

NIDA Protocol

**Project Aware: HIV Rapid Testing & Counseling
in STD Clinics in the U.S. -- an Adaptation of CTN
0032**

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October 4, 2010

Version 7.0

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1.0 LIST OF ABBREVIATIONS

AE	Adverse Event
ACASI	Audio Computer-Assisted Self-Interview
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
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
MSM	Men Who Have Sex with Men
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 Infection
STD	Sexually Transmitted Disease

2.0 STUDY SYNOPSIS

Study Objectives: An estimated 56,300 Americans are newly infected with HIV every year (Hall et al., 2008). Among the more than one million Americans living with HIV, approximately one-fifth 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.

Widely expanded access to routine HIV testing is now a major HIV prevention strategy in the United States. The goal of widespread HIV screening is that everyone should know his/her status. Approximately 21% of persons who are HIV-infected do not know their status, and some estimate that more than half of new cases are transmitted by persons unaware that they are HIV-infected. Increasing the number of people who know their HIV status has the potential to reduce new HIV infections by almost one-third (Holtgrave & Pinkerton, 2007). Knowledge of HIV infection motivates HIV-infected persons to reduce risk behaviors. It is also beneficial for persons to know their status early so they obtain HIV care that can delay or avoid HIV/AIDS morbidity and mortality. Early diagnosis facilitates obtaining early access to antiretroviral therapy which is also associated with decreased HIV transmission risk due to suppressed viral replication and reduced risk-behavior. Studies suggest that expanded HIV screening in outpatient settings is cost effective when evaluated by cost-utility benchmarks used to evaluate medical and public health interventions (Sanders, et al. 2005). Paltiel and colleagues estimate that widespread routine HIV screening would produce substantial health benefits (Paltiel et al, 2005).

The recent introduction of rapid HIV testing offers a critical public health screening approach for facilitating earlier diagnoses of HIV infection. Rapid tests permit a sensitive and specific, fast, simple, minimally invasive, and cost-effective method to screen for HIV. These tests provide results in approximately 20 minutes. If negative, the result is considered conclusive; if positive/reactive, follow-up confirmatory testing is required. In a review of 17 studies conducted with more than 20,000 clients, rapid-testing clients were almost twice as likely to receive HIV testing results compared with conventional testing and counseling clients (Hutchinson et al., 2004). 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).

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 health care settings (Branson et al., 2006). As part of these recommendations, and in departure from prior long-standing recommendations, the CDC recommended that prevention counseling (specifically pre-test counseling) not be required with HIV rapid testing or as part of HIV screening in health care settings, including high-risk medical settings such as STD clinics (Hall et al., 2008). Reasons for counseling being identified as a barrier include the additional time required for counseling and current staff potentially being uncomfortable or lacking the training to conduct the counseling. The CDC recommendations stated, "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 cites a meta-analysis published in 1999 that examined 27 published studies that assessed HIV sexual risk behavior before and

after HIV counseling and testing (Weinhardt et al., 1999). Results 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. However, there was no direct comparison of testing only versus testing and counseling. Holtgrave and McGuire questioned the appropriateness of this meta-analysis as justification for abandoning prevention counseling (Holtgrave & McGuire, 2007). They point out that this meta-analysis was based on 23/27 studies that were published before the CDC issued counseling and testing guidelines in 1993, which endorsed counseling, and that the CDC themselves had issued cautionary advice on the findings of the meta-analysis published in 1999. The CDC even confirmed that studies conducted after 1997 had supported the effectiveness of counseling approaches.

The CDC's decision to move away from prevention counseling in the HIV testing context has been controversial. There are multiple sources of scientific evidence in support of the effectiveness of prevention counseling in the context of HIV testing for HIV-negative persons. Foremost is the CDC's Project RESPECT study, a randomized controlled trial conducted in STD clinics in the mid-1990s before the advent of highly active antiretroviral therapy and before the advent of rapid testing (Kamb et al., 1998). RESPECT showed that a 2-session, client centered counseling session based on behavioral theory with HIV testing was superior to a program with HIV testing and didactic information. Specifically, those in the counseling arm had more consistent use of condoms and a statistically significant reduction of STIs compared to those in the didactic information arm. However, RESPECT did not examine the effect of offering counseling on the uptake of HIV testing, did not include MSM (who account for 53% of all new HIV infections in the U.S.), and did not examine the cost effectiveness of the intervention. The follow-up RESPECT study (RESPECT-2) did include MSM, but this trial compared a 1-session counseling session with rapid testing to 2-session counseling with traditional testing and did not address the question of whether counseling and testing is more effective than testing alone. It should also be noted that the original RESPECT and RESPECT-2 trials hired dedicated research staff, rather than clinical staff as counselors.

Drs. Lisa Metsch and Grant Colfax are currently conducting a trial examining the effect of counseling in non-medical settings. The HIV Rapid Testing and Counseling in Drug Abuse Treatment Study (CTN 0032) is a NIDA-sponsored randomized controlled clinical trial being conducted in the NIDA Clinical Trials Network (CTN). CTN 0032 will determine the effect of on-site testing and counseling on testing rates and reducing sexual risk behaviors among drug treatment clients, compared to testing only and referral. The trial was launched on January 5, 2009, in 12 community treatment sites, completed recruitment of 1,272 participants over 4 months and has a 97% follow up rate at 1 month post randomization. In contrast to CTN 0032, there are no experimental studies underway to examine the effect of testing with and without counseling in traditional health care settings. Therefore, adapting CTN 0032 to sexually transmitted disease (STD) clinics will provide important and timely data on the effect of counseling in high-risk populations tested in health care settings. In this adaptation of CTN 0032, we will assess the relative effectiveness and cost-effectiveness of (1) on-site HIV rapid testing with brief, participant-tailored prevention counseling vs. (2) on-site HIV rapid testing with information only (as recommended in the CDC guidelines).

Study Design: This is a randomized controlled clinical trial in which individuals seeking medical or health services at STD clinics will be recruited to participate in a multi-center HIV testing and counseling study. We will assess the relative effectiveness and cost-effectiveness of (1) on-site HIV rapid testing with brief, participant-tailored prevention counseling vs. (2) on-

site HIV rapid testing with information only. We will evaluate the effect of counseling on one primary outcome: STI incidence. We will also conduct sub-group analyses to examine the effect of counseling by HIV risk group, race/ethnicity, gender, and age because the literature suggests possible differential effects depending on these characteristics (Metcalf et al, 2005). Secondary outcomes will be reduction of sexual risk behaviors, substance use during sex (i.e., being under the influence during sex) and cost and cost effectiveness of counseling and testing. Participants will be assessed for STIs, HIV testing history and sexual and drug use risk behaviors at baseline and at 6-months follow-up.

Refer to Figure 1 for a visual overview of study activities. Note that while Figure 1 illustrates the ideal flow and order of study activities and assessments, the actual order will be flexible to accommodate normal clinical flow as long as 1) written informed consent is obtained before subsequent activities, 2) the baseline assessment (ACASI) occurs before randomization and 3) randomization is performed immediately prior to the intervention being administered.

Study Population: Approximately 5,000 individuals seeking medical or health services from approximately 9 STD clinics throughout the United States will be randomized. We will randomize an estimated 556 participants from each clinic.

Eligibility Criteria: As detailed below, there are minimal eligibility criteria for site (STD clinic) participation and minimal eligibility criteria for patient participation at the sites.

Site eligibility: STD clinics are eligible if they meet the following criteria: (1) high rates of STIs and HIV in their geographic target area, (2) sufficient number of patients so that they would be able to recruit the required 556 participants over the study time period, (3) prior participation in research and clinical studies, and (4) previous collaboration with investigators.

As part of site selection, our study team asked each potential site to complete a survey that addressed their clinic volume and demographics, rates of STIs and HIV, their HIV testing policies, previous research experience, and basic information about their clinic flow. We followed up with individual telephone interviews to discuss the proposed study with each site and visited the majority of the sites.

Participant eligibility: Participants must: (1) be seeking medical or health services at the participating STD clinic, (2) be at least 18 years old, (3) report being HIV-negative or status unknown, (4) provide informed consent, (5) provide locator information, (6) be able to communicate in English, (7) agree to be tested for STIs/STDs and HIV; (8) sign a HIPAA form and/or medical record release form to permit medical record abstraction of HIV and STI/STD tests, results and treatment; and (9) report living in the vicinity of the clinic and being able to return to the clinic for the 6-month follow-up visit.

STI Testing: After giving informed consent, participants will be screened for STIs. Participants will receive a battery of STI tests, regardless of risk behaviors or symptomatology. The battery of STI tests will screen for *Neisseria gonorrhoea* (GC), *Chlamydia trachomatis* (CT), *Trichomonas vaginalis*, Herpes Simplex 2 (HSV-2) and *Treponema pallidum* (syphilis). All participants found to have an STI will receive treatment on site, guided by national STD treatment guidelines and according to clinical standard of care. Partner notification services will be conducted outside of the study and according to state and local guidelines.

HIV Testing: On-site rapid HIV testing and confirmatory testing will be conducted. Participants whose test result is reactive will receive a confirmatory HIV blood test that day, with results delivered 5-10 days later. STD clinics will follow the state-specific standard for reporting positive HIV results.

Interventions: After providing Informed Consent and subsequently completing the baseline assessment on ACASI, participants will be randomly assigned to either the HIV testing/counseling arm or the HIV testing and information only arm. These groups are briefly described below and detailed further in section 6.0.

Group 1: HIV testing and brief, client-centered counseling

Participants will receive a rapid HIV test with brief prevention counseling that addresses risk reduction based on an evidence-based counseling approach (RESPECT-2 counseling). Depending on local and/or state HIV testing guidelines, study participants may also be required to provide a separate written consent for HIV testing prior to the rapid test being conducted.

Group 2: HIV testing and information only

Participants will receive a rapid HIV test with information only. Depending on local and/or state HIV testing guidelines, study participants may also be required to provide a separate written consent for HIV testing prior to the rapid test being conducted.

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 STIs, 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 will receive a confirmatory HIV blood test that day, with results delivered 5-10 days later. The study staff will work to ensure that the confirmatory test is conducted and the result given to the participant.

All participants will provide informed consent prior to their involvement in the protocol. Additionally, depending on local HIV testing guidelines, participants may also be required to provide a second consent in order to proceed with HIV testing.

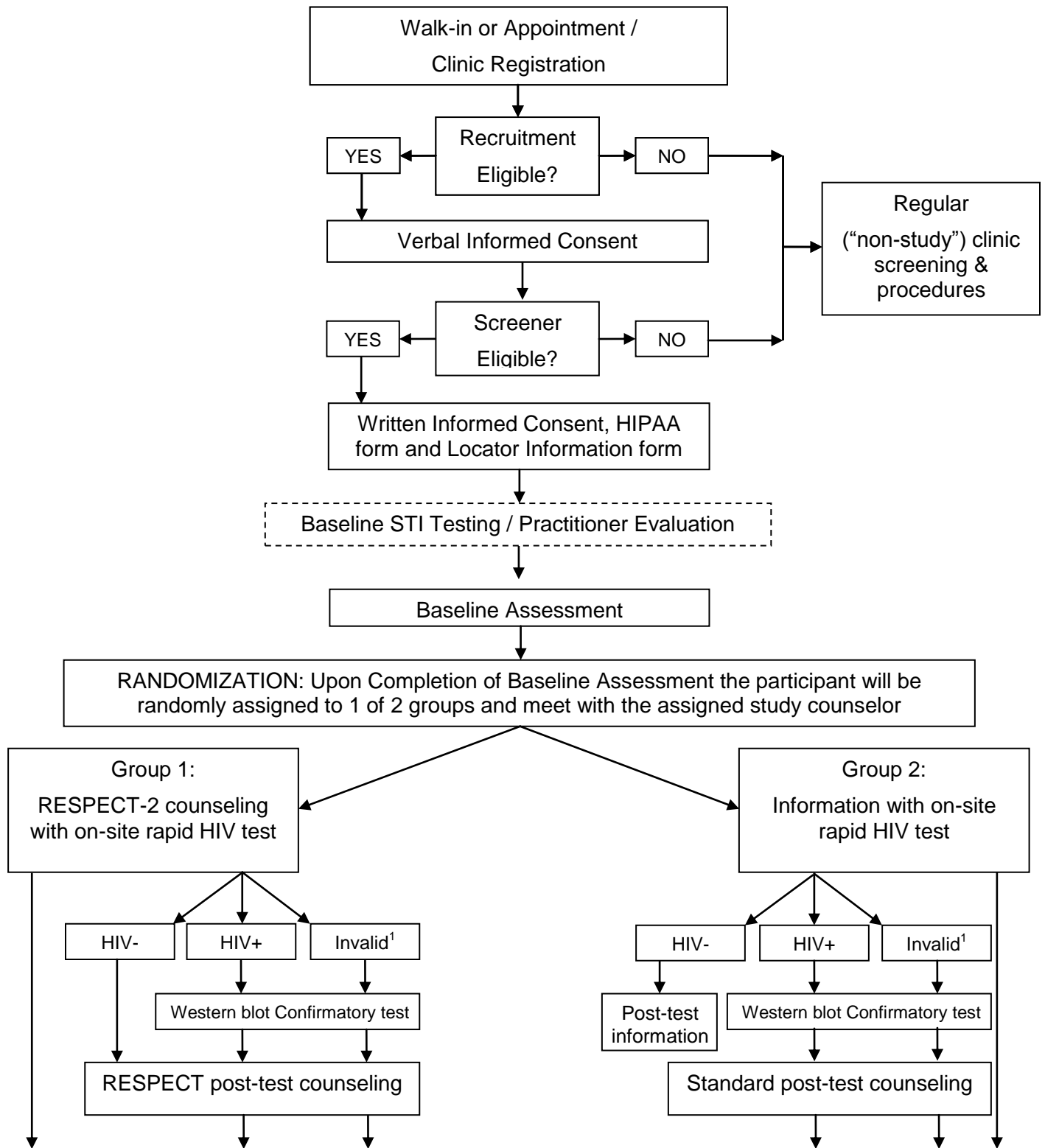
Safety Assessment: There will be ongoing monitoring of adverse events. Adverse events will be collected at each research visit.

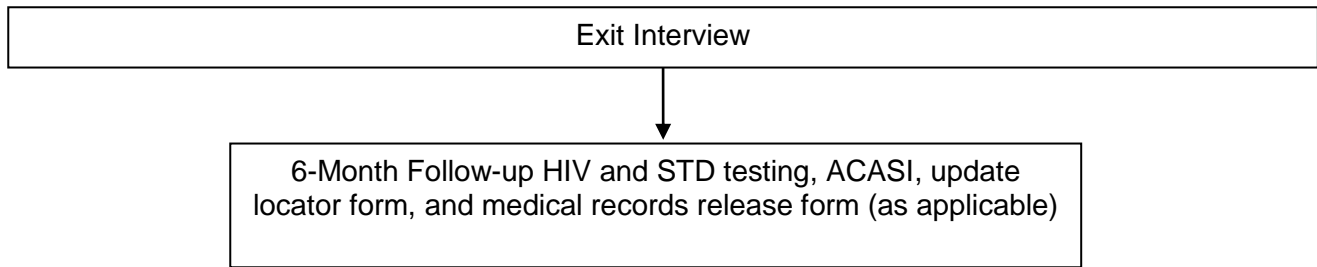
Outcomes: There is one primary outcome for this study. The outcome is composite STI incidence at 6-month follow-up in which a person is considered positive for STIs if they are positive on any tested STI. Secondary outcomes will include self-reported sexual risk behavior, being under the influence of substances and/or illicit drug use during sexual activity and cost and cost-effectiveness.

Analysis: The primary outcome will be analyzed using logistic regression for the binary outcome, new diagnoses of STIs (Yes/No). The logistic regression analysis will predict 6-month STI incidence as a function of randomization group controlling for the baseline incidence of STI. ANCOVA will be used for the secondary continuous outcomes, number of sexual risk behaviors and number of sexual episodes involving substance use. Costs will be compared based on study records supplemented by site-level data collection (detailed further in Section 10.4). Primary 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.

Figure 1: Flow of Activities





¹Note: Participants with invalid initial rapid test results will be tested via rapid test a 2nd time prior to confirmatory testing.

3.0 BACKGROUND AND SIGNIFICANCE

3.1 HIV Rapid Testing and Counseling

The overall goal of this study is to evaluate the effect of counseling on STI incidence among individuals receiving medical or health services in sexually transmitted diseases clinics 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 high risk for HIV. We then describe the HIV rapid 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 two proposed testing groups and present our research questions and planned comparisons.

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 gained¹ (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.

Reason #2: Knowledge of one's serostatus and risk reduction counseling reduces 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, Dyattlov, & 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 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

¹ Notably, cost-effectiveness changes based on the prevalence of disease in a particular population or setting. |

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).

Scientific Basis for Selecting Rapid HIV testing and RESPECT-2 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 or venipuncture 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. OraQuick rapid test is a single-use, fingerstick using whole blood to detect HIV antibodies. It has 99.6% sensitivity and 100% specificity. The rapid HIV test is intended for use as a point-of-care test and is CLIA-waived. Participants whose test result is reactive receive a confirmatory HIV blood test via Western blot, with confirmatory results available 5-10 days later.

HIV counseling: In the proposed protocol, participants in both of the groups will receive rapid HIV testing. In one group, it will be accompanied by information only, per the new CDC guidelines, and in the other group it will be accompanied by brief prevention counseling using the RESPECT-2 single visit counseling intervention. RESPECT-2 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-2 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. Project RESPECT counseling was tested and shown to be efficacious (Kamb et al., 1998) in reducing STI 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 STIs and at 12 month follow-up, 20% fewer participants in the two session intervention compared with the didactic information only session had new STIs. RESPECT-2 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 Project RESPECT counseling to the rapid testing era, the RESPECT-2 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 Project 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 STIs 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-2 delivered in two sessions, pre-and post-testing, during a single visit.

3.2 Need for Current Initiative and Research Question:

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.² The CDC is currently working on developing HIV testing guidelines for non-medical care settings. 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. This study presents an ideal opportunity to provide relevant data that can be used to inform public health officials and policymakers on the more effective HIV testing strategy to implement in outpatient health care settings throughout the United States. By collaborating with STD clinics throughout the United States, we will be able to answer a critical public health question about the role of counseling in this new era of routine rapid HIV testing:

Among patients seeking medical or health services at STD clinics, what is the effectiveness of brief, participant-tailored prevention counseling in reducing STI incidence?

Persons visiting STD clinics are at high risk of becoming infected with HIV and STIs, and a high proportion of HIV cases in STD clinics are missed due to the absence of routine HIV testing. The majority of STD clinic attendees report STI symptoms, contact with a person with STI symptoms or getting a “check-up” as reasons for clinic attendance.

Multiple other behavioral interventions have measured both behavioral and biologic outcomes. This counseling intervention is expected to reduce risk behavior, and, as a result, STIs. However, we believe it is critical to measure STIs as our gold standard endpoint, rather than depending on self-reported risk behavior change, because several trials have shown that measured reductions in risk behavior do not necessarily correspond with reductions in STI rates. Because STIs are the result of high risk, unprotected behavior, they are considered excellent surrogate markers for HIV risk. While some STI trials have shown that STI treatment does not reduce HIV infection rates (Wawer et al., 1999), this should not be confused with the fact that the high risk behaviors that result in STI infection can also result in HIV acquisition or transmission (Fleming & Wasserheit, 1999).

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 include rapid HIV testing onsite; one group receives HIV testing with brief prevention counseling (RESPECT-2) and the other group receives 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 STD 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

² *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

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 STI 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 HIV rapid testing remains a critical issue.

We will assess differences in intervention effect by relevant demographic and risk subgroups. Previous findings from the subgroup analysis of the RESPECT-2 study that compared traditional testing with pre- and post-test counseling to rapid testing with counseling indicated that MSM in the rapid-test group had higher subsequent STI incidence than those in the standard-test counseling group, though this was of borderline statistical significance (Metcalf et al, 2005). However, the RESPECT-2 study was not powered for nor originally designed to look at the potential differential effects of counseling on MSM versus heterosexuals (Branson, personal communication, 3/18/2009; Malotte, personal communication, 5/18/2009). As detailed in the analysis section, our sample size will allow the investigation of whether there is a differential effect of counseling on different sub-groups including MSM versus heterosexuals, African American and other race/ethnic groups, gender and age (Metcalf et al, 2005).

We will assess differences in intervention effect among substance users: The intervention explores risk factors and creates motivation to reduce risk factors. One such risk factor is substance use. STD clinics provide services to a broad range of persons including persons who use illicit drugs or heavy alcohol use. It is well established that both injection and non-injection substance use is associated with a higher risk for STDS among women, heterosexual men, men who have sex with men, and youths (Hser, Chou, Hoffman, & Anglin, 1999). Accordingly, 20% of STD clinic attendees have a substance use disorder (Aktan, Calkins, & Johnson, 2001). At

STD clinics, prevalence of recent use of substances include up to 28% of STD clinic patients reporting methamphetamine use, 20% cocaine use, 30%-50% heavy alcohol use, and 10% injection drug use. Being under the influence during sex is independently associated with sexual risk taking behavior and acquisition of STIs including HIV, is frequently reported with 20% of urban STD clinic attendees reporting sex while “high on alcohol” and 7% reporting sex while “high on cocaine or heroin (Hutton, Lyketsos, Zenilman, Thompson, & Erbelding, 2004).

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 with counseling or information only should be delivered in STD clinics. We will evaluate the effect of counseling on STI incidence at 6-month follow-up. We will also determine the effect of counseling on self-reported sexual risk behaviors and substance use during sex. Furthermore, we will determine the cost and cost-effectiveness of HIV testing with counseling versus information only.

4.0 STUDY AIMS AND HYPOTHESES

Primary Outcome

The primary outcome is composite STI incidence at 6-month follow-up in which a person is considered positive for STIs if they are positive on any tested STI.

Secondary Outcomes

Secondary outcomes include self-reported sexual risk behavior, being under the influence of substance and/or illicit drug use during sexual activity and cost and cost-effectiveness. The sexual risk and substance use behavior secondary outcomes will be measured at baseline and six months post-randomization as the self-reported number of unprotected sex acts (vaginal and/or anal sex without a condom) and sex while high on drugs or alcohol, which will be measured as the number of sexual occasions when substance use was involved. The cost analysis will consider the budgetary perspective of STD clinics, because decision makers in these programs may be unwilling to implement HIV counseling and testing unless they are reimbursed for costs according to their clinic's budgetary guidelines. The cost-effectiveness analysis will be conducted from the societal perspective (Hall et al., 2008), taking into account the time and expenses incurred by participants. Cost-effectiveness from payer perspectives will be considered in secondary analyses.

4.1 Primary Aim and Hypothesis

Aim 1: To determine the effectiveness of brief, participant-tailored prevention counseling in reducing STI incidence among patients seeking medical or health services at STD clinics

H1: The incidence of STIs among participants offered an HIV test with counseling will differ from participants offered an HIV test with information only.

5.0 STUDY DESIGN AND ACTIVITIES

5.1 Overview of Study Design

This study will use a prospective, randomized, controlled design to assess the relative efficacy in STD clinics of (1) on-site HIV rapid testing with brief, participant-tailored prevention counseling vs. (2) on-site HIV rapid testing with information only (as recommended in the 2006 CDC guidelines). We will evaluate the effect of counseling on STI incidence. Secondary outcomes will be reduction of sexual risk behaviors, being under the influence of substances or illicit drug use during sex, and cost and cost-effectiveness of counseling and testing. Participants will be assessed for STIs, HIV testing history and sexual and drug using risk behaviors at baseline and at 6 months follow-up. The target population is HIV-negative or status unknown individuals who are seeking any medical or health services at the participating STD clinic.

STD clinics are eligible if they meet the following criteria: (1) have high rates of STIs and HIV in their geographic target area, (2) have a sufficient number of patients so that they would be able to recruit 556 participants over the study time period, (3) have previously participated in research and clinical studies and (4) have previously collaborated with investigators. As part of site selection, we asked each site to complete a survey that addressed their clinic volume and demographics, rates of STIs and HIV, their HIV testing policies, previous research experience, and basic information on their clinic flow. We followed up with individual telephone interviews to discuss the proposed study with each site and visited the majority of the sites.

Individuals seeking any medical or health care services at the STD clinic will be recruited 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. After signing the informed consent form individuals will be enrolled, tested for STIs, 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 and STI testing behaviors, sexual risk behaviors, and drug-using risk behaviors (see description of measures in section 5.4). To minimize participant and staff burden, the instrument will take no more than 45 minutes to complete. After completion of the baseline ACASI, participants will be randomized to one of the two study groups:

- Group 1 – Participants will receive on-site rapid HIV testing with brief prevention counseling (described further in section 6.1)
- Group 2 – Participants will receive on-site rapid HIV testing with information only (described further in section 6.2)

At 6-months post-randomization, participants will be tested for STIs, tested for HIV (if baseline test was negative) and complete a follow-up assessment to measure changes in their self-reported 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. 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 STD clinic settings, 2) using actual clinic staff to help deliver the interventions, 3) allowing STD clinics flexibility in how they set up staffing for this trial, reflecting adaptability and flexibility needed in a “real world” setting and 4) minimizing patient eligibility criteria. Additionally, our control condition is more consistent with an effectiveness approach because it represents the omission of counseling (testing/information only arm) as suggested in the new CDC guidelines for offering HIV testing in medical care settings. The Project RESPECT-rapid testing intervention, our counseling intervention approach, has been previously tested in an efficacy trial. Therefore, this hybrid approach is appropriate for this trial.

5.2 Number of Sites and Participants

A target of approximately 5,000 participants from 9 STD clinics will be randomized, to include approximately 556 participants per participating STD clinic. Participants will be randomized at an average of 18 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 STD clinic sites in which we are recruiting.

5.3 STD Clinic, Counselor, and Participant Eligibility

5.3.1 STD Clinic Eligibility

Site selection was guided by the goal of obtaining diversity in geographic region, race/ethnicity and gender. Additionally, STD clinics were eligible if they met the following criteria: (1) high rates of STIs and HIV in their geographic target area, (2) sufficient number of patients so that they would be able to randomize the required 556 participants over the study time period, (3) previously participated in research and clinical studies and (4) previous collaboration with investigators. As part of site selection, we asked each site to complete a survey that addressed their clinic volume and demographics, rates of STIs and HIV, their HIV testing policies, previous research experience, and basic information on their clinic flow. We followed up with individual telephone interviews to discuss the proposed study with each site and visited the majority of the sites.

5.3.2 Counselor Eligibility

Counseling procedures will be conducted by appropriate, designated staff members that are willing to participate in the trial. All participating 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 STD clinics. However, all study procedures will be standardized. Designated staff will obtain informed consent, perform rapid testing and perform 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 two study interventions, the study team wants to be able to describe counselor characteristics.

5.3.3 Participant Eligibility and Recruitment

Participant must:

- 1) Be seeking any medical or health services at the participating STD clinic,
- 2) Be at least 18 years old,
- 3) Report being HIV-negative or HIV status unknown,
- 4) Provide informed consent,
- 5) Provide locator information,
- 6) Be able to communicate in English,
- 7) Agree to be tested for STIs and HIV,
- 8) Sign a HIPAA form and/or medical record release form to permit medical record abstraction of HIV and STI/STD tests, results and treatment,
- 9) Report living in the vicinity of the clinic and being able to return to the clinic for the 6-month follow-up visit.

In order to assess how representative the study sample is of the population of clients receiving services at participating STD clinics, the clinics will provide summary information about the clients who access services at the clinic during the 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 attempt to approach all clients seeking medical or health services. 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, proceed with the informed consent process. Screening may be conducted by the recruiter who initially approached the client or by another study staff member who is waiting for interested clients in a nearby screening area. Interested clients will be screened for eligibility and, if eligible, scheduled for the informed consent process.

Note that it is possible that some individuals will be approached after they have already completed their regular (off protocol) clinic visit. To allow maximum flexibility, we may permit these individuals to enroll without having to repeat the full battery of STI tests required for study entry. This would be allowable if they provide permission for us to abstract their clinic record to verify that one or more of the STI tests in the study battery were completed on the day of study enrollment and allow us to record the tests, results and treatments (as applicable) in our study record. Under these circumstances, the individual would not be required to repeat a given verified STI test(s) to take part in the study. However, if the STI test(s) cannot be verified or if the individual desires, s/he may undergo the battery of STI tests to take part in the study.

5.4 Measures and Assessments

Table 1 presents a schedule for study activities and assessments. Study assessments will be conducted during a minimum of two points in time: 1) screening and baseline visit and 2) 6-month post-randomization follow-up visit. If a participant requests to break up study activities over more visits (e.g. written consent and STI testing in one visit and baseline assessment, randomization and intervention in a second visit), then this will be allowed, as the study timeline permits. 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 various criteria. Eligible individuals will be free to enroll in the study after providing written informed consent. Individuals who screen as ineligible will be 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. Some sites may elect to compensate individuals in the amount of \$5 for screening regardless of eligibility according to their local research practices.

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 the follow-up visit 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 throughout the study, as applicable.

HIPAA and/or Medical Record Release Forms: Participants will complete these forms (as applicable) in order to grant permission to study staff to review their STD clinic records, including HIV testing records and HIV primary care records. The purpose of medical records review is to document the HIV and STI tests, results and treatments needed to evaluate the primary and secondary outcomes. Additionally, we will abstract medical record information to corroborate participants' self-report of HIV diagnosis and utilization of HIV primary care and progression of disease. We will abstract records back to 30 days before study enrollment (as needed) to determine whether participants tested positive and received treatment for any STDs

or HIV shortly before entering this study. While participants are enrolled, abstraction will occur throughout the study (as needed).

5.4.3 STI Testing

After giving informed consent, participants will be screened for a battery of STIs. MSM will be screened for rectal and urine *Neisseria gonorrhoea* (GC), *Chlamydia trachomatis* (CT), *Treponema pallidum* (syphilis), and *Herpes Simplex 2* (HSV-2). Women will be screened for vaginal GC and CT, *Trichomonas vaginalis* (TV), syphilis and HSV-2. Men who have sex with women will be screened for urine GC and CT, HSV-2 and syphilis. Gonorrhea and chlamydia will be measured by Gen-Probe Aptima combined nucleic acid amplification test (NAAT) which will be performed on urine, vaginal and rectal specimens. *Trichomonas vaginalis* will be measured by validated Gen-Probe Trichomoniasis Analyte Specific Reagent (ASR). All participants will have blood samples drawn to screen for syphilis and HSV-2. The diagnosis of syphilis will be determined by clinical history, positive non-treponemal (RPR or VDRL), followed by positive treponemal antigen tests (TPPA or FTA-ABS). We will use the Focus ELISA to assess HSV-2 seropositivity. The subset of positive HSV-2 samples will be confirmed via Western Blot (WB). This WB tests for HSV-2 and HSV-1 concurrently. Therefore, we will receive and provide both HSV-2 and HSV-1 results according to standard clinical guidelines and practice. While not part of our study outcome, we will analyze the HSV-1 results to understand HSV-2 and HSV-1 co-occurrence.

Specimens obtained for STI testing will be collected at baseline and 6-month follow-up, processed, and results will be recorded according to standard clinical guidelines and practice. Serum specimens obtained for HSV-2 testing will be collected at baseline and at 6 month follow-up. Specimens will be shipped to a central laboratory for initial storage and testing. In order to economize, the 6 month sample will be run first, if positive or indeterminate, the baseline sample will then be processed. If the 6 month sample is negative, the baseline sample will be discarded. In the event that a participant is lost to follow-up and does not return for the 6-month visit, we will process the baseline sample, as funding permits. Doing so will allow us to ascertain the baseline prevalence of HSV-2 among study participants. For women, the vaginal swab used for TV will be shipped to a central laboratory for processing and TV testing. TV specimens will be shipped and processed regularly so that results can be reported to each of the sites and appropriate patient follow-up can occur.

After completion of study procedures, all participants will receive standard of STI treatment and follow-up according to local, state, and national STI treatment guidelines and standards of clinical care and practice. This may include, as per local practices, partner notification services, expedited partner treatment, and/or referral to additional medical or social services. STI and HIV test results will be recorded in both the medical and study records.

Lastly, a subset of Project Aware participants may provide additional biological samples for future testing. If participants are willing to take part in optional future studies related to STI and HIV, and resources for such studies are available, study staff will contact Project Aware participants to describe such future study opportunities.

5.4.4 Exit Interview

Staff will conduct a brief exit interview with participants after they complete their regular clinical evaluation with the non-study clinician. The purpose of the exit interview is to document and measure any intervention exposure that occurs off-protocol at the baseline visit. The exit interview will consist of a few questions that solicit information from the participant about whether or not his/her visit with the clinician involved discussion of sexual risk behaviors and steps to take to prevent contracting STDs and HIV.

5.4.5 Baseline and Follow-up Assessment Battery (ACASI)

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 will be used to minimize underreporting of risky 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; STD clinic 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.

Primary and secondary outcomes have been outlined in sections 10.3 and 10.4. Participants will be compensated for their time and effort dedicated to completing each of the baseline and follow-up visits. The following measures will be collected at baseline and 6-months post-randomization.

Sexual Risk Behaviors/Unprotected Sex:

We will use self-report data to evaluate the secondary 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 (Noar, Cole, & Carlyle, 2006). 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 have adapted 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.

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 include a minimal set of other variables to limit the length of the assessments and to conserve statistical power. These variables have been identified as important behavioral mediators that may be affected by the counseling intervention or have been shown to either moderate or mediate sexual risk behavior. They include the following items, most of which have established psychometric properties, that will be asked at baseline and 6-month follow-up: (1) demographics and socio-economic factors (e.g., employment, housing status); (2) *Condom Use Self-Efficacy Scale*; (3) attitudes towards HIV testing; (4) HIV and STI testing history; (5) health care utilization history; (6) quantity and frequency of drug use including alcohol, methamphetamine, cocaine, heroin, poppers, club-drugs, frequency and types of drugs injected, and sharing of drugs, needles, and other paraphernalia; (7) DAST-10 (Drug Abuse Screening Test) to identify patients currently abusing substances; (8) alcohol use in the past 30 days using the 3-item AUDIT-C (Alcohol Use Disorders Identification Test) and (9) the 10-item Centers for Epidemiologic Studies-Depression Short Depression Scale (CES-D 10) instrument. We will also ask participants at the 6-month follow-up whether they have been exposed to any HIV prevention interventions or counseling. 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 and Socio-economic Factors: 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, health care access and utilization, living arrangement including homelessness, 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 and STI testing history: HIV and STI testing history are important covariates to assess for the primary outcome. Individuals who have sought testing in the past 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 and STI 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. Additionally, we will ask about potential STI and acute HIV symptoms today and in the past 6 months. We will also ask whether the participant has disclosed presence of STDs or HIV to his/her partners and vice-versa.

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. 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 six-month assessment, with an appropriate adjustment to the time-period of recall. Additionally, we will measure if a participant is in drug 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, 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 study 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.

Drug Abuse Screening Test: The DAST-10 (Drug Abuse Screening Test) will be used to identify those patients that are currently abusing substances. This reliable and valid test was designed to be used in a variety of settings to provide a quick index of drug-related problems (excluding alcohol) by yielding a *quantitative* index of the degree of consequences related to drug abuse. Modeled after the Michigan Alcoholism Screening Test, the measurement properties of the DAST were initially evaluated using a clinical sample of 256 drug-alcohol-abuse clients (Skinner, 1982). The DAST-10 correlates very highly ($r = 0.98$) with the longer DAST-20 and has high internal consistency reliability for a brief scale (0.92 for the total sample and 0.74 for the drug-abuse sample). The DAST may be administered in a questionnaire, interview, or computerized format. Respondents are instructed that "drug abuse" refers to (1) the use of prescribed or over-the-counter drugs in excess of the directions and (2) any non-medical use of drugs. The DAST total score is computed by summing all items that are endorsed in the direction of increased drug problems. A score of 3 or more on the DAST-10 indicates the likelihood of substance abuse or dependence. Subsequent research has evaluated the DAST with various populations and settings including psychiatric patients (Coco, 1998; Maisto, Carey, Carey, Gordon, & Gleason, 2000; Staley & el-Guebaly, 1990), prison inmates (Peters et al., 2000), substance-abuse patients (Gavin, Ross, & Skinner, 1989), primary care (Maly, 1993), in the workplace (El-Bassel, Schilling, & Schinke, 1997), and adapted for use with adolescents (Martino, Grilo, & Fehon, 2000). Overall, these studies support the reliability and diagnostic validity of the DAST in diverse contexts.

Alcohol Use Disorders Identification Test: To assess alcohol use in the past 30 days, we will implement the 3-item AUDIT-C (Alcohol Use Disorders Identification Test). The AUDIT-C is a brief, modified version of the AUDIT, designed to measure alcohol consumption and identify active DSM-IV alcohol abuse or dependence and/or risk drinking in the last year via a three item, multiple choice screener. The AUDIT-C effectively identifies both non-drinkers and a wide range of hazardous drinkers, and in conjunction with the patient's alcohol treatment history, is an accurate identifier of active alcohol use disorder (Bush et al., 1998).

Smoking Index: We will use the Heaviness of Smoking Index (HSI) to determine participant's smoking habits. The HSI (Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989) consists of a two-item scale that assesses the number of cigarettes smoked per day, while using the time from waking to the first cigarette of the day, to assess how dependant a person is to cigarettes. An individual who smokes 30 minutes to their waking time, and who smokes 25 cigarettes per day on average is probably more dependent on nicotine and hence requires more treatment. The HSI scale was taken from a lengthier assessment of nicotine dependence, the Fagerstrom Tolerance Questionnaire (FTQ) (Fagerstrom, 1978) in which an 8-item self-report scale determined dependence levels. Responses are coded and added up to produce a total score, from 0-11, in which a lower score indicated a lower dependence, and a higher score (greater or equal to 7) indicated a higher dependence.

Depression: We will use the Center for Epidemiologic Studies-Depression Short Depression Scale (CES-D 10) which is a shorter version of the CES-D (Radloff, 1977). The CES-D was developed to measure symptoms of depression in community populations and measures depressive feelings and behaviors during the past week, with questions ranging from depressed mood, feelings of worthlessness, feelings of hopelessness, loss of appetite, poor concentration, and sleep disturbance. The CES-D 10 has demonstrated good predictive accuracy when compared to the full-length 20-item version of the CES-D and has shown an expected positive correlation with poorer health status scores and a strong negative correlation with positive affect (Andresen, Malmgren, Carter & Patrick, 1994) Subjects are asked to rate each item on a scale from 0 to 3 on the basis of “how often you have felt this way during the past week”: 0 = rarely or none of the time (less than 1 day), 1 = some or a little of the time (1–2 days), 2 = occasionally or a moderate amount of time (3–4 days), and 4 = most or all of the time (5–7 days).

Table 1
Schedule of Study Activities and Assessments

Study Activities/Measures	Screen	Baseline	6-month Follow-up
Verbal Informed Consent	X		
Screening	X		
Written Informed Consent		X	
Locator Information Form		X	X
HIPAA Form and/or Medical Record Release Form		X	
STI Testing		X	X
Group 1 or 2 Intervention		X	
HIV testing Informed Consent (as applicable)		X	
HIV Testing		X	X
Visit with clinician and STI/HIV treatment (as applicable)		X	X
Exit Interview		X	
Medical Record Release Forms (as applicable for HIV primary care)			X
Randomization		X	
*Medical Record Abstraction		X	X
The below measures (Demographics through Smoking) are captured via the ACASI			
Demographics	X	X	
Global sex behaviors		X	X
HIV and STI Testing Behavior		X	X
Attitudes Toward HIV Testing		X	X
Readiness for HIV testing		X	X
Readiness to use condoms		X	X
Attitudes toward safer sex		X	X
Global substance use		X	X
Injection risk behavior		X	X
Intervention Exposure			X

Depression		X	X
Utilization of Health Care		X	X
Utilization of HIV Care for Persons who test Positive			X
Alcohol and Substance use		X	X
Smoking		X	X
AEs/SAEs	To be collected any time post-randomization.		
Study Completion	To be collected upon formal drop out, investigator's removal or participant's study end date.		
*Abstraction of STI clinic records will begin approximately 3 weeks post-baseline and 3 weeks post- 6-month visit to allow ample time for STI test results to be processed and filed in the clinic record. Abstraction of HIV primary care records (as applicable) will begin as soon as possible after securing permission to abstract the records.			

5.4.6 Rapid HIV Testing, Confirmatory Testing, and False Positives

As previously indicated, participants will be asked to provide a separate consent for HIV testing if necessary depending on local/state guidelines. 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”). OraQuick rapid test is a single-use, test using whole blood to detect HIV antibodies. It has 99.6% sensitivity and 100% specificity. The rapid HIV test is intended for use as 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.

Participants whose test result is reactive (also known as “preliminary positive”) will receive a confirmatory HIV blood test that day. With a target sample size of approximately 5,000 study participants, some discordant results between the initial reactive rapid test and follow-up tests may occur. In this case, and per FDA guidelines, the follow-up test will be considered the gold standard for diagnosing HIV infection. During the study consent process, HIV testing consent process (as applicable) and the testing and counseling session (in both arms), participants will be advised of the possibility and meaning of discordant test results. STD clinics will follow the local/state standard for reporting positive HIV results, and participants will be notified of these guidelines as part of the informed consent process.

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 who test HIV positive in section 6.3 of the protocol). For this confirmatory HIV test, counselors will collect additional blood using a needle and test tube. 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. 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, another testing site, or a medical provider. The main study consent addresses 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 also be placed in medical records.

With a target sample size of approximately 5,000 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 repeated in one month per CDC guidelines.

5.4.7 Safety Assessments

Adverse events will be captured post-randomization as described in section 7.11.

5.4.8 Survey of Counselors and Intervention Recordings

As previously mentioned, we will conduct a brief survey of counselors (and back-up counselors) prior to 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 the two study interventions, 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. While intervention sessions will be audio-recorded for the purpose of monitoring intervention fidelity, they may also be analyzed to describe how the sessions were conducted. In addition, we will examine whether participation in the trial has a significant effect on counselor attitudes.

5.5 Follow-up and Retention

5.5.1 Follow-up Visits

All participants will be scheduled for follow-up visits at 6 months post-randomization and to receive any HIV and STI testing results that are not immediately available. At the follow-up, participants will complete an ACASI behavioral assessment regarding HIV test result receipt, sexual risk behaviors, and drug-using risk behaviors as well as complete the STI test battery and HIV testing (if not HIV-positive at baseline). Study staff will work closely with the STD clinic staff to determine the best times within a given target window to hold follow-up visits. 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 Team on a regular basis. The tracking sheet will contain the participant ID, baseline enrollment date and the associated follow up windows. A retention specialist and STD clinic retention staff will continually monitor the completed follow-up visit to ensure the visit is occurring within the allowable window period.

5.5.2 Enhancement of Retention

To maintain high statistical power and maximize the generalizability of results, we aim to retain a minimum of 85% of the 5,000 randomized participants 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 verified and updated regularly prior to the six-month follow-up visit 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 and telephone, reminders may be made via e-mail or text message according to participants' request and permission provided in the Locator Information form. In addition, staff will physically go to locations specified by participants on the Locator Information forms, as needed. Participant retention will be enhanced in several other ways as outlined below.

- We will employ one full-time retention specialist working across study sites that 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, the retention specialist will identify STD clinic-specific and cross-site barriers to retention and problem solve with STD clinic staff. This retention specialist will be based at the University of Miami and will keep the principal investigators and other co-investigators informed in the event that a higher level of intervention with a STD Clinic is needed.
- During the baseline 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 their follow-up visit 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 who do not have a phone.
- If the participant cannot come to the clinic, we will conduct the 6-month follow-up visit in the field, as permitted by local IRBs, local and state guidelines and available staffing.

6.0 TREATMENTS

After providing Informed Consent and subsequently completing the baseline assessment on ACASI, participants will be randomly assigned to one of the two treatment groups described below. Randomization will be stratified by site and within site by race/ethnicity, gender and by MSM vs. heterosexual among males. The DSC will prepare in advance computer-generated randomization sequences. 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-2 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-2 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/STI 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 discuss 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 participants 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 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 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 may 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 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 result. 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, letter or other means as specified on the Locator Information form 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 newly 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 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 visit (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.

At the 6-month follow-up, 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 and research assistants at each of the STD clinics will be trained on how to deliver the linkage intervention.

6.4 Counseling Quality Control

For quality control purposes, all study counselor/participant sessions in both arms (testing with RESPECT-2 counseling and testing with information only) will be audio-recorded.

Individual counselors at all study sites will be working with participants in both 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 both study arms and sites. The recordings to be reviewed will be randomly selected within each STD clinic 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 or research assistants to stop the recording at any time. Counselors and research assistants 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, research team members will work with the individual or site to improve and maintain adherence to the manualized counseling protocol. Additionally, fidelity raters may provide feedback to counselors on reviewed recordings to either support and reinforce appropriate counseling efforts or encourage the improvement of existing counseling skills.

On a weekly basis, STD clinic sites will send randomly selected session recordings to study fidelity raters. Fidelity raters will review the session recordings within 1-3 weeks 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.

6.5 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 \$90, although the specific amounts, format and distribution schedule will be determined by the participating STD clinic with the approval of the principal investigator, site investigator, and the corresponding IRB(s).

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 (excluding the initial eligibility screening) 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 form(s) 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. A separate consent form will be used for HIV testing as required by local/state regulations and IRB(s).

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 STD clinic 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

Trained QA monitors at the participating universities will conduct on-site visits to ensure study procedures are followed and study data are collected, documented and reported in compliance with the protocol, good clinical practice and applicable regulations. Monitors will audit, at mutually agreed upon times, regulatory and study documents, participant safety documentation, case report forms and corresponding source documents. Monitors will work with the investigators to verify that all site teams are trained and able to conduct the protocol appropriately. If monitors' review of study documentation indicates that additional training of study personnel is needed, the Lead Team will undertake or arrange for that training.

7.8 Data and Safety Monitoring Board

An independent NIDA 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 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 a departure from prescribed procedures and requirements outlined in the protocol that may compromise the participant safety, participant informed consent or rights, inclusion/exclusion criteria or study data and could be cause for corrective actions to rectify the violation or prevent it 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 eCRF. Additionally, each site is responsible for tracking and reporting Protocol Violations to their IRB as required by IRB regulations. The Principal Investigators, and the Data and Statistics Center must be contacted immediately if an unqualified/ineligible participant is randomized into the study.

The following event will not be considered a protocol violation in this study:

Randomized participants not providing complete locator information. As long as the participant has provided his/her name, address(es), and telephone number(s) and at least some contact information for at least two friends or family members, a protocol violation will not be incurred.

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 principal investigators and/or site investigators will obtain a federal Certificate of Confidentiality (CoC). The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating STD clinics 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)

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 eCRF. The AE eCRF is also used to record follow-up information for unresolved events reported on previous visits. A site principal 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 and STI test samples (e.g. irritation at the testing site); and
 - Additional adverse 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.

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 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 treatment, 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/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 6-months follow-up visit. 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

principal 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 PI (or designee) 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.

Quality assurance monitors will review the 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. 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 principal investigator (or designee) 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 and/or STI tests or intervention; follows a known response pattern to the HIV and/or STI 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) or designee 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 completed 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 Duke Clinical Research Institute (DCRI). The DSC will be responsible for developing the electronic case report forms (eCRFs), developing and validating the study database, ensuring data integrity, and training study staff and participating university staff on applicable data management procedures. A web-based distributed data entry model will be implemented. This system is 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 sites 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 PIs 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 Storage, Security and Access

The ACASI assessments (for baseline and follow-up) will run as web browser applications. Logging in to the applications requires a unique User ID and password. No data are stored on the local personal computer (PC), but are transmitted in real time to the database server at Nathan Kline Institute for Psychiatric Research (NKI), a secured server residing in the restricted-access NKI Computer Center. Note that NKI is subcontracted by the Duke Clinical Research Center (DCRI). For the CTN 0032 study (and other studies), DCRI was contracted by NIDA CTN to serve as the Data and Statistical Center (DSC) to establish systems for data

management, design and perform statistical analysis, and review and monitor the quality of data for this and other CTN trials. For this protocol, we will contract directly with DCRI for these services.

Transmission of data between the site's browser and NKI occurs over SSL, the standard 128-bit encrypted secured web protocol, which NKI guarantees with the use of a recognized third-party web server certificate. All laptops distributed to the sites for the ACASI will have hard drive encryption implemented; thus the drive is unreadable without the encryption password, protecting the data in case of loss of theft.

Individuals cannot access or change previously entered data through the web-based application. Other features of the ACASI to ensure data security include an audit log that records all changes to data, a time-out period which locks out idle browser sessions, software-enforced User ID and password policies, and secure, audited procedures for resetting forgotten passwords.

Paper-based information will be kept in on-site locked file cabinet(s) designated for study materials. Data collection instruments or forms containing participant names will be stored in separate secure locations from those instruments or forms containing participant research identification (RID) numbers, and both will be stored separately from the master list linking the RID and names. Paper-based information will be accessible only to study personnel who need access to the information for study purposes.

8.5 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 sites, 4) monitor preliminary analysis data cleaning activities, and 5) rigorously monitor final study data cleaning.

8.6 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 and the investigators to monitor the site's progress in responding to queries.

8.7 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 site is responsible for storing the research records for the studies in which they participate. In all NIDA sponsored studies, study records must be maintained for

three years (after data lock) or longer if specified by local institutions/agencies or FDA regulations.

8.8 Data Systems Training

The training plan for STD clinic 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, we will attempt to recruit counselors (including back-up counselors) from the existing staff of the STD clinics to deliver the study interventions. Priority will be given to counselors with HIV education experience. Procedures for training and administration of the study interventions will maximize adherence to each intervention. Counselors will attend a national training to receive training that will encompass administration of study procedures and facilitation of the interventions. Intervention manuals will be developed and provided at the national intervention trainings.

9.2 Training on Administration of Rapid HIV Test

The initial training on administration of the rapid HIV test using whole blood will be conducted locally and led by clinic staff or the clinics' standard trainers. 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. Study staff 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 (including back-up counselors) will be trained to deliver both 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 both interventions, the study is able to: (1) reduce the possibility of confounding intervention with facilitator effect; (2) deliver training in two interventions rather than one, to clinic facilitators; and (3) broaden the range of STD clinics that can participate, particularly small-staff programs. In addition, the study is able to provide the STD clinics with the benefit of training their staff on how to deliver participant centered HIV prevention counseling.

Intervention training will be facilitated by the lead investigative team. It will consist of a presentation and discussion regarding the content and counseling techniques involved in each of the two intervention groups as outlined below followed by break-out sessions in which counselors and research assistants 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-2 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.

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 research staff unable to attend the national training will be conducted at each local site in consultation with the lead investigators.

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 two 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 (approximately 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 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 the 6-month follow-up assessment interview. As part of the 6-month ACASI interview, we will ask participants if they have taken part in any HIV prevention discussions anywhere outside of this study.

10.0 STATISTICAL ANALYTIC PLAN

10.1 Objectives of the analysis

One primary hypothesis is proposed for this trial with the intention of testing whether 1) HIV rapid testing with brief prevention counseling and 2) HIV rapid testing with information only have different rates of incident STI at 6-month follow-up.

10.2 Randomization

Participants will be randomized to one of two treatment groups. Randomization will be stratified by site and within site, by race/ethnicity, gender and within males, by MSM versus heterosexual. The randomization procedure will be conducted in a centralized process through the Duke Clinical Research Institute (DCRI). Specifically, randomization schedules will be created by the study statistician for each randomization stratum 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 providing Informed Consent and subsequently completing the baseline assessment on ACASI and the STI testing, the site research coordinator (or designee) will perform the randomization. The research coordinator will contact the central randomization center to determine the appropriate condition for the site. The method of this notification will be by computer-assisted telephone. The research coordinator will enter the appropriate participant characteristics (site, participant ID, gender and ethnicity) by pushing appropriate telephone buttons. The treatment assignment will then be transmitted by computer voice (by telephone) and by fax or computer screen. The DCRI statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan.

10.3 Primary Outcome

STI INCIDENCE: The primary outcome is composite STI incidence (Yes/No) at 6-month follow-up in which a person is considered positive for STIs if they are positive on any tested STI.

10.4 Secondary Outcomes

Secondary Outcomes will include sexual risk behavior, being under the influence of substances and/or illicit drug use during sexual activity and cost/cost-effectiveness. The sexual risk and substance use behavior secondary outcomes 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) and sex while high on drugs or alcohol, which will be measured as the number of sexual occasions when substance use was involved. The cost analysis will consider the budgetary perspective of STD clinics, because decision makers in these programs may be unwilling to implement HIV counseling and testing unless they are reimbursed for costs

according to their clinic's budgetary guidelines. The cost-effectiveness analysis will be conducted from the societal perspective (Hall et al., 2008), taking into account the time and expenses incurred by participants. Cost-effectiveness from payer perspectives will be considered in secondary analyses.

10.4.1 Risky Sexual Behavior Secondary Outcomes

The sexual risk behavior secondary outcomes are all continuous variables and are all self-reported. Examples of the secondary outcomes to be tested are:

- a) Number of unprotected vaginal and anal sex acts with non-primary partners (all partners other than most recent primary) in the past six months
- b) Number of unprotected vaginal and anal sex acts with primary partner in the past six months
- c) Number of total vaginal or anal sex partners in the past six months
- d) Proportion of all vaginal and anal sex acts which involved drugs or alcohol in the past six months

10.4.2 Cost and Cost-effectiveness Secondary Outcomes

Cost Measures: To determine staff and participant time delivering and receiving the information or counseling session and testing, we will utilize data collected on case report forms that include start time and stop times. The self-reported session times will be independently validated when the study team fidelity raters review audio tapes representing approximately 10% of all sessions. We will use data collection tools that have been developed for a previous NIDA clinic trial (CTN 0032) to identify and measure the resources used for counseling training and quality assurance/fidelity assessment from study administrative records. During 1-2 day site visits, we will use structured interview guides adapted from guides used at CTN 0032 sites to collect data on site-level resources incurred for start-up activities, staff time that occurs outside of the intervention session but is directly related to the intervention, and overhead. To value personnel time, we will compare national average wage and fringe benefit rates to local wage and fringe benefit rates reported by the sites. The advantage of using national labor rates is that they provide a benchmark that can be adjusted uniformly to reflect different settings where the interventions might be implemented (Gold, Siegel, Russell, & Weinstein, 1996). Because some sites will use a staffing model in which HIV counseling and testing will be conducted by existing STD clinic staff members (not research staff), we assume that they can be deployed in other activities when not involved in implementing the intervention (i.e. no excess capacity). The cost of the rapid test will be the price paid by recipients of CDC funds for expanded rapid HIV testing. We will determine start-up costs, variable costs, and total costs (with overhead) by multiplying unit costs by the number of resource units consumed, and then calculate a cost per participant by study arm. Results will be reported as mean values and standard deviations, and differences between arms will be compared using chi-square and Fisher's exact test. Frequencies and percentages will be compared between sites and by individual cost element in order to identify outliers. Differences in costs by site and participant characteristics (e.g., age, gender) will be explored using multilevel modeling techniques. If we observe substantial skewness in specific costs, median values and inter-quartile ranges will be reported, and we will use Wilcoxon tests to compare medians and non-parametric bootstrap to compare means between study arms. We will also perform sensitivity analyses on costing assumptions that can vary by site location (e.g.

wage rates) or client volume (e.g., overhead).

Cost-Effectiveness: We will evaluate the cost-effectiveness of counseling and testing compared to information only and testing, by comparing the additional costs incurred in the counseling arm as described above with potential cost savings from the following sources: (1) avoided costs of treating STIs, (2) avoided costs incurred for individuals with untreated or ineffectively treated STIs, (3) avoidance of increased HIV transmission susceptibility with an STI and (4) lower HIV incidence due to risk behavior change. Table 2 summarizes this approach with representative data. STI treatment costs will be determined from the clinics and compared to published estimates, costs of complications of untreated STIs will be derived from the literature on the cost-effectiveness of STI screening, and data on HIV transmission risks will be from meta-analyses. We will use the results from the trial primary outcome to determine the impact of the counseling arm on reducing new STIs of each type, and multiply each of the STIs avoided by the weighted average cost of treated and untreated STIs (depending on the proportion likely to be treated in a non-research setting). This will provide us with an estimate of direct cost savings from the intervention. We will then consider the additional cost savings from avoiding HIV transmissions across a range of HIV incidence estimates, to determine the “threshold” incidence at which the intervention will be cost-saving. Secondary cases of STIs or HIV avoided among partners of the participants will not be considered in the primary analysis, but their impact can be estimated in a similar threshold analysis.

STD	Cost to treat (F=female, M=Male)	Long-term complications if untreated	HIV susceptibility multiplier
<i>Neisseria gonorrhoea</i>	\$37 (F), \$40 (M)	pelvic inflammatory disease, ectopic pregnancy, infertility, urethritis, epidymyitis	2.1
<i>Chlamydia trachomatis</i>	\$42 (F), \$45 (M)		
Syphilis	\$53	advanced disease**	2.2
HSV-2	\$800 (F), \$450 (M)	relapse, maternal-fetal transmission	2.5
<i>Trichomonas vaginalis</i>	\$46	preterm delivery	2.7
HIV	\$303,100	advanced disease**	1.5
*discounted lifetime cost from time of infection (Schackman et al. 2006)			
**maternal-fetal transmission is rare in the United States due to effective prenatal screening			

10.5 Overview of Analysis Plan

The primary outcome will be analyzed using logistic regression for the binary outcome, new diagnoses of STIs (Yes/No). The logistic regression analysis will predict 6-month STI incidence as a function of randomization group controlling for the baseline incidence of STI. The test of the

hypothesis will be based on a likelihood ratio test comparing the model with and without the indicator for randomization group.

ANCOVA will be used for the secondary continuous outcomes, number of sexual risk behaviors and number of sexual episodes involving substance use. For example, the number of sexual risk behaviors at 6 months will be the outcome and the level of sexual risk behaviors at the baseline assessment will be the only covariate. The STI outcome, the test of the hypothesis will be based on an ANCOVA type specification test comparing models with and without the randomization group indicator. Costs will be compared based on study records supplemented by site-level data collection as described above. All analyses will be performed under intent-to-treat (ITT) criteria.

The planned subgroup analyses will test for differences between sets of subgroups (MSM versus non-MSM, African American versus all other race/ethnic groups, men versus women, young (<25) versus older) on the difference in rates of STI by treatment status. Planned exploratory analyses will calculate effect-sizes for subgroups, defined by MSM, heterosexual male, female, all racial/ethnic categories, presence of STI at baseline and use of (any) substances during sex at baseline. Planned exploratory analyses will also examine the extent to which the covariates explain variability in outcomes. First, the baseline levels of condom use self-efficacy, substance use/abuse and depression will be assessed for any potential moderating (interaction) effects on the hypothesized outcomes. Second, the impact of the intervention on these same set of variables will be assessed. For any of these covariates that are affected by the intervention, additional analyses will examine the relationship between changes in these potential mediators and study outcomes. Note that true tests of mediation are not possible due to the lack of temporal precedence in these changes. Prior to all analyses the distributions of outcomes will be examined and the appropriateness of planned analysis strategies assessed. For example, sexual risk and drug use frequently have the characteristics of a count variable. If this is the case, the ANCOVA framework will be utilized within the context of a Poisson, Zero-inflated Poisson or a Negative Binomial model, depending on which has the best fit to the data.

Missing data is a ubiquitous problem in human subject research, primarily due to dropping out and refusal. Missing data can lead to biased estimates and reduction of power, impacting the generalizability of the study. While we will make every effort to minimize the amount of missing data, in follow-up analyses we will attempt to assess the impact of the missing observations. 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. If nonrandom missingness is of concern, this problem can be addressed by applying propensity-score matching so that the impact of bias can be assessed.

10.6 Statistical Power and Sample Size Calculation

All power calculations assume that the Type I error rate, α , is .05. Power calculations for main effects for treatment were made with PASS 2005. Power for interaction effects was calculated using a simulation program written in SAS 9.1.3. The original RESPECT study showed a significant effect of 6-month rate of new STIs which were 7.2% in the counseling arm and 10.4% in the didactic arm, for a difference of 3.2%. Though underpowered to be definitive, subgroup analysis of RESPECT-2 suggested that there is a differential effect of counseling on MSM compared to heterosexuals.

We therefore decided to power this study both to uncover a risk difference of 3.2% (with a higher base rate of STI incidence of 12.0%) and to have sufficient power to test for an interaction between MSM and non-MSM in which the ratio of risk ratios was approximately 2.0. Simulations showed that to have over 80% power for both the 3.2% risk difference overall and a 2 fold risk ratio interaction between MSM and other study participants required 1663 per group or 3326 total sample at the six month assessment. Although we anticipate closer to 85% follow-up, we used the conservative assumption of 70% retention for calculation of power. With the assumption of 70% retention, this means that 5000 must be randomized. Simulations assumed that 1/3 of the participants were MSM. Power for other, separate sub-group comparisons should be similar to that described above for MSM vs. non-MSM as long as the smaller subgroup in the comparison approaches or exceeds a third of the sample composition, which is consistent with the data we have obtained from the sites. For the secondary hypotheses of sexual risk behavior and substance use during sex there will be over 80% power to uncover a standardized difference between groups of .10, which is considered a small effect.

11.0 REFERENCES

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