale in which 0 = strongly agree and 4 = strongly disagree. Internal consistency for the entire scale (Cronbach's alpha = 0.91) and subscales (Cronbach's alpha = 0.78 – 0.82) is high.

Readiness to Change**:** Because post-intervention behavior tends to be a function of participants' pre-intervention readiness to change (Prochaska et al., 1992), it is important to assess readiness for change as a covariate for both primary outcomes. We will include one

question to assess participants' readiness for HIV testing. The question will be adapted from a single measure that has been previously used to assess readiness to enter medical care for HIV infection (Brewer et al., 2007; Gardner et al., 2007). We will include a four-item scale, previously used by Brown-Peterside, Redding, Ren and Koblin (2000), to assess participants' readiness to use condoms consistently.

Demographics: We will collect basic demographic information including age, gender, race and ethnicity. This information will be collected prior to written informed consent. Additional information, including years of formal education, income, employment status, health insurance, living arrangement including homelessness, number of children (under 18), and incarceration and/or corrections history will be collected at the baseline assessment after written informed consent. The collection of this information will be used to describe the study sample and to assess for any differences between intervention groups and also differences between study participants at follow-up and those lost to follow-up.

HIV testing history: HIV testing history is an important covariate to assess for both primary outcomes. Individuals who have sought testing in the past may be more likely to accept HIV testing as part of the study. Additionally, they may have sought testing in the past as part of a risk reduction plan or may have been more actively considering behavior change, possibly making them more amenable to practicing sexual risk reduction behaviors. We will determine history of HIV testing and receipt of results within the past year, including the approximate date of the most recent HIV test. All participants who self-report being HIV-tested at any time during the prior year will be asked to identify the corresponding testing venue for their most recent test.

Attitudes Toward Safer Sex: Increasing positive attitudes towards safer sex is another important behavioral goal of the RESPECT counseling used in study group 1. As part of a meta-analysis to quantify the relationship between psychosocial variables and self-reported condom use, Sheeran and colleagues (1999) investigated the correlation between attitudes toward condom use and actual condom use in 38 studies. The average correlation was positive and of medium magnitude ($r+ = 0.32$), indicating that positive attitudes toward condom use are a reliable predictor of condom use. We will use the 13-item Attitudes Toward Condom Use subscale (Cronbach's alpha = 0.88) from the Sexual Risks Scale (DeHart & Birkimer, 1997) to assess participants' attitudes toward condom use. The subscale was developed to reliably and validly measure variables hypothesized to be influential in predicting HIV sexual risk behaviors.

Global Substance Use Measure: It is important to measure substance use as a means of describing the study sample particularly among those participants who receive HIV-positive test results. It is also important to examine substance use as a moderator of sexual risk behaviors, particularly among participants who report low or no levels of sexual activity at baseline. It is also important to document any effect of the intervention on level of drug use. The addition of HIV testing into the drug treatment context may have negative, positive or no effects on drug use outcomes. We will ask about days and quantities of substances used over the preceding 6 months, using standardized ACASI substance use measures (Colfax et al., 2004; Koblin, Chesney, Coates, & EXPLORE Study Team, 2004; Macalino, Celentano, Latkin, Strathdee, & Vlahov, 2002; Metzger et al., 2000). We will ask about frequency and amount of use, including alcohol, methamphetamine, cocaine, heroin poppers, club-drugs, frequency and types of drugs injected, and sharing of drugs, needles, and other paraphernalia. We will ask about overdoses and any drug-related hospitalizations. This measure will be repeated at the one and six month assessment, with an appropriate adjustment to the time-period of recall.

Additionally, we will measure the point at which a participant is in his/her course of drug treatment. To minimize client burden, we will ask the following three questions at baseline and

both follow-up visits: 1) Are you in treatment right now? (2) What treatment are you in? (e.g., "Using a brief list which distinguishes types of treatment such as detox, halfway house, inpatient counseling, and outpatient counseling"). (3) How many days have you been in this treatment?

Injection Risk Behavior: Injection drug use is a well-established risk behavior that may lead to HIV transmission/acquisition (Santibanez et al., 2006). Therefore, we will measure injection drug use in the prior 6 months and the last time injected. We will measure type and frequency of drug injection, frequency of receptive and distributive needle sharing, sharing of injection paraphernalia, use of syringe exchange, use of syringe disinfection practices, and number and types of different needle sharing partners.

Intervention Exposure (when assessed through participants' self-report): We will include a few items to measure exposure to intervention content at the CTP site such as discussion of sexual risk reduction, discussion of drug-using risk reduction, and development of an HIV risk reduction plan. We will also ask clients if they have talked about this study with other clients and if they have shared anything with others that they learned from this study.

Depression: It is important to examine depression as a covariate of sexual risk behaviors because depression has been associated in some studies with increases in sexual risk-taking behavior (Stein, Solomon, Herman, Anderson, & Miller et al., 2003; Sterk, Theall, & Elifson, 2006; Williams and Latkin, 2005). Depression will be measured using the QIDS-SR-16 (Quick Inventory of Depressive Symptomatology-Self-Report-16) (Rush et al., 2003). The QIDS-SR-16 is a 16-item depression scale, yielding scores from 0-27, which covers the symptom domains of major depressive disorder, for the time frame of the past week: mood; concentration; suicidal ideation; anhedonia; loss of energy; insomnia; appetite change; psychomotor agitation/retardation; as well as self-esteem. As such, it covers the content of the CES-D. It has high internal consistency (Cronbach's alpha =.86), convergent validity with the Hamilton Depression Inventory (HAM-D)(r=.86) and its "parent" instrument (from which it was derived), the (30-item) Inventory of Depressive Symptomatology-Self Report (IDS-SR)(r=.96), and sensitivity to change that is comparable to the HAM-D and IDS-SR, in a trial of 681 outpatients with non-psychotic major depressive disorder in a 12-week trial of nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination.

| Table 4<br>Schedule of Study Activities and Assessments | | | | |
|---|---|---|---|---|
| **Study Activities** | **Screen** | **Baseline** | **1-month Follow-up** | **6-month Follow-up** |
| Verbal Informed Consent | X | | | |
| Screening Instrument | X | | | |
| Written Informed Consent | | X | | |
| Locator Information Form | | X | X | X |
| HIPAA Form (as applicable) | | X | | |
| Medical Record Release Forms (as applicable) | | | X | X |
| Randomization | | X | | |
| *HIV testing Informed Consent | | X | | |
| Intervention | | X | | |
| Demographics | X | X | | |
| Global sex behaviors | | X | X | X |
| Episode-level sex and substance use behaviors | | X | X | X |
| HIV testing behavior | | X | X | X |
| Readiness for HIV testing | | X | X | X |
| Readiness to use condoms | | X | X | X |
| Self-efficacy for safer sex behavior | | X | | X |
| Attitudes toward safer sex | | X | | X |
| Global substance use | | X | X | X |
| Injection risk behavior | | X | X | X |
| Intervention Fidelity | | | X | X |
| Depression | | X | | X |
| Utilization of HIV Care for Persons who test Positive | | | X | X |
| AEs/SAEs | To be collected any time post-randomization. | | | |
| Study Termination | To be collected upon formal drop out or participant's study end date. | | | |

* Applicable for participants randomized to Groups 1 and 2 only.

### 5.4.4 HIV Testing Consent

Participants who are randomized to receive offers of on-site HIV rapid testing, who accept those offers and wish to be tested will be asked to provide a second consent in order to proceed with HIV testing.

### 5.4.5 Rapid HIV Testing, Confirmatory Testing, and False Positives

On-site rapid HIV testing will be conducted using a test such as the OraQuick *ADVANCE* Rapid HIV-1/2 Antibody test (hereafter referred to as "rapid HIV test"). This is a single-use, qualitative immunoassay to detect antibodies to HIV-1 and HIV-2 in oral fluid. The oral fluid sample is collected by swabbing the gums with a paddle-shaped test device. After swabbing, the test device is added to a developer vial. If HIV antibodies are present in the specimen, they bind to a strip containing peptides within the test device, causing a red line to appear in the test location. A red line at both the test and control locations indicates a valid reactive test result; a red line only in the control location indicates a valid negative test result. If no line appears at the control location or if lines appear outside the designated areas, the test is considered invalid and should be repeated with a new device.

The rapid HIV test is intended for use as a point-of-care test to assist in the diagnosis of infection with HIV-1 and HIV-2. It is easy to perform with a negligible chance of error and, therefore, is CLIA-waived.

As previously mentioned in section 3.3, participants whose initial rapid test (via oral fluid) result is preliminary positive will receive a second fingerstick rapid test via whole blood sample as illustrated in Figure 1. Additionally, participants whose test result is preliminary positive will receive the current standard of care: participants will be informed of their preliminary positive test result in a confidential face-to-face manner, receive counseling and referrals, and will receive a confirmatory HIV test (additional information is provided on the counseling for persons to test HIV positive in section 6.4 of the protocol). For this confirmatory HIV test, counselors will collect from participants a second oral fluid sample using an oral fluid HIV test kit. The second sample will be sent to an external laboratory that will perform a supplemental test which will serve as confirmation of the participants' HIV status. Participants will be scheduled to return for the result of the confirmatory test approximately 5-10 days after providing the sample. We will try to follow-up these individuals if they do not return for their test results. This will not affect the outcome, "receipt of results" since we will evaluate this outcome on the basis of whether participants receive any (rapid and/or confirmatory) test results.

Study participants may refuse confirmatory HIV testing. If this occurs, participants will be asked to consider confirmatory testing at some specific future date with confirmatory testing to be conducted by study counselor, testing site, or a medical provider. The HIV testing consent will cover confirmatory testing so no additional consenting will be needed for confirmatory testing. Confirmatory test results will be recorded on study CRFs which will include participant ID numbers but not names; confirmatory test results will not be placed in medical records.

With a target sample size of approximately 1,272 study participants, some false positives may occur. During both the HIV testing consent process and the testing and counseling session participants will be advised of the possibility and potential meaning of testing false positive. The HIV testing consent will contain clear language discussing the possibility and potential meaning of receiving a false positive test result. Participants receiving a false positive test result will be referred to a medical provider for further testing including HAV, HBV, and HCV. Participants will be encouraged to contact research counselors if they need additional support or referrals around the false positive result.

Any confirmatory test result that is indeterminate or negative will be followed up by a referral to a medical provider for repeat confirmatory HIV testing in one month per CDC guidelines.

The preliminary test results and confirmatory test results will not be a part of the patients' medical record and the site will follow the state specific standard for reporting positive HIV results.

### 5.4.6 Safety Assessments

Adverse events will be captured as defined in Section 7, beginning after randomization.

### 5.4.7 Survey of Counselors

As previously mentioned, we will conduct a brief survey of counselors prior to the trial launch (randomizing study participants) and after the intervention is completed to garner basic information about counselors' demographics, level of experience with HIV testing and prevention counseling, and attitudes and beliefs about HIV testing. Because it is the counselor's role in the study to provide each of the three study interventions and, in most cases, to administer and process the HIV rapid tests, the study team wants to be able to describe counselor characteristics which will be reported in the primary outcome manuscript to give the context of study implementation. In addition, a planned secondary analysis will examine whether there is significant variability in treatment effects at different sites and whether counselor characteristics and attitudes may be related to these differences. In addition, we will examine whether participation in the trial has a significant effect on counselor attitudes and whether any observed change in counselor attitudes is related to the rates of testing experienced within the trial at the counselor's particular site.

## 5.5 Follow-up and Retention

### 5.5.1 Follow-up Visits

All participants will be scheduled for follow-up visits, at 1 and 6 months post-randomization. At each follow-up, participants will complete an ACASI behavioral assessment regarding HIV test result receipt, sexual risk behaviors, and drug-using risk behaviors. We will attempt to schedule both follow-up visits in accordance with participants' regular visits with their drug abuse treatment counselors. Study staff will work closely with CTP staff to determine the best times within a given target window to hold follow-up visits. The target date for the 1-month follow-up visit is 30 days post-randomization; the target window for this visit will be between approximately 1 week before and 4 weeks after the 1-month target date. The target date for the 6-month follow-up visit is 180 days post-randomization; the target window for this visit will be between approximately 1 week before and 8 weeks after the target date. Specific windows will be detailed in a SOP prior to study commencement. Sites will detail ongoing recruitment of study participants in a tracking sheet which will be submitted, via secure electronic transmission, to the Lead Node on a regular basis. The tracking sheet will contain the participant ID, baseline enrollment date and the associated follow up windows. Retention specialists and CTP retention staff will continually monitor completed follow-up visits to ensure visits are occurring within the allowable window periods.

### 5.5.2 Enhancement of Retention

To have sufficient power to examine our outcomes, we estimate that of the 1,272 enrolled participants, we will need to retain a minimum of 85% at the one-month and 70% at the six-month follow-up point. A number of strategies will be employed in order to achieve these minimum retention rates.

Participants will be asked to complete a Locator Information Form on which they will provide contact information for themselves and at least two friends or family members which will make it easier for us to locate them for follow-up appointments. Permission will also be requested to obtain locating information from additional databases. Locator information will be updated at the one- and six-month follow-up visits and maintained at the site. Staff will provide mail and telephone reminders to participants.

In addition to providing reminders of upcoming follow-up visits via mail, telephone and/or physically going to locations specified by participants on the Locator Information forms, participant retention will be enhanced in several other ways.

- We will employ two full-time retention specialists working across study sites who will track all participants' follow-up windows, monitor retention activities and work closely with research staff to ensure that they are conducting reminder and outreach activities according to specified follow-up windows. Additionally, they will identify CTP-specific and cross-site barriers to retention and problem solve with CTP staff. These retention specialists will be based at the lead nodes and will keep the lead investigators and national coordinators informed in the event that a higher level of intervention with a CTP or their node is needed.
- At each visit, participants will receive a reminder card with the date and time of their next visit. Reminder cards will be discreet with regard to the nature and purpose of the study.
- We will provide each site with a computerized program to help them monitor the participants' windows and due dates for follow-up.
- Participants may be compensated for contacting research staff prior to each of their follow-up visits and confirming/updating their locator information.
- If a participant fails to attend a scheduled appointment without prior notification, staff will attempt to re-contact and re-schedule the appointment.
- We will do home visits and outreach to find participants who do not return to the treatment programs, whose phones have been disconnected or do not have a phone.

# 6.0 TREATMENTS

After completing the baseline assessment on ACASI, participants will be randomly assigned to one of the three treatment groups described below. Randomization will be stratified by site and within site by race/ethnicity and gender. The DSC will prepare in advance computer-generated randomization sequences. As in previous CTN studies, the site will call a central computer and enter client data via touchtone in order to obtain the client's random assignment.

## 6.1 On-Site Rapid HIV Testing with RESPECT-2 Counseling (Group 1)

Participants randomized to group 1 will receive rapid HIV testing and RESPECT counseling which has been shown to be feasible and acceptable to both clients and counselors (Lalesta et al., 2000; Metcalf et al., 2001) and which is consistent with CDC recommendations for HIV testing and counseling (Centers for Disease Control and Prevention, 1993b; Centers for Disease Control and Prevention, 2001). RESPECT is an interactive HIV prevention counseling model that is both empathic and client-centered (tailored to the specific needs of the person being served). It considers the client's level of readiness to change behavior (Prochaska & DiClemente, 1983; Prochaska & DiClemente, 1986) and tailors personalized prevention messages and risk reduction plans according to the individual client's current stage of behavior change (pre-contemplative, contemplative, preparing for action, action or maintenance). The RESPECT-2 counseling protocol, specifically designed for use with the rapid HIV test, involves a brief (approximately 20-40 minute) counseling session which includes an orientation to the rapid testing procedure, an explanation of the testing window period, routes of HIV transmission and the meaning of test results, a personalized exploration of risk, the creation of a risk-reduction plan, identification of sources for support and referrals, and HIV test results.

The RESPECT-2 protocol separates the single session into two parts, the "initial" (testing) section and the "follow-up" (results) section. In the testing section counselors will first provide "introductions and orientation" which includes: explaining the counselor's role, reviewing the rapid test process, outlining the content of the session (collecting and processing the test specimen, exploring HIV/STD risks, discussing strategies to reduce risk, developing a risk reduction plan, and providing referrals) and addressing any immediate questions and concerns. In this part of the session, counselors will seek to motivate participants to get HIV tested. Counselors then proceed with discussing behaviors that have put participants at risk for HIV using the most recent or most salient risk incidents. The goal here is to increase awareness of sexual risk behaviors and facilitate understanding of the specific factors contributing to risky sexual behavior (i.e. substance use, partner type, and mood). The next step involves exploring with participant's any and all risk reduction efforts instituted in the past, supporting those efforts proven successful and examining the barriers involved in less successful risk reduction efforts. Counselors then "summarize and characterize" for participants their patterns of sexual risk behavior and specific triggers contributing to their sexual risk behavior with the objective of enhancing participant collaboration in arriving at a risk reduction plan. Lastly, counselors help participants develop a risk reduction plan, a crucial component of the counseling session. Counselors will steer participants away from creating a plan that is global such as "always using condoms" or "never having sex again" and, instead, design a plan which is incremental, concrete, and specific such as: "tonight I will purchase condoms and put them on the bedside table" or "starting this weekend, I will call John and Marie, my non-substance using friends, to

go to the movies and hang out together." Counselors will suggest scenarios in which specific obstacles may be encountered and encourage participants to problem solve or revise their plan. Counselors will provide support and encouragement to participants for implementing risk reduction plans and assist participants in identifying additional support and resources which will increase the likelihood that participants will be successful in implementing risk reduction measures. Specifically, counselors will encourage participants to pick trusting friends or family members with whom participants will share their risk reduction plan and with whom participants may enlist in putting the plan into action. Once the rapid test is administered (for those who accept the test), participants will be offered magazines to read until the test results are ready (approximately 20-40 minutes). Once the test results are ready, counselors will proceed with the follow-up or results section of this single session counseling protocol.

The follow-up or results section includes: providing the test results, summarizing and supporting participants' risk reduction plan and identifying sources of support and providing referrals. As participants may be quite anxious for test results, counselors will promptly and confidentially provide the HIV test results within 20-40 minutes of taking the oral fluid sample. If the results are negative counselors will review with participants the window period the test results cover, explicitly noting that the test results may not cover the most recent risk episode (if risk was within the past three months). If warranted, counselors may suggest a specific time period for retesting which covers the most recent risk episode. The counselor will inform participants about available HIV testing services in their community. Lastly, if counselors have identified participants who need specific professional or support services, counselors will be prepared to provide specific referrals.

## 6.2 On-Site Rapid HIV Testing and Information Only (Group 2)

Participants randomized to group 2 will receive HIV testing as recommended by the CDC in its September 2006 guidelines for HIV testing (Centers for Disease Control and Prevention, 2006): The objectives of the CDC recommendations are "to increase HIV screening of patients….", foster earlier detection of HIV infection; identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services." Specifically, the CDC states that HIV "prevention counseling should not be required as a part of HIV screening programs in health care settings." The CDC is also now considering the role of counseling in HIV screening programs offered in non-health care settings (B. Branson, personal communication, October 12, 2007).

Counselors working with participants in group 2, therefore, will provide an orientation to the rapid testing procedure, discuss the window period of time the test result covers and the transmission routes of HIV, explain the various possible results (negative, preliminary positive, inconclusive), the need for repeat testing if the result is inconclusive and the need for confirmatory testing if the initial test result comes back preliminary positive. This informational component will take less than five minutes to complete. Once the rapid test is administered, participants will be offered magazines to read until the test results are ready (approximately 20-40 minutes). Once the test results are ready, counselors will provide participants with the results which will take approximately five minutes to complete. If participants attempt to engage counselors in a conversation around HIV sexual or drug use risk behaviors or risk reduction planning, counselors will reinforce participants' desire to change by providing appropriate referrals.

## 6.3 Referral for Off-Site HIV Testing (Group 3)

Participants randomized to group 3 will receive a referral list for local HIV testing agencies, the standard of care at sites not offering HIV testing. Each CTP will have previously prepared an extensive referral list of testing sites in the surrounding geographic area. The referral list will include the name of the testing agency, address, telephone number, website, and hours of operation.

## 6.4 Study Participants Who Test Reactive; Newly HIV Positive

All participants who test reactive to the HIV rapid tests will be provided with an explanation of the meaning of a reactive or preliminary positive test results. This explanation will emphasize: 1) that in a very small number of cases people who are actually HIV negative can have a rapid test that is reactive; 2) the necessity of confirmatory testing and the need for scheduling and following through on a return visit for the confirmatory test results; and 3) the importance of taking precautions to avoid the possibility of transmitting infection to others while awaiting the results of confirmatory testing. Additionally, participants who test reactive will be assessed for potential suicidality, encouraged to have specific plans for that day to reach out to a friend or family member most likely to be supportive or have plans to do something specific for self-care and will be reassured that if the confirmatory results are also positive that the participant will receive appropriate referrals for care and support. Participants will review and update, if necessary, participant locating information, be provided with an appointment card for the results visit, and receive a reminder call or e-mail prior to the results visit. If a participant misses the confirmatory results visit, staff will immediately attempt contact with the participant through phone, e-mail, and/or letter to reschedule the confirmatory results visit. If necessary, a participant's listed contacts will be contacted solely for the purpose of reaching a participant for scheduling a return visit. All study sites will use a standardized tracking form to ensure that the proper procedures are followed to maximize the likelihood that a participant will return for the confirmatory test results visit.

All participants receiving a confirmatory HIV test result will receive counseling and support, per standard local care, for their test results. Participants will 1) be assessed for potential suicidality; 2) will receive referrals for appropriate medical, psychological, and social services; 3) prior to leaving the study site, will be encouraged or assisted in calling to schedule an appointment with at least one referral agency; 4) will be provided with an information sheet about being HIV-positive; and 5) will be scheduled and given an appointment reminder card for a check-in visit either on-site or by phone within two weeks for the purpose of providing further support and encouragement of linkage to care. Additionally, participants will be counseled on ways in which they may reduce their risk of exposing others to HIV, and, at sites where available, a referral will be made for local partner counseling and referral services (PCRS) to assist participants in the process of informing sexual/drug partners of possible HIV exposure (Centers for Disease Control and Prevention, 1998b). Participants will be encouraged to contact the counselor if they need additional referrals or support between the results visit and the next scheduled phone or on-site visit. Participants will be provided a reminder call or e-mail for the upcoming on-site or phone visit. Participants will be informed that they are still enrolled in the study and will be enlisted to complete the remaining study visits (at 1 month and at 6 months). A standardized tracking form will be used by all sites to promote appropriate procedures and increase the potential that participants will be linked to appropriate care.

If participants in the referral only arm do seek testing at an outside agency, test newly HIV positive and inform study counselors of the test results, participants will be offered counseling as well as referral for medical, psychological, and social services. Using the same standardized tracking form for participants in the other two arms, study counselors will encourage, assist, and track participants in accessing appropriate services. Participants will be informed that they are still enrolled in the study and will be encouraged to complete the remaining study visits (at 1 month and at 6 months).

At the 6-month follow-up (this is the last assessment point), we will offer our study participants who have not linked to HIV primary care a brief case management intervention that has been shown to be efficacious in linking persons to HIV care (Gardner et al., 2005). This intervention will be offered as a study service and will not affect study outcomes as it will be offered after participants complete their 6-month follow-up interview. This brief intervention is a three to five session intervention, guided by strengths-based case management aimed at linking persons living with HIV to primary medical care and connecting them with case management services (if available) at their clinic. It is designed to increase knowledge, motivation and skills as a way to reduce barriers and facilitate use of primary medical care among low-income, recently diagnosed HIV-positive individuals. Throughout the sessions, the case manager helps the client to identify his/her strengths in other areas of life and works toward transferring these successes to the client's HIV-care seeking behavior. This intervention also recognizes and addresses both individual and structural barriers to obtaining medical care. Counselors at each of the CTPs will be trained on how to deliver the linkage intervention.

## 6.5 Counseling Quality Control

For quality control purposes, all study counselor/participant sessions in all three arms (testing with RESPECT counseling, testing with information only, and referral only) will be audio-recorded.

Individual counselors at all study sites will be working with participants in all three arms of the study. To ensure accuracy of presentation and conformity to the protocol not only from each counselor, but across all sites, fidelity raters will review approximately 10% of all recorded sessions across all study arms and sites. The recordings to be reviewed will be randomly selected within each CTP and each arm. For each reviewed tape, the time spent with the participant will also be recorded.

Participants will provide written consent for audio-recording as part of the initial informed consent and may refuse to have their conversations recorded or may ask counselors to stop the recording at any time. Counselors will be required to make a note of this and these instances will be tracked by the individual site as well as by the protocol team.

If, in reviewing the recordings, a concern arises about content drifting from one arm to another arm, lead and/or co-lead protocol team members will work with the individual or site to improve and maintain adherence to the manualized counseling protocol.

On a weekly basis, CTP sites will send randomly selected session recordings to study fidelity raters. Fidelity raters will be required to review the session recordings within a week of receiving recordings. If study enrollment proceeds more quickly than expected, additional staff hours will be devoted to fidelity rating to ensure current review of session recordings.

## 6.6 Participant Incentives

Participants will be reimbursed for their time and effort for non-treatment assessment visits. Participants may receive a maximum amount of up to approximately $140, although the specific amounts, format and distribution schedule will be determined by the participating CTP with the approval of the lead investigator or co-lead investigator and the corresponding IRB.

# 7.0 REPORTING AND MONITORING

## 7.1 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, ICH GCP guidelines, the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented.

## 7.2 Regulatory Files

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

## 7.3 Informed Consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. All participants must read, sign, and date a consent form(s) prior to undergoing any study-specific procedures and participating in the study. The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect study participation. A copy of the informed consent(s) form will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty.

Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance. Separate consent forms will be used for study participation and HIV testing.

## 7.4 Health Insurance Portability and Accountability Act (HIPAA)

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

## 7.5 Investigator Assurances

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

## 7.6 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 54, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to date signed financial disclosure form on file with the sponsor.

## 7.7 Monitoring

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

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

## 7.8 Data and Safety Monitoring Board

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

## 7.9 Protocol Violations Reporting and Management

A protocol violation is any departure from procedures and requirements outlined in the protocol. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored at each site for (1) significance, (2) frequency, and (3) effects on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

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

## 7.10 Confidentiality

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC) and will distribute it to all sites when received. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary.

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

## 7.11 Adverse Events (AE)

This study proposes to use a targeted required adverse event reporting process. The protocol has identified specific events as expected outcomes for participation in this research study. These include:

- Anxiety
- Depression
- Friends treating participant differently
- Worry about risks of loss of confidentiality
- Partner abuse/domestic violence
- New unstable housing environments
- Increase in substance use/abuse

Research staff will use a standard checklist and event specific follow-up questions to document reports of these events at each research visit following randomization. This information will be

collected by interview with the research staff and will be documented in the study database via CRF. This information will be available for analysis and reporting to the DSMB at regular reporting intervals as part of the safety profile for this protocol.

Other adverse events (AE), defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered clinically significant, will only be reported if considered related to the study intervention(s). A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All reportable AEs must be submitted on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits. A site study investigator will classify each AE as serious or non-serious and follow appropriate reporting procedures.

For the purpose of this study, only the following events will be required for reporting as AEs:

- Only medical events that are directly related to the collection of the HIV test sample (e.g., oral swab induced injury, irritation at the testing site); and
- Additional adverse events (including expected events) to be reported in the database for this study will be assessed based on report of untoward events that the participant or investigator believes are a direct result of the study intervention or assessments. Events reported that are considered unrelated to study procedures by BOTH the participant and the investigator will not be reported as AEs or EEs.

Other safety information is based on spontaneous reports and not specifically required by the study team. The benefits to this system will include safety reporting to assess the effects of the intervention on the study population, reducing reporting burden on the sites, reducing duplicative data entry of events (reporting the same event on a clinical assessment form and an adverse event form), which eliminates the need to reconcile the same data reported in two locations.

**Definition of a Serious Adverse Event (SAE)**

A serious adverse event (SAE) is defined as any untoward physical or psychological occurrence during the study that suggests a significant hazard, side effect, or precaution.

This protocol will only require SAE reporting of any deaths that occur during study participation and of any other events meeting the criteria defined below if the investigator or the participant believes the event is related to the participant's role in the study.

This study is using a standard definition of SAE categories, which includes, but is not be limited to any of the following events:

- Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported
- Life-threatening: Any adverse therapy experience that places the participant or participants, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death)

- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- An event that required intervention to prevent one of the above outcomes

Events that do not meet any of the above criteria and are not considered related to study procedures will not be reported as SAEs.

Additionally, for the purpose of this study, the following will **not** be considered SAEs:

- Admission to a hospital or freestanding residential facility for drug detoxification;
- Admission to a hospital/surgery center for preplanned/elective surgeries;
- Admission to a hospital for scheduled labor and delivery.

**Eliciting and Monitoring Adverse Events**

Appropriate research staff will elicit participant reporting of AEs/SAEs. Adverse events (medical and/or psychiatric will be collected starting after participant randomization and at the 1- and 6-months follow-up visits. The research staff will obtain as much information as possible about the AE/SAE to complete the AE/SAE forms and will consult with designated staff as warranted. A site study investigator will review all AEs reported at the site during the previous week for seriousness, severity, and relatedness. Appropriate site staff will review all adverse event (AE) documentation and verify accuracy of assessments during each clinician visit with the participant to ensure that all AEs are appropriately reported and to identify any unreported SAEs. AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization, even beyond the end of the study. Each participating site's Protocol PI is responsible for study oversight, including ensuring human research protections by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Protocol monitors from the CCC will review the study sites and study data on a regular basis and will promptly report any previously unreported safety issues and ensure that the SAEs are being followed appropriately by the research staff. The CCC monitors will ensure that any unreported or unidentified SAEs discovered during visits are promptly reported by the site in the data entry system and to the IRB per local IRB requirements, and will be reported on the monitoring report. Staff education, re-training or an appropriate corrective action plan will be implemented at the participating site when unreported or unidentified AEs or SAEs are discovered, to ensure future identification and timely reporting by the site.

### Assessment of Severity and Relatedness

The site investigator will review each AE for seriousness, relatedness, and severity. The site investigator will review all AEs and SAEs for severity and relatedness during each visit with the participant, and will consult with other research personnel as needed. The severity of the experience refers to the intensity of the event. The relatedness of the event refers to causality of the event to the study. Relatedness requires an assessment of temporal relationships, underlying diseases or other causative factors, and plausibility.

#### Severity

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

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

#### Relatedness

Relationship to therapy is defined as:

- Definitely related: An adverse event that follows a temporal sequence from administration of the HIV test or intervention re; follows a known response pattern to the HIV test or intervention and, when appropriate to the protocol, is confirmed by improvement after stopping the intervention (positive dechallenge) and by reappearance of the reaction after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.
- Probably related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention; follows a known response pattern to the intervention, is confirmed by improvement after dechallenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.
- Possibly related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention and follows a known response pattern to the intervention, but could have been produced by the participant's clinical state or by other therapies.

- Unrelated: An adverse event that does not follow a reasonable temporal sequence after administration of the intervention; and most likely is explained by the participant's clinical disease state or by other therapies. In addition, a negative dechallenge and/or rechallenge to the intervention would support an unrelated relationship.

## 7.12 Reporting and Management Procedures of AE/SAEs

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

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

The Site Principal Investigator (PI) must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be removed from the intervention. The Site PI may consult with the Safety Monitor as needed. If necessary, an Investigator must suspend any trial interventions and institute the necessary medical therapy to protect a participant from any immediate danger. Subsequent review by the Medical Monitor, DSMB, ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor and DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable. A participant may also voluntarily withdraw from the intervention due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant should be asked to continue (at least limited) scheduled evaluations, complete an end-of-study evaluation and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or their condition becomes stable.

A NIDA-assigned Safety Monitor is responsible for reviewing all serious adverse event reports. The monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum.

Serious adverse events will be followed until resolved or considered stable, with reporting to the NIDA-assigned Safety Monitor through the follow-up period. The site must actively seek information about the SAE as appropriate until the SAE is resolved or stabilized or until the participant is lost to follow-up and terminated from the study. The Study EC Chair or the NIDA-assigned Safety Monitor may also request additional and updated information. Details regarding remarkable adverse events, their treatment and resolution, should be summarized by

the Investigator in writing upon request for review by the NIDA-assigned Safety Monitor, local ethics Committee/IRBs or regulatory authorities.

# 8.0 DATA MANAGEMENT

## 8.1 Design and Development

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

## 8.2 Data Collection Forms

Data will be collected by study sites on eCRFs. The DSC will provide sites with a final set of standardized eCRFs and CRF completion instructions. The eCRFs will be distributed electronically to the participating CTPs by the DSC or uploaded by the DSC into ACASI. These forms will be completed on an ongoing basis during the study. Instructions will be provided for the site personnel to instruct the participant in the use of ACASI and additional instructions will be provided by the ACASI to the participant. The computerized system ensures that participants complete all items. However, the local investigative team is responsible for maintaining accurate, complete and up-to-date records, and progress notes are required by the protocol and the SOPs. The investigative team is also responsible for maintaining any source documentation related to the study.

## 8.3 Data Acquisition and Entry

Participant surveys will be collected using ACASI. Consequently, participants will enter their own data at baseline and follow-up (except when physical impairments do not permit a participant to enter their own data, or in the case when the LIs approve to have a research staff person enter data for conditions such as, but not limited to, a phone interview required when a participant moves out of town). Accordingly, data entry into electronic CRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's written signature or electronic signature, as appropriate.

## 8.4 Data Center Responsibilities

The DSC will 1) provide final eCRFs for the collection of all data required by the study, 2) develop data dictionaries for each eCRF that will comprehensively define each data element, 3) conduct ongoing data monitoring and quality control activities on study data from all participating CTPs, 4) monitor preliminary analysis data cleaning activities, and 5) rigorously monitor final study data cleaning.

## 8.5 Data Editing

Completed data will be entered into the DSC automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated and distributed to treatment programs for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the DSC automated data acquisition and management system. Data status reports will be issued monthly to assist the site, the corresponding RRTC (node) and the lead investigators to monitor the site's progress in responding to queries.

## 8.6 Data Lock / Transfer

The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive. Each Node is responsible for storing the research records for the studies in which they participate. In all CTN sponsored studies, study records must be maintained for three years (after data lock) or longer if specified by local institutions/agencies or FDA regulations.

## 8.7 Training

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

# 9.0 COUNSELOR SELECTION, TRAINING, AND SUPERVISION

## 9.1 Selection and Training of Counselors

As previously mentioned, counselors will be recruited from the existing counseling staff of the CTP sites to deliver all three study interventions. Priority will be given to counselors with HIV education experience. Procedures for training and administration of all three study interventions will maximize adherence to each intervention. Counselors will attend a regional training workshop to receive training that will encompass administration of the rapid HIV test and facilitation of the interventions. Intervention manuals will be developed and provided to the counselors at the regional intervention trainings.

## 9.2 Training on Administration of Rapid HIV Test

The initial training on administration of the rapid HIV test using both oral fluid and whole blood (via fingerstick) will be led by the CDC and senior study staff and will consist of a presentation and discussion regarding the details of the rapid HIV test, training on how to perform the test, followed by practice sessions in which counselors perform and interpret the test using positive and negative control materials. The training will also encompass quality assurance and data collection activities. Because the rapid HIV test is waived under Clinical Laboratory Improvement Amendments (CLIA) Certificate of Waiver, there are no specific federal requirements on who can perform the test; however, sites will be responsible for complying with any state or local requirements. Counselors will be fully trained on how to perform their assigned tasks and responsibilities with regard to administering the test. Specifically, they will be trained on the following:

- Procedures performed before the test (i.e. checking and recording the temperatures of the testing and storage areas, setting up the testing area, preparing and labeling the test, running external controls and providing the “participants Information” pamphlet which provides information to participants about the limitations of the HIV test and interpretation of preliminary positive or negative test results)
- Procedures performed during the test (i.e. procedures for collecting the specimen and running the test)
- Procedures performed after the test (i.e. interpreting the test result, disposing of used test materials, documenting results, re-testing for invalid results and providing referrals for reactive/preliminary positive results)
- Integration of the test into the overall study
- The importance of quality assurance and the elements of the study’s QA program, and
- The use and importance of Universal (or Standard) Precautions/biohazard safety
- The possibility of false positive results occurring and how to handle such situations if they arise.

## 9.3 Training on Intervention Delivery

Counselors will be trained to deliver all three interventions. While it is important to acknowledge the possible advantage (to protect the discreteness of each group) of using distinct facilitators for each intervention, the study investigators believe that the advantages of using the same facilitators outweigh potential disadvantages. Thus, it is proposed that, in using the same facilitators to administer all three interventions, the study is able to: (1) reduce the possibility of confounding intervention with facilitator effect; (2) deliver training in three interventions rather than one, to CTP facilitators; and (3) broaden the range of CTPs that can participate, particularly small-staff programs. In addition, the study is able to provide the CTPs with the benefit of training their staff on how to deliver HIV rapid testing and participant centered HIV prevention counseling.

Intervention training will be facilitated by the CDC and the lead investigative team. The investigators are planning to videotape the training so it will be available in the case of counselors leaving the project and being replaced by other counselors. It will consist of a presentation and discussion regarding the content and counseling techniques involved in each of the three intervention groups as outlined below followed by break out sessions in which counselors take turns performing, observing and critiquing mock intervention sessions. An overview of the content and techniques covered within each intervention training follows:

- Training on the group 1 intervention (Rapid HIV Testing with RESPECT Counseling) will encompass the following counseling techniques: orienting the participant to the rapid testing procedure; providing an explanation of the testing window period, routes of HIV transmission and the meaning of test results; keeping the session focused on HIV risk reduction; performing an in-depth, personalized risk assessment; acknowledging and providing support for positive steps already made; providing motivation to make positive steps in the future; clarifying critical (rather than general) misconceptions about HIV risk; negotiating a concrete, achievable behavior-change step that will reduce HIV risk; avoiding a one-size-fits-all counseling approach by being flexible in the counseling technique and process; providing and explaining test results; and providing referrals for confirmatory testing and/or other services, as needed.
- Training on the group 2 intervention (Rapid HIV Testing and Information Only) will encompass orienting the participant to the rapid testing procedure; discussing the window period of time the test result covers and the transmission routes of HIV; explaining the various results possible (negative, preliminary positive, inconclusive); explaining the need for repeat testing if the result is inconclusive and the need for confirmatory testing if the initial test result comes back preliminary positive; and providing referrals for confirmatory testing and/or other services, as needed.
- Training on the group 3 intervention (Referral Only) will encompass how to provide the participant with a passive referral to one or more local testing sites while strictly avoiding initiation or facilitation of any discussion concerning HIV, HIV sexual or drug use risk behavior or risk reduction strategies.

Intervention training will emphasize counselors' need to follow and adhere to intervention manuals at all times as well as their need to exercise self-restraint in limiting discussion of intervention material strictly to the study groups for which they are intended. Training for counselors unable to attend the regional workshop will be conducted at each local site in consultation with the Lead Node, or the lead node via telecommunications.

Training will also be provided on the brief linkage case management intervention that will be delivered at 6-month follow-up to participants who have not seen an HIV primary care provider since having tested positive in this study.

## 9.4 Quality Control of Interventions Administered

Quality control of the three interventions will be maintained through the following two procedures: 1) Interventions will be guided by detailed, written intervention manuals on which training and ongoing administration will be based; 2) Interventions will be audio-recorded and a random sample (10%) of the recordings across all sites will be reviewed by designated fidelity raters on a regular basis; adherence or deviation from a given intervention manual will be documented and discussed with the counselor during ongoing intervention fidelity meetings.

## 9.5 Concomitant Therapy

During part or all of participants' participation in the study, they will also be participating in substance abuse treatment. This may include discussion of HIV risk and/or preventive behavior. Participants may also be exposed to HIV street outreach, media campaigns, and/or other HIV prevention intervention. It would be both unethical and unfeasible to impede these activities. Therefore, to account for these activities, we will document them in the ACASI administered to study participants at each follow-up assessment interview. As part of the ACASI interview, we will ask participants if they have taken part in any HIV prevention discussions as part of their substance use treatment, as well as anywhere outside of their substance use treatment and the study.

# 10.0 STATISTICAL ANALYTIC PLAN

## 10.1 Objectives of the analysis

Three primary hypotheses are proposed for this trial all with the general intention of testing if one or more of the groups defined by (1) HIV rapid testing with brief prevention counseling, (2) HIV rapid testing with information only, and (3) referral, affects receipt of HIV testing results and a reduction of sexual risk behaviors.

## 10.2 Randomization

Participants will be randomized to one of the three treatment groups. Randomization will be stratified by site and within site, by race/ethnicity and gender. The randomization procedure will be conducted in a centralized process through the Data and Statistical Center (DSC). Specifically, randomization schedules will be created by the study statistician for each gender by race/ethnic group within each site. The race/ethnicity categories will include: African American, Hispanic, European American, and other). Note that Hispanics of African origin will be classified as Hispanic for the purpose of randomization. The randomization schedules will be of a randomized-block nature to ensure relative equality of assignment across condition across the recruitment period and to prevent the potential for study staff guessing the next assignment which is heightened when a fixed block-size is used. After the baseline assessment, the site research coordinator will perform the randomization. The research coordinator will contact the central randomization center to determine the appropriate condition for the site. The exact method of this notification is yet to be determined, but will be by computer-assisted telephone, web-site or some combination (to provide redundancy). In any case, the research coordinator will enter the appropriate participant characteristics (site, participant ID, gender and ethnicity) either by pushing buttons (if by phone) or by entering into a web-form (if by website). The treatment assignment will then either be transmitted by computer voice (if by telephone) or by computer screen (if by web).

## 10.3 Primary Outcomes

a) RECEIPT OF HIV TEST RESULTS: The primary outcome variable will be receipt of HIV test results defined as binary (Yes/No) self-reported receipt of test results during the 1 month post-randomization assessment window.
b) NUMBER OF RISKY SEXUAL BEHAVIORS: The second primary outcome variable will be measured at 6 months post-randomization and defined as number of unprotected anal and vaginal sex episodes with either primary or non-primary partners.

## 10.4 Secondary Outcomes

Secondary outcomes are divided into those related to HIV testing and those related to risky sexual behaviors. Note that the date of randomization is the point from which all outcomes will be measured.

### 10.4.1 HIV Testing Secondary Outcomes

The HIV testing secondary outcomes are all binary (Yes/No). Examples of the secondary outcomes to be tested are:

a) Self-reported receipt of test results by six months

b) Medical records validated receipt of HIV test results by one month

c) Medical records validated receipt of HIV test results by six months

d) Self-reported completion of HIV test by one month

e) Self-reported completion of HIV test by six months

f) Medical records validated completion of HIV test by one month

g) Medical records validated completion of HIV test results by six months

Please note that the reasons for doing these analyses differ. The reason for 10.4.1.a is to explore whether more individuals might have completed testing after one month post-randomization and determine if this affects the results of the primary conclusion. The reason for 10.4.1.b and c is to confirm the self-reported receipt of results through medical records. The reason for 10.4.1.d and e is to decompose the results of the primary hypothesis (and the 6 month follow-up secondary analysis) into its constituent parts. To receive test results, an individual must both have the test performed and receive the results of that test. The primary analysis tests these two jointly with returning (or staying) to be told the results of the test. The reason for 10.4.1 f and g is to confirm the self-reported completion of testing through medical records.

Counselor characteristics will be reported in the primary outcome manuscript to give the context of study implementation. In addition, a planned secondary analysis will examine whether there is significant variability in treatment effects at different sites and whether counselor characteristics and attitudes may be related to these differences. In addition, we will examine whether participation in the trial has a significant effect on counselor attitudes and whether any observed change in counselor attitudes is related to the rates of testing experienced within the trial at the counselor's particular site.

### 10.4.2 Risky Sexual Behavior Secondary Outcomes

All risky sexual behavior secondary outcomes are self-reported.

a) Number of unprotected vaginal and anal sex acts with non-primary partners (all partners other than most recent primary) in the past one month

b) Number of unprotected vaginal and anal sex acts with non-primary partners (all partners other than most recent primary) in the past six months

c) Number of unprotected vaginal and anal sex acts with primary partner in the past one month

d) Number of unprotected vaginal and anal sex acts with primary partner in the past six months

e) Number of total vaginal or anal sex partners in the past six months

f) Proportion of all vaginal and anal sex acts which involved drugs or alcohol in the past six months

g) Attitudes toward safer sex in the past six months

h) Self-efficacy for safer sex in the past six months

i) Proportion of unprotected vaginal or anal sex at most recent sexual encounter (with either a primary or non-primary partner) in the past six months

Please note that our primary hypothesis focuses on an overall measure of the most risky sexual behavior. Secondary analyses 10.4.2.a-f and i are other potential risky behaviors or ways of measuring risky behavior that are of interest to many sexual risk researchers. Secondary analyses 10.4.2.g and h are self-reports of attitudes/cognitions about safer sex.

### 10.4.3 Injection Drug Use Secondary Outcome

Injection drug use secondary outcomes are self-reported and include:

a) Prevalence of use of any injection drugs in the past six months

b) Frequency of injecting any drugs in the past six months

c) Number of injecting partners in the past six months

d) Frequency of having reused needles/syringes in the past six months

e) Frequency of having reused injection paraphernalia in the past six months

f) Use of syringe exchange in the past six months

The purpose of the injection drug use secondary outcomes is to document whether the intervention does or does not have any effect on behaviors related to injection drug use.

## 10.5 Overview of Analysis Plan

### 10.5.1 Overview of the Analysis of the Primary Outcomes

As specified in the aims, three *a priori* contrasts are to be tested, two for receipt of testing results, and one for number of risky sexual behaviors. To conservatively control for the Type-I error rate, we will employ a Bonferroni Correction (see, for example, Fleiss J. L., 1986) to account for the two outcomes {thus dividing the overall Type-I error rate (level alpha) into two components (p=0.05/2=0.025)}. All treatment comparisons will be run under the Intent to Treat (ITT) criterion.

For the simple binary outcome, receipt of test results at 1 month, for the 2 contrasts listed below, we will use logistic regression equation, both to test the omnibus group difference of self-reported receipt of test results (yes/no) and for the follow-up tests of the orthogonal contrasts (see below). The second outcome, number of risky sexual behaviors will be measured at 6 months post-randomization. To analyze each outcome, a Generalized Estimating Equations (GEE) model will be employed (Zeger & Liang, 1986) as implemented in SAS. Whereas correlation between patients within a site is anticipated to be quite small if not zero in this trial, the GEE inference will be statistically correct regardless of the existence of even a small amount of such a correlation.

As noted above, the assumption of normality will likely not be met for the variable, number of risky sexual behaviors. Specifically, the data will likely be right skewed. If possible, we will attempt to bring about near normality through transformation (e.g. Log-transform, or square root). The GEE model is tolerant to violations of normality, and if necessary, the model can be easily modified to other common distributions of the data (e.g., Poisson, negative binomial, etc.).

### 10.5.2 Covariates

Randomization should ensure that our groups are equal at baseline. Thus, in the abstract, the analysis is straightforward, the association of the particular contrasts of group on the particular outcome. Our primary analysis will not control for any covariates. Nevertheless, to assess the effects of and control for any unintended impact group differentials across the range of covariates, in a second sensitivity analysis, the simple analysis listed above will be extended to additionally control for an indicator for site, age at baseline, race and ethnicity, gender, and primary type of drug use (injection drug use vs. non-injection drug use, opiate vs. non-opiate, stimulant vs. non-stimulant). For the outcome, *Receipt of Testing Results*, we will additionally control for the number of times previously tested in lifetime, while for the outcome, *Number of Risky Sexual Behaviors*, the level of sexual activity at baseline will be controlled. The significance levels for any of these covariates will be noted, but will not affect the conclusions of the primary analysis. As listed below, the effects of these variables on risky behaviors and receipt of testing will be explored more fully in the secondary aims. We will also assess the interaction of each of these covariates with group membership as they affect the two primary outcomes. If statistically significant, the results of these analyses will not affect the conclusions to the primary analyses. However, the results will be reported in the secondary analyses sections (see section 10.5.4).

### 10.5.3 Tests of the Specific Aims

**Aim 1a:** To evaluate the effectiveness of offering on-site HIV rapid testing on receipt of HIV test results (measured via self-report) among clients in substance use treatment centers.

> **H1a:** The self-reported HIV test result receipt rate in Groups 1+2 (offer of on-site HIV rapid testing) will differ from the self-reported rate of HIV test result receipt in Group 3 (offer of a referral for off-site HIV testing) at one month post-randomization.

Using the logistic GEE model, if an overall difference between the three groups in receipt of test results is declared, the odds ratio contrasting Groups 1 and 2 against Group 3 in receipt of test results will be calculated and the statistical significance assessed by use of a Wald test.

**Aim 1b:** To evaluate the effectiveness of offering counseling as part of rapid testing procedures on receipt of HIV test results (measured via self-report) among clients in substance use treatment centers.

> **H1b:** The self-reported HIV test result receipt rate in Group 1 (offer of on-site HIV rapid testing with brief prevention counseling) will differ from the rate of self-reported HIV test result receipt in Group 2 (offer of on-site HIV rapid testing with information only) at one month post-randomization.

Using the logistic GEE model, if an overall difference between the three groups in receipt of test results is declared, the odds ratio contrasting Group 1 against Group 2 (rapid testing with brief

prevention counseling against rapid testing with information only) in receipt of test results will be calculated. Statistical significance will be determined by p-value associated with the Wald test.

**Aim 2a:** To evaluate the effectiveness of offering brief prevention counseling with rapid testing on sexual risk behavior (anal or vaginal sex without a condom) among substance use treatment clients.

> **H2a:** The number of risky sex acts in Group 1 (offer of on-site HIV rapid testing with brief prevention counseling) will differ from the number of risky sex acts in Group 2 (offer of on-site HIV rapid testing with information only) at six months post-randomization.

Using the GEE model the risk of group 2 (rapid testing with information only) will be compared to group 1 (rapid testing with brief prevention counseling) and statistical significance will be determined by p-value associated with the Wald test.

### 10.5.4 Tests of the Secondary Outcomes

Each of the stated secondary outcomes listed in section 10.4 will be tested using analogous comparisons as are planned for the two primary hypotheses. That is, there will be a comparison of Group 1 + 2 versus 3, and Group 1 versus Group 2. The statistical methods used will also mirror the methods used for the two primary hypotheses. Those secondary outcomes that are binary will be tested as described for hypothesis 1 using logistic regression; whereas those secondary outcomes that involve either continuous or ordinal variables will be tested as described for hypothesis 2. Note that the exact method of analysis will depend on the realized distribution of the particular outcome in this trial for example, an expected count data variable may need to be modeled using a zero-inflated Poisson Regression rather than a Poisson regression if there are too many zero observations to fit the standard Poisson. Table 5 summarizes the secondary outcomes to be analyzed.

In the analysis of the primary outcomes, we listed several covariates to be included in a secondary sensitivity analysis: site, age at baseline, race and ethnicity, gender, and primary type of drug use (IV vs. non-IV, opiate vs. non-opiate, stimulant vs. non-stimulant), lifetime testing, and number of risky behaviors at baseline. In addition to models which add main effects for these variables on the outcomes without respect for randomized group we will test the effects of these variables on the group effect by testing if there is an interaction between the particular variable and randomized group on the two primary outcomes. In addition, we will have several other important confounders (HIV status -- positive, negative, unknown) and, for Number of Risky Sexual Behaviors, we will know whether they accepted HIV testing and received the results. For these analyses, the overall Type-I error will not be controlled, rather, the reader of any resulting journal article will be alerted to the fact that these analyses were the result of *post-hoc* exploratory analyses, and that any statistically significant results may have resulted from a Type-I error, and require replication.

Table 5 Secondary Outcomes

| Secondary Hypotheses/ Measures | Times of Assessment | Most Likely Analysis Type |
|---|---|---|
| **HIV Testing Hypotheses** | | |
| 1.Self-Report Receipt of Test Results | 6 Mos | Logistic Regression |
| 2. Medical Records confirmed Receipt of Testing | 1 & 6 Mos | Logistic Regression |
| 3. Self-Report Completion of HIV testing | 1 & 6 Mos | Logistic Regression |
| 4. Medical Records confirmed completion of Testing | 1 & 6 Mos | Logistic Regression |
| **Sexual Risky Behavior Hypotheses** | | |
| 1. Number of unprotected vaginal and anal Sex Acts *w/non-primary partner* | 1 & 6 Mos | Poisson Regression |
| 2. Number of unprotected Anal and Vaginal Sex Acts *w/primary partner* | 1 & 6 Mos | Poisson Regression |
| 3. Number of total vaginal or anal sex partners | 6 Mos | Poisson Regression |
| 4. Proportion of all vaginal and anal sex acts that included drugs or alcohol | 6 Mos | Regression Analysis |
| 5. Attitudes toward safer sex | 6 Mos | Regression Analysis |
| 6. Self Efficacy toward safer sex | 6 Mos | Regression Analysis |
| 7. Proportion of unprotected vaginal or anal sex at most recent sexual encounter *with either primary or non-primary partner* | 6 Mos | Logistic Regression |
| **Injection Drug Use Secondary Outcomes** | | |
| 1. Prevalence of injection drug use | 6 Mos | Logistic Regression |
| 2. Frequency of injecting any drug | 6 Mos | Poisson Regression |
| 3. Number of injecting partners | 6 Mos | Regression Analysis |
| 4. Frequency of having reused needles/syringe | 6 Mos | Poisson Regression |
| 5. Frequency of having reused injection paraphernalia | 6 Mos | Poisson Regression |
| 6. Prevalence of syringe exchange | 6 Mos | Logistic Regression |

### 10.5.5 Ancillary Analyses

All intervention sessions will be audio-taped for quality assurance with the permission of the participant. Approximately 10% of the intervention sessions (around 127 sessions) will be randomly selected and rated for fidelity to the three intervention conditions. A smaller subset, about 15% of the 10% (approximately 20 audiotapes) will be rated by two raters. The double rated cases will be used to calculate a kappa statistic to assess the inter-rater reliability of the fidelity instrument. On the full sample of rated intervention sessions, a simple ANOVA will be used to compare the 3 conditions on the ratings of various behaviors performed during the intervention. Depending on the realized distribution of the ratings, a non-parametric test, the Kruskal-Wallis test, may be substituted for the ANOVA procedure. These means and the associated test-statistics will be reported in the primary outcome manuscript and the final report to describe intervention fidelity. It is expected, for example, that only Group 1, the HIV rapid testing and Project Respect arm will have high ratings of the items that reflect the discussion of sexual risk behaviors.

To provide data for economic analyses of human resources required to conduct the on-site interventions, counselors will record the duration of each intervention session on the fidelity questionnaires they complete after each session. Descriptive analyses of counselor-reported intervention durations by study arm (means, medians, and standard deviations) will be conducted. Similar analyses will also be conducted of the durations of the 10% random sample of audio-taped sessions, and for each of these sessions the counselor-reported duration will be compared to the duration of the audio-taped session and a kappa statistic will be calculated. If this analysis indicates frequent discrepancies in session duration, the analysis will be repeated using a larger random sample to identify session characteristics associated with a discrepancy. To provide data for economic analyses of human resources required for off-site testing, 1-month and 6-month follow-up participant assessments include questions to determine time and travel requirements for participants who receive an HIV test off-site. Descriptive analyses of the responses to these questions will also be conducted.

## 10.6 Missing Data

Missing data is a ubiquitous problem in drug research, primarily due to dropping out and refusal. Missing data can lead to biased estimates and reduction of power, affecting the generalizabilty of the study. We will make every effort to minimize the amount of missing data and in the primary analyses we will include only patients with available data. In all cases missingness patterns will be identified and analyses will be conducted to determine if there is a differential attrition by treatment arm, and if missingness is related to any of the covariates. In the case that covariates predict the missing data, the data is called ”Missing at Random,” (MAR. Little & Rubin, 1987). GEE analyses are only appropriate if data are “Missing Completely at Random,” which means that no observed covariates predict the occurrence of missing data. The multiple imputations procedure can be used to fill in the data without artificially compressing the variance associated with the imputed data (Schaefer, 1997). Therefore, if observed covariates predict the existence of missing data, multiple imputation will be used in the secondary analyses of the primary outcomes to assess the effects of missingness on the reported results. If nonrandom missingness is of concern (Missing not at Random, MNAR), this problem will be addressed by applying pattern-mixture, propensity score or related models so that the effect of bias can be assessed in sensitivity analyses.

## 10.7 Interim Analysis

The DSMB will monitor the trial's progress for unexpectedly large differences in efficacy among treatment groups. A single interim analysis is planned early in the study conduct following accrual of approximately one quarter of the expected total number of subjects' data (n=319, ~106 subjects/arm) to assess the first outcome, differential efficacy of self-report of acceptance of testing by treatment arm; usual care (arm 3) will be compared with rapid testing (arms 1 and 2). Although planned, the interim analysis will be conducted only if the DSMB/NIDA deem it appropriate. To determine whether an interim analysis is warranted, the NIDA Data and Statistics Center will prepare a report for the DSMB once the study approaches 319 randomized participants. The report will include information on the recruitment rate and other descriptive statistics that will help determine the possible impact on the study if the interim analysis is carried out. If carried out, the results and direction of the results of the interim analysis (see method below) will determine the subsequent conduct of the trial. Trial monitoring guidelines for early stopping considerations of benefit is based on an O'Brien-Fleming boundary (O'Brien & Fleming, 1979) using a 2-sided 0.05-level upper boundary. Only efficacy (and not futility) will be assessed.

If the interim analysis occurred exactly at 319 subjects with 107 subjects in Referral and 212 subjects in Rapid Testing, then the critical values at the point of each of these analyses would be Z=4.33, ($p<0.001$). Depending on the base rate of acceptance in the rapid testing arm and the direction of the findings, different rates of acceptance in the referral arm will be required. For pedagogy, we note that if the base rate in Rapid Testing arms is 0.2, 0.45, or 0.7, to reject the null hypothesis and declare for efficacy, the rates in the Referral arm would need to be 0.228, 0.26 and 0.218 higher respectively.

**Two sided assessment of efficacy:**

This interim analysis emphasizes the effect of referral on acceptance of testing relative to the two rapid testing groups. While the comparison of the groups is two-tailed, testing if efficacy in the referral arm is greater or diminished relative to rapid testing, the direction of the results will lead to different subsequent conduct of the trial. If the usual care (referral) arm participants accept testing at a statistically significant **lower** rate ($p<0.05$) then randomization to this arm will cease immediately, and subjects will be randomized only to arms 1 and 2 (rapid testing), with a total expected continued accrual of 424 subjects per arm. Final study results comparing counseling versus information in the 2 rapid testing arms will use only subjects from these 2 arms. If, however, the unexpected result occurs that usual care has a **greater** rate of acceptance of testing ($p<0.05$), then the study will be closed, no further subjects will be randomized, and the results of the interim analysis will be published, which will show that referral compared to on-site testing is a more effective way to increase HIV testing rates.

Because the DSMB meeting may not correspond to the study obtaining the exact amounts of information described above and slightly more or less subjects may actually have data, the critical z-value will be adjusted for the exact amount of information collected at the point of the interim analysis using a-spending function approximating O'Brien-Fleming boundaries used by the software package, East 2000, by Cytel Software Corporation (2000).

The monitoring guidance for early stopping considerations for futility will not be assessed in this interim analysis. Additional interim looks will be performed (with or without formal testing) as per the DSMB's request and these analyses will not affect continued interim assessments of safety. If formal testing of the outcome measures is requested by the DSMB, the alpha spending function will be adjusted to reflect the additional analyses.

## 10.8 Power

**Assumptions:** We assume a test of two hypotheses, with Bonferroni correction to control the overall Type-I error rate as listed above for the two outcomes. Sample sizes are assumed equal in all three arms with a total of 1,272 subjects. This number was derived by various power analyses and our assumptions about attrition and HIV serostatus which are summarized herein. We assume that 5% (or 64) of participants will be found to be HIV-positive. While previous studies have shown a range of prevalence estimates for HIV in drug treatment programs, the most recent estimates suggest a prevalence range from 3% - 5% (McFarland, Kellogg, Louie, Murrill, & Katz, 2000; Hwang et al., 2000). Whereas the primary analysis for number of risky sexual behaviors will not distinguish HIV status, we calculate power for number of risky sexual behaviors using the n associated with the expected number of HIV-negative participants, 1208. For the purposes of defining power, we adjust for two outcomes tested using the conservative Bonferroni criteria (0.05/2=0.025). Finally, to account for normal attrition inherent in trials on drug abuse, we assume a 15% dropout rate in the first month (affecting the analysis of the receipt of HIV test results outcome) and 30% at 6 months (affecting the analysis of the number of risky sexual behaviors outcome). This yields an attrition corrected sample size of 1,080 (360 per group) for receipt of HIV test results and an attrition corrected sample size of 846 (282 per group) of HIV-negative participants in the number of risky sexual behaviors outcome. We calculate the power of the assumed differences as well as the differences detectable (odds ratios for the receipt of HIV test results and differences in means for number of risky sexual behaviors) assuming an 80% power.

**Receipt of Testing:** A 10% difference in the rate of test result receipt has been previously used in studies examining HIV testing acceptance and receipt of results (Speilberg et al., 2005) and was considered to be a clinically significant difference. For the purposes of generating power, we assume group 3 will receive test results at a 10% rate, group 2 at a 20% rate, and group 1 at a 30% rate. The base rate of 10% for referral was chosen because it matches data from the NDATSS for percentage of those surveyed receiving HIV testing through referral (See Section 3.3 of the protocol) and previous literature has shown low acceptance and completion of testing rates with drug users recruited from needle exchange sites (Speilberg et al., 2005); there are no similar studies with drug users recruited from drug abuse treatment sites, but we have increased the expected rates at which people will receive their results because our study population will be drug users, the majority of which are not currently in withdrawal and, therefore, should be more willing to wait and receive testing and counseling.

If groups 1 and 2 have rates of testing of 30% and 20% respectively, the rate for the two groups combined is 25%. Comparing this combined group (1+2) to group 3 with an anticipated rate of testing of 10% results in a 15% raw difference in rates. Using these rates of testing to calculate odds ratios shows that the two proposed odds to detect are: H1 (groups 1 + 2 vs. 3)=3.0 and H2: (group 1 vs. 2)=1.71. Power and odds ratios detectable are calculated using the formulas due to Fleiss (Fleiss J., Levin, & Paik, 2003) and are shown in Table 6. For each of two scenarios, two numbers are shown. First, the power assuming the rates and sample sizes listed

above, and, second, the odds detectable given the assumed underlying rate and sample size. As can be seen in Table 6, power is well over 80% with the exception of the Bonferroni and attrition corrected contrast of group 1 and group 2 for receipt of HIV test results. In that case, where group 2 having a base of 20% and group 1 having a rate of 30% implies an odds ratio of 1.71, the power is 78%. Note that there is over 80% power to uncover an odds ratio of 1.74 or larger. This implies a 10.3% difference in the rate of testing of group 1 and group 2. If group 2 has a 20% base rate then group 1 has a rate of 30.3% for there to be 80% power.

Clearly the limiting case for power is the group 1 and group 2 comparison. Table 7 shows the power as the difference between group 1 and 2 varies. You can see that as the difference varies from 9% to 12% power varies from 69% to 85%. Power for this comparison also does vary as a function of the base-rate. The lowest power when comparing proportions occurs when the differences are clustered around 50%. You can see from Table 7 that with a base rate of 45% that power varies from 54% to 82% as the difference between groups varies from 9% to 12%. Therefore, our statistical power remains good with over 80% power to uncover 12% difference between groups if a higher base rate (such as if 45% was found in one of the intervention groups).

**Number of Risky Sexual Behaviors:** For the purposes of power, we fix the sample size and attrition rate, and calculate the difference detectable. Using SAS PROC POWER, we calculate the standardized difference attainable fewer than three conditions (unadjusted for multiple tests, adjusted for two outcomes, and adjusted for two outcomes and a 30% attrition rate).

For the contrast of interest, the maximum difference attainable at 80% power is a standardized difference of .261, deemed slightly above ”small” in the statistical analysis literature (Cohen, 1987) where small=.2, medium=.5, and large=.8. Assuming mean and variance estimates from the work of a CTN study with a similar outcome[5] we estimate the mean (weighted) is 16.5 behaviors with a pooled standard deviation of 11.5. Estimates from that study showed a decrease in risky acts of about 3 and effect size near .25. Assuming a standardized difference between the group .261, we are 80% powered to declare significance if group 1 (HIV rapid testing with brief prevention counseling) leads to a decrease of an average of 3.00 (=.261*11.5) behaviors relative to group 2 (HIV rapid testing with information only). If instead the change in risk is 2.5 (standardized difference of .217) the power is 63%; whereas if it was 3.5 (standardized difference of .304) then power would be 91%

[5] This CTN study, “HIV/STD Safer Skills Groups For Women in Methadone Maintenance or Drug-Free Outpatient Treatment Programs” conducted in 12 CTPs between May, 2004 – October, 2005. This estimate reflects their baseline mean behaviors (Tross, 2007).

Table 6: Power for each test is shown below:

| Outcome | Contrast | Adjusted for 2 tests | | Adjusted for 2 tests + Attrition | |
|---|---|---|---|---|---|
| | | Power[1] | Difference Detectable[2] | Power[1] | Difference Detectable[2] |
| Receipt of Testing Results | Grps 1+2 vs Grp 3 | >99% | O.R=1.63 | >99% | O.R=1.71 |
| | Grp 1 vs. Grp 2 | 85.3% | O.R.=1.66 | 78.0% | O.R.=1.74 |
| Number of Sexual Risk Behaviors | Grp 1 vs. Grp 2 | 80% | Mean Diff. =.218 | 80% | Mean Diff. =.261 |

[1] Power for fixed n and 10%, 20% and 30% receipt of test results rates for groups 3, 2, 1, respectively.
[2] Detectable effect size (odds ratio) for fixed n and 80% power.

**Table 7**

| Rate in Group 2 | Rate in Group 1 | Δ | Odds Ratio | Power |
|---|---|---|---|---|
| 20% | 29% | 9% | 1.63 | 69% |
| 20% | 30% | 10% | 1.71 | 78% |
| 20% | 30.3% | 10.3% | 1.74 | 80% |
| 20% | 31% | 11% | 1.80 | 91% |
| 45% | 54% | 9% | 1.43 | 54% |
| 45% | 55% | 10% | 1.49 | 64% |
| 45% | 56% | 11% | 1.56 | 74% |
| 45% | 57% | 12% | 1.62 | 82% |

In conclusion, correcting for multiple analyses as well as decreased sample size due to attrition, the study will have over 80% power to detect a difference with an associated odds ratios of 1.71 or greater for the Group 1+2 (on-site rapid testing) versus Group 3 (referral) comparison and over 80% power to detect a difference (10.3%) with an associated odd ratio of 1.74 or greater for the Group 1 (HIV rapid testing with brief prevention counseling) versus Group 2 (HIV rapid testing with information only) comparison. This is a conservative estimate of effect size for the first comparison given the advantages of on-site rapid testing over referral. In the case of the comparison of the two rapid testing conditions, this is an effect size which corresponds to the minimal clinically significant effect size. Similarly, for the key test of number of sexual risk behaviors the study will have 80% power to detect a standardized difference of .261 for number of sexual risk behaviors between participants assigned to on-site rapid HIV testing and counseling versus on-site rapid testing and information only. This is a reasonable clinical difference and will help to clarify the importance of counseling versus information only in the context of providing rapid HIV testing in drug treatment programs.

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# 12.0 Appendix I

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention
Atlanta GA 30333

May 29, 2007

Lisa Metsch, Ph.D.
Associate Professor
Department of Epidemiology and Public Health
University of Miami School of Medicine
1801 N.W. 9th Avenue, Suite 330
Miami, Florida 33136

Dear Lisa,

I am writing to commend your proposed study of rapid HIV testing and counseling among drug users, as submitted to the National Institute on Drug Abuse. I am glad to offer my continued collaboration as the proposal and study proceed.

With CDC's 2006 revised recommendations for HIV screening in health-care settings (including substance abuse treatment centers), a study such as yours – a critical examination of comparisons between referral for conventional testing, on-site HIV testing, rapid tests, and of prevention counseling associated with HIV testing – will be particularly informative. To my knowledge, this is the only large-scale trial of rapid HIV testing in drug treatment centers across the U.S. As I'm sure you know, several proposals to increase opt-out HIV testing in substance abuse treatment centers have been advanced, and data from studies like yours will be essential to maximize the effectiveness of these efforts. The results of this study will be relevant for both current practice and the development of coherent policies.

I appreciated the opportunity to provide technical input into some aspects of your proposal, particularly with respect to rapid HIV tests, an important priority for CDC. I am eager to see your project begin, and look forward to using the results to inform CDC's prevention efforts in substance abuse programs. This project also promises to significantly enhance collaboration between CDC and NIDA.

If you have any questions, please feel free to contact me.

Sincerely,

Bernard M. Branson, M.D.
Associate Director for Laboratory Diagnostics
Division of HIV/AIDS Prevention
National Center for HIV, Viral Hepatitis, STD,
and TB Prevention