HIV/STD SAFER SEX SKILLS GROUPS FOR WOMEN IN METHADONE MAINTENANCE OR DRUG-FREE OUTPATIENT TREATMENT PROGRAMS

(A companion protocol to: HIV/STD Safer Sex Skills Groups For Men In Methadone Maintenance Or Drug-free Outpatient Treatment Programs)

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Lead Investigator:	Susan Tross, Ph.D. – Long Island Node, N.Y. State Psychiatric Institute, N.Y., N.Y.
Co-Lead Investigator:	Donald Calsyn, Ph.D. – Washington Node, Puget Sound Health Care System, Department of Veteran Affairs, Seattle, Wa.
Project Manager:	Jennifer Manuel, C.S.W. – Long Island Node
Protocol Managers:	Aimee Campbell, M.S.S.W. – Long Island Node Lisa Cohen, Ph.D. – Long Island Node
CTP Collaborators:	Peter Benson, Psy.D. – Washington Node Al Cohen, M.A., M.F.T. – Pacific Node Janet Lerner, D.S.W.. – Long Island Node Paul McLaughlin – New England Node Deborah Orr, Ph.D. – Florida Node
Scientific Collaborators:	Anthony Floyd, Ph.D. – Washington Node Judy Harrer, Ph.D. – Ohio Valley Node Therese Killeen, Ph.D. – South Carolina Node Rob Malow, Ph.D. – Florida Node Edward Nunes, M.D. – Long Island Node Gloria Miele, Ph.D. – Long Island Node Eva Petkova, Ph.D. – Long Island Node Steve Shoptaw, Ph.D. – Pacific Node George Woody, M.D. – Delaware Valley Node Nabila El-Bassel, D.S.W. – HIV/STD Safer Skills Group Intervention Expert, Columbia University School of Social Work
Data Management:	Molly Carney, Ph.D. – Washington Node James Robinson, Ed.D. – New York, Long Island, Rocky Mountain Nodes
Design and Analysis:	Susan Silva, Ph.D. – North Carolina Node
Quality Assurance:	Karen Loncto, M.S. – Long Island Node
Training:	John Baer, Ph.D. – Washington Node Gloria Miele, Ph.D. – Long Island Node
Dissemination:	Elizabeth Wells, Ph.D. – Washington Node
Regulatory Affairs:	Jennifer Lima – Long Island Node
NIDA:	Ming Shih, Ph.D.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACASI	Audio Computer Assisted Structured Interview
AE	Adverse Event
AIDS	Acquired Immuno-deficiency Syndrome
ASI	Addiction Severity Index
CDCP	Centers For Disease Control and Prevention
CIDI	Composite International Diagnostic Interview
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DSMB	Data Management and Safety Board
DMAS	Data Management and Analysis Subcommittee
DMC	Data Management Center
HE	HIV education
HIV	Human Immuno-deficiency Virus
IRB	Institutional Review Board
ITT	Intent to Treat
MEM	Mixed Effects Models
MMSE	Mini-Mental State Examination
MMTP	Methadone maintenance treatment program
NIDA	National Institute on Drug Abuse
NIH	National Institute of Health
ODF	Outpatient Drug Free Treatment
RBS	Risk Behavior Survey
SADAR	Sex and Drug Abuse Relationship Questionnaire
SERBAS	Sexual Experiences and Risk Behaviors Assessment Schedule
SRPS	Sexual Relationship Power Scale
SSB	Safer Sex Skills Building Group Intervention
SOP	Standard Operating Procedure.
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection

SYNOPSIS

Study Objectives: Drug treatment, itself, has been a powerful deterrent to HIV drug use risk behavior. However, sexual risk behavior has received less attention and has been slower to change. The proposed study will bring El Bassel's and Schilling's (Schilling et al., 1991; El Bassel and Schilling, 1992) proven, manual driven, gender-specific safer sexual skills building (SSB) intervention to frontline drug abuse counselors in methadone maintenance (MMTP) or outpatient drug-free treatment (ODF). The proposed study is intended to test the effectiveness of El Bassel's and Schilling's safer sexual skills building group intervention to reduce unprotected sexual risk behavior in sexually active women in MMTP or in drug-free outpatient treatment. Due to the need for comparable interventions for male drug users in treatment, the proposed trial is intended for simultaneous implementation with its companion protocol for men. The concurrent delivery of 2 parallel protocols is planned as a streamlined, cost-effective way to carry out both protocols with shared research staff, materials and resources.

Study Design: The study will use a randomized trial to test the effectiveness of the 5 session safer sexual skills building group intervention, as compared to a 1 session group standard HIV education intervention (HE) comparison condition. A repeated measures battery will be administered at 4 points: 1) baseline; 2) immediate post- intervention (i.e. for secondary efficacy and intervention fidelity measures only); 3) 3-months post-intervention; and 4) 6-months post-intervention.

Subject Populations: Subjects will be approximately 480 women (i.e. 240 women/intervention condition) in methadone maintenance (N=240) or drug-free outpatient treatment (N=240) who fulfill criteria for being at heightened risk for HIV/STD heterosexual transmission. Inclusion of both MMTP and ODF will provide the opportunity to reach 2 important subgroups of female drug users: those whose primary substance of abuse is heroin (MMTP); and those whose primary substance of abuse is likely to be stimulants, alcohol or multiple drugs (ODF).

Eligibility Criteria: The eligibility criteria are: any unprotected penetrative (vaginal or anal) intercourse with a male partner within the past six months; capacity to give informed consent; and 18 years of age or older. Exclusion criteria are: 1) observable, gross mental status impairment – including severe distractibility, incoherence or retardation; 2) immediate plan to become pregnant, and 3) MMTP participant enrolled in methadone treatment for less than 30 days.

Study Interventions: There are 2 interventions. SSB is characterized by 3 defining features of effective HIV sexual prevention programs for women, identified in a comprehensive literature review (Exner, Seal and Ehrhardt, 1997). These are: (1) gender specificity; (2) use of (cognitive, behavioral and affective) skills building; and (3) relatively high intensity (i.e. $\geq$ 4 sessions). It is a 5 session (90 minutes per session) skills building group, consisting of: HIV risk assessment, HIV safer sex obstacle problem solving, condom use skill building, negotiation skill building, and assertiveness training. The HIV education condition will consist of a single 60-minute session using the HIV/STD education offered in the initial SSB intervention session. Female CTP counselors will provide both manual-driven interventions in groups of approximately 3 – 8 women. These features make technology transfer to CTPs highly likely.

Outcome Measurement: The primary outcome will be number of unprotected (vaginal or anal) penetrative intercourse occasions during the 3-month and 6-month follow-up periods. Secondary outcomes will include: proportion of drugs or alcohol with sex occasions of all sex occasions; proportion of unprotected sex occasions (of all sex

occasions); carrying condoms; perceived self-efficacy to carry out safer sex; and gender role beliefs. Possible intervention mediators will include extent of perceived self-efficacy to carry out safer sex and extent of observable condom use or negotiation skills. Possible moderators will include frequency of drug use and extent of current partner abuse, extent of perceived barriers to safer sex, and monogamy status. Mixed effects modeling (MEM) will be used to test differences in the primary and secondary outcomes between the 2 conditions on repeated measures, while examining possible differences between individual programs, and differences between women in monogamous versus non-monogamous relationships. Analysis of number of penetrative intercourse occasions that are unprotected will permit identification of the possible impact of intervention to reduce this risk behavior in the sample.

PROTOCOL SCHEMA
FIGURE 1

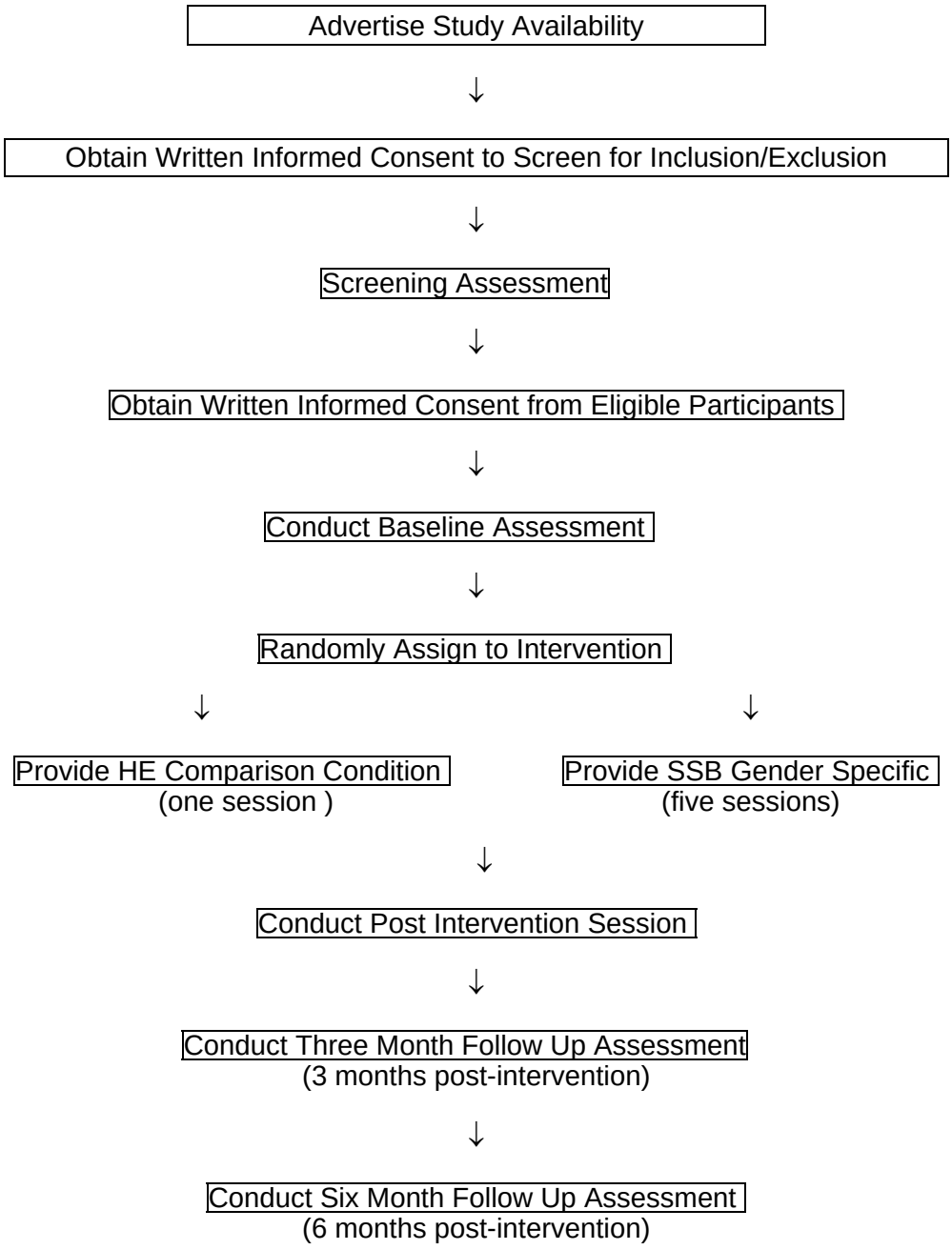


TABLE 1: STUDY FLOW CHART

Protocol Number 0019						
Study Activity	Visit 0	Visit 1	TX Session 1-5[a]	Visit 2	Visit 3	Visit 4
	Day #	Day #	Day #			
Consent for screening assessment	1					
Screening assessment	1					
Obtain written informed consent	1					
Conduct baseline assessment		1-30				
Randomization of cohort			When 3 participants (but no more than 8) are in the cohort			
Attend intervention session(s)			Start approx day 8-36, attend over 1 or 3 weeks			
Conduct post intervention assessment				21 days after 1st treatment session		
Conduct 3 mo. Follow up assessment					15 weeks after 1st treatment session	
Conduct 6 mo. Follow up assessment						27 weeks after 1st treatment session

1.0 Introduction

1.1 Background

1.1.1. Scope and Nature of HIV Sexual Risk

Women in high drug use communities are currently among the fastest growing groups of people with AIDS in the U.S. While the proportion of female AIDS cases due to injection drug use has declined from 39% to 28% in the past few years, the proportion due to heterosexual transmission has rapidly increased to 40% in the same period. In 28% of these cases, the infected man is an IDU; in 66% the transmission factor of the man is unknown, and could represent additional transmission from IDU partners (CDCP, 2000). Among all female AIDS cases for whom lack of an identified risk factor was systematically investigated, 68% were later attributed to heterosexual transmission (CDCP, 1999). At the same time, heterosexual transmission also carries the risk of infection with other STDs. Although data are only available on rates of STDs among young (i.e. 15 to 24 year old) female state family planning clinic attendees and 16 to 24 year old, female U.S. Job Corps entrants in 1998, these rates suggest that chlamydia may be a significant problem among women in high drug use communities. In state family planning clinics, rates of chlamydia ranged from 2.4% to 11.3%. In the U.S. Job Corps, rates ranged from 4.6% to 20.3% - with higher rates occurring among poor, younger women (CDCP,1999).

Female drug users, even if they are in drug treatment, are at especially high risk for heterosexual transmission of HIV. First, they are often in primary sexual relationships with male drug users. Second, like their male peers, despite treatment, some may actively use drugs, either the one they are being treated for or others (Ball and Ross, 1991). Under the influence of drugs, especially cocaine or crack, they are vulnerable to hypersexuality, disinhibition, and barely resistible drug hunger that can compel them to trade sex for drugs. (DeHovitz, Kelly, Feldman, et al., 1994; Edlin, Irwin, Faruque, et. al, 1994)

1.1.2. CTN HIV Snapshot

Third, although drug treatment, itself, has been a powerful deterrent to HIV drug use risk behavior (Metzger, Navaline and Woody, 1998; Sorenson and Copeland, 2000), sexual risk behavior has received less attention, and has been slower to change. The CTN-HIV Workgroup conducted a ‘snapshot’ survey of CTN CTPs’ HIV assessment and prevention practices in spring 2001. Most programs (80.4%) provide some type of HIV education to all clients. Of those that did not, most provided HIV education to clients deemed to be at high risk for HIV. For most programs (85.4%), the amount of education provided ranged from 30 to 90 minutes, delivered in a single group or individual session. The bulk of the education delivered is limited to providing information. Skills building interventions, using tools such as role-plays, were infrequent.

1.1.3 Efficacy of Gender-Specific HIV Skills Building Intervention

Despite these obstacles, drug treatment offers one of the best opportunities to engage women in programs to improve self-care, including HIV/STD safer sexual behavior. It is a rare context for their ongoing participation in therapy, alongside of female peers - in lives that are otherwise chaotic and disenfranchised.

El Bassel's (El Bassel and Schilling, 1992) and Schilling's (Schilling et al., 1991) HIV safer sexual skills building intervention with female methadone maintenance treatment program (MMTP) patients offers an efficacious, manual-driven model for use in CTPs. It embodies three defining features of effective HIV sexual prevention programs for women, identified in a comprehensive literature review (Exner, Seal and Ehrhardt, 1997). These are: (1) gender specificity of intervention content and technique; (2) use of (cognitive, behavioral and affective) skills building, in contrast to information only; and (3) relatively sustained dosage (i.e. consisting of a minimum of four sessions). El Bassel and Schilling (Schilling et al., 1991; El Bassel and Schilling,1992) used a randomized trial to compare: (1) a five-session skills building group consisting of HIV risk assessment, HIV safer sex obstacle problem-solving, condom use skill building, negotiation skill building, and assertiveness training; and (2) one session HIV education. They obtained significant increases in frequency of condom use, frequency of taking condoms from open clinic supplies, and strength of perceived self-efficacy to negotiate safer sex and of other preventive attitudes in the skill-building condition, as compared to the education condition, at immediate (i.e. two week) post-intervention follow-up (Schilling et al., 1991). At 15-month post-intervention follow-up, significant differences in frequency of condom use and strength of perceived self-efficacy and of other preventive attitudes between conditions still held (El Bassel and Schilling, 1992). Their results contrast with lack of significant effects on safer sexual behavior of other intervention trials that included male and female participants and/or used shorter durations of intervention, and may have produced significant decreases in drug use and needle use risk behaviors (Calsyn et al., 1992a, 1992b; McCusker et al., 1993).

At the same time, we are keenly aware that men, especially male drug users, who have sex with women, whether heterosexual or bisexual, are, by definition, essential participants in the heterosexual transmission process. Like their female partners, they enter sexual relations with powerful constraints on mutual, negotiated, safer sexual behavior of their own. Like their female peers in drug treatment, despite the best intentions of under-resourced drug treatment programs, they also often lack exposure to interactive, interpersonal skills-based, gender-specific safer sex interventions that are most likely to make a difference. Therefore, there is a pressing need for parallel interventions with these features explicitly tailored for and carried out with men. This need will be separately detailed in a separate, but parallel and intended to be concurrent, protocol for men.

2.0 Study Rationale

Due to heterosexual transmission, female drug users remain at heightened risk for HIV and STD infection. For them, as well as their male peers, drug treatment, itself, has been a powerful deterrent to HIV drug use risk behavior. However, sexual risk behavior has received less attention and has been slower to change. Because of the complex role that sexual behavior plays in heterosexual relationships, safer sex intervention must proceed from multiple priorities for change in: (male and female) condom use; problem-solving and decision-making skills; communication skills; and drug relapse prevention skills. Because of the distinctly passive nature of the female gender role and the salience of male-controlled condom use as a recommended safer sex strategy, safer sex intervention for women must impart new values and new levels of self-confidence as well as new behaviors for being in heterosexual relationships. In order to do this effectively,

this intervention must be gender-specific, active, and intensive. Due to the need for comparable interventions for male drug users in treatment, the proposed trial is intended for simultaneous implementation with its companion protocol for men. The concurrent delivery of 2 parallel protocols is planned as a streamlined, cost-effective way to carry out both protocols with shared research staff, materials and resources. The companion protocol for men will be separately detailed in its own document.

3.0. Objectives and Hypothesis

3.1 Primary Objective

The proposed trial is intended to test the effectiveness of El-Bassel's and Schilling's five-session safer sexual skills building group (SSB) intervention for female patients in MMTP or in drug-free outpatient treatment. The effects of this intervention will be compared to those of 1 standard group HIV education session (HE). There will be one primary outcome: number of unprotected (vaginal or anal) penetrative intercourse occasions within the prior 3 months. It is hypothesized that women in the SSB intervention will decrease their number of unprotected penetrative sexual behaviors at 3 and 6 month follow up assessments significantly more than women in the HIV education intervention.

3.2 Secondary Objective

Secondary outcomes will include: proportion of drugs or alcohol with sex occasions of all sex occasions***;*** proportion of unprotected sex occasions (of all sex occasions); carrying condoms; perceived self-efficacy to carry out safer sex; and gender role beliefs. It is hypothesized that women in the SSB intervention will decrease their proportion of drugs or alcohol with sex occasions (of all sex occasions), decrease their proportion of unprotected sex occasions (of all sex occasions), increase their condom carrying, increase their sense of self-efficacy to carry out safer sex, and increase their endorsement of egalitarian gender role beliefs significantly more than women in the HIV education intervention.

4.0 Study Design

The proposed study will use a randomized trial to assess the relative efficacy of a five-session safer sexual skills building group intervention, as compared to a single HIV education session for current female patients in MMTP or in ODF. Subjects will be approximately 480 women (i.e., 240 women/intervention condition) in MMTP (N = 240) or outpatient drug treatment (N=240) who have had unprotected (vaginal or anal) penetrative intercourse with a male partner within the past 6 months. A repeated measures battery will be administered at four points: 1) baseline; 2) immediately post-intervention; 3) three-months post-intervention; and 4) six months post-intervention. The schema for the study design is presented in Figure 1. Clients in treatment will be invited to complete the screening interview for the study via several channels, including advertisements and flyers, announcements by counselors, and general clinic announcements. Individuals meeting the study inclusion criteria and agreeing to participate will provide written consent and be administered the baseline assessment battery. After completing the baseline assessment, participants admitted to the study will be placed into an open cohort of subjects waiting for randomization. The cohort will close once there are at least 8 women in the cohort or four weeks has passed since the first subject was placed in the cohort. In the event that 3 participants have not been

recruited in four weeks, the window will stay open until at least 3 participants have been recruited. Once closed, subjects will be randomly assigned to attend either the five SSB intervention or the one session standard HIV education intervention. Participants who drop out of the study prior to notification of randomization will be replaced since it is assumed dropping out is not related to randomization outcome. The use of a single HIV education session as a comparison is intended to serve as a standard-of-care condition reflecting the current day-to-day practice of most CTPs as reflected in the CTN snapshot described in section 1.1.2. The proposed design does not control for attention differences between the (5-session) SSB intervention and the (single-session) HE intervention. The protocol development team chose the single-session standard-of-care comparison over a possible attention-placebo condition because of its closer fit with actual CTP practices. A repeated measures battery will be administered at four points: 1) baseline; 2) immediately post intervention; 3) three months post intervention, and 4) six months post intervention. Follow up data will deemed to be collected on time if it is collected within 14 days prior to or 30 days after the scheduled date for 3-month and 6-month follow-up and within 14 days after the scheduled date for the immediate post-intervention follow-up. There will be one primary outcome: number of penetrative intercourse occasions that are unprotected. Secondary outcomes will include: proportion of drugs or alcohol with sex occasions of all sex occasions; carrying condoms; extent of perceived self-efficacy to carry out safer sex; and gender role beliefs.

5.0 Study Population

5.1 Number of Sites and Subjects

The study will be carried out in approximately 6 MMTPs and 6 ODFs who can each provide about 40 sexually active women, who have had unprotected penetrative intercourse with a male within the last 6 months. As much as possible, the same sites will also participate in the companion protocol for men. Final site selection will occur only after the protocol has been certified, and will observe CTN/CTP procedures for protocol selection. Site selection will be guided by the goal of obtaining diversity – in terms of ethnicity, region and primary drug of abuse.

Subjects will be approximately 480 women (i.e. 240 women/intervention condition) in MMTP (N = 240) or outpatient drug treatment (N=240) who fulfill criteria for being at heightened risk for HIV/STD heterosexual transmission. This will include women of all racial and ethnic groups. Inclusion of both MMTP and other outpatient drug treatment will provide the opportunity to reach two important subgroups of female drug users: those whose primary substance of abuse is heroin (MMTP); and those whose primary substance of abuse is likely to be cocaine or other stimulants (outpatient drug treatment). In as much as women often face a distinct set of powerful obstacles to safer sex - especially associated with gender role pressures (for interpersonal and sexual submissiveness), gender role responsibilities (for motherhood and childrearing) and vulnerability to domestic violence, - restriction to women only is an essential feature of the skills building intervention. It is under these conditions that El-Bassel (El Bassel and Schilling, 1992) and Schilling (Schilling et al., 1991) proved its efficacy. As such, it has the disadvantage of excluding men. The companion protocol for men will offer a comparable trial of a gender-specific intervention to men in the same settings.

Subjects will be recruited through a number of vehicles, as appropriate at each site. Recruitment may include posters and fliers conspicuously placed in CTP waiting rooms; announcements about the study to clinic patients, and directly through a participant's individual counselor. These will invite all women to see the research assistant situated in the CTP, or to call the study phone or voicemail.

5.2 Duration of Study and Visit Schedule

The Study Flow Chart presents the timetable for all visits and research activities of the study. Once the protocol has been certified, it is anticipated that about 3-6 months will be required to enroll and prepare sites for subject recruitment. It is anticipated that subjects will be recruited over approximately an 8-12 month period. After final subject enrollment, about 9 months will be required to complete follow-up assessment. Data analysis and dissemination of findings will be completed over the following year. Based on this timetable, at least 33 months will be required to complete the study.

5.3 Informed Consent

Written informed consent for study participation will be obtained at 2 key points: screening and entry into the main intervention trial. The staff member and the patient will discuss the basic features described in the informed consent form. These include: voluntary nature of participation and freedom to withdraw without consequences to clinic services received, purpose, procedures, randomization, confidentiality, risks and benefits. It also notifies the participant that all study interviews and treatment sessions will be audiotaped for supervisory and quality assurance purposes. A copy of the protocol consent forms are provided in the appendix.

5.4 Inclusion Criteria

The eligibility criteria are: unprotected penetrative (anal or vaginal) intercourse with a male partner within the past six months; 18 years of age or older; capacity to give informed consent, as demonstrated in discussion with the research assistant or site coordinator introducing the study; and active participation in substance abuse treatment . It should be noted that unprotected oral sex was considered and rejected as an inclusion criterion by the protocol development committee. This was based on recent evidence that it is a low risk behavior for HIV transmission (Page-Shafer, Osmond and Ball et al., 2002).

5.5 Exclusion Criteria

Exclusion criteria include: 1) immediate plan to become pregnant; 2) observable, gross mental status impairment including severe distractibility, incoherence or retardation, and 3) MMTP participant enrolled in methadone treatment for less than 30 days.

5.6 Subject Discontinuation Criteria

Subjects are free to withdraw at any time from the study without consequence to their drug abuse treatment in their CTP. During the treatment phase of the study, a patient may be discontinued from the study for a variety of reasons. These include: a serious adverse experience which places her at risk if study participation is continued; serious concurrent illness; or non-compliance with clinic policy or study protocol. Although we anticipate it will be a rare event, a potential problem would arise if a participant drops out of substance abuse treatment (or is discharged from treatment), but wishes to continue attending the protocol intervention to which she is assigned. Since the intent of the

study is to evaluate the interventions conducted within treatment programs these individuals will not be allowed to attend intervention sessions, but will be followed to complete follow up assessments. In addition these individuals will be referred to community resources for HIV prevention information if so desired.

5.6.1 Required Termination

Subjects must be withdrawn if participation is determined to be harmful to them, in the opinion of the Protocol PI, CTP Site Coordinator, Lead Investigators, IRB, or CTN DSMB. The possibility of abusive partner behavior and/or a marked increase in emotional distress are the foreseeable adverse effects of participation. Recognition of and intervention for this possible problem is discussed in sections 8.5 and 9.1.3. It is anticipated that subject discontinuation due to perceived intervention detriment will be rare.

5.6.2 Consideration of Early Termination

The Lead Investigators, the Protocol PI, CTP Site Coordinator, IRB, or CTN DSMB may decide to discontinue a subject's participation, if it poses a significant risk to her well-being. The possibility of abusive partner behavior and/or a marked increase in emotional distress are the foreseeable adverse effects of participation.

5.6.3 Procedures for Discontinuation

A subject choosing to withdraw from study, of her own accord, will inform the staff, and be withdrawn, as requested. Such subjects will not be contacted to obtain follow-up assessments.

A subject who is judged, by clinical or research staff, to be placing herself at serious risk for harm by continued study participation will be asked to meet with the CTP Site coordinator and the subject's therapist(s) jointly. The subject, CTP study site coordinator and the subject's therapist(s) will discuss the pros and cons of participation. If the subject chooses to continue, while the coordinator continues to view intervention participation as detrimental, the subject will be withdrawn from intervention but retained in follow-up assessment. As discussed in sections 8.5 and 9.1.3, subjects who are being discontinued will receive crisis intervention from the CTP Site Coordinator and referral for ongoing abuse-protective services, psychiatric treatment and/or other services as needed.

5.7 Replacement of Subjects

Subjects who withdraw from study after notification of randomization will not be replaced and will be included in all statistical analyses according to the intention to treat (ITT) design.

6.0 Study Treatments

6.1 Study Therapies

There are two intervention conditions in the proposed study: 1) five-session SSB group; and 2) a single standard-of-care HIV education session, serving as a comparison condition. Both interventions will be carried out by CTP female drug treatment counselors who receive approximately 20 hours of training. In El-Bassel's and Schilling's

studies, skills building intervention training required 20 hours. Both interventions are manual-driven. These two features will make ongoing technology transfer to the CTPs highly likely. The HE condition consists of one approximately 60-minute session, while the SSB will consist of 5 approximately 90-minute groups. Each condition will consist of 3-8 women. Each intervention condition will be run by two female co-leaders.

6.1.1 HIV Education (HE)

This intervention will consist of the HIV information covered in the first session of the SSB intervention using discussion, flip chart visual materials and informational and resource handouts. This will be an approximately 60 minute group session covering: HIV definitions, transmission, testing and counseling, treatment, and prevention. Certificates will be distributed at the end of the session. Participants will be paid for their attendance to the treatment groups. Reasonable and non-coercive reimbursement sums will be determined on a site-by-site basis. Women will be paid in cash or vouchers (as determined by the CTP) for their participation. It is recommended that participants are paid only if they attend the majority of the session (40 minutes), although the decision to do this may vary based on local IRBs. Paying participants to attend treatment sessions calls into question the issue of sustainability. In the CTPs, patients are not paid to attend sessions. The current protocol is voluntary research. It is the investigators' experience that it is difficult to attract a wide distribution of patients at voluntary sessions without monetary incentives. If the SSB intervention proves efficacious, then CTPs could make it a mandated part of treatment and, thus, eliminate the need for incentives.

6.1.2 Safer Sexual Skills Building (SSB)

This intervention will consist of 5 approximately 90-minute group sessions. Participants will be paid for their attendance to the treatment groups in cash or vouchers. Reasonable and non-coercive reimbursement sums will be determined on a site-by-site basis. It is recommended that participants are paid only if they attend the majority of the session (60 minutes), although the decision to do this may vary based on local IRBs.

Primarily through active problem-solving, behavioral modeling, role play rehearsal, interval practice, troubleshooting, and peer feedback and support, this intervention will build cognitive, affective and behavioral skills for safer sexual decision making and behavior. The 5 sessions entail:

1) Using discussion, flipchart visual materials, and informational and resource handout materials, the counselor will conduct a 90 minute session covering: HIV/STD definitions, transmission, testing and counseling, treatment, and prevention.

2) Using discussion, flipchart visual materials, risk vignettes, and risk assessment worksheets, women will assess their own personal risk for HIV/STDs. Using discussion, flipchart visual materials, HIV sexual risk behavior and alcohol and drug use vignettes and triggers assessment worksheets, women will identify the internal and external triggers to HIV sexual risk behavior. Particular emphasis will be placed on the role of (1) partner pressure, threat and abuse; and (2) alcohol and drug use effects. Women will also identify sources of support for safer sexual behavior and ways of seeking their help.

3) Using discussion, flipchart visual materials, and male and female genital models, women will: a) observe male and female condom handling, insertion and removal; b) rehearse these skills; and c) give feedback about these methods. Women will use the SODAS (stop; options; decide; action; self-praise) problem-solving model to brainstorm constructive responses to HIV sexual risk and drug use vignettes. Women will identify

adverse effects posed by safer sexual behavior and negotiation for them. Particular emphasis will be placed on risk of partner violence, sexual abuse and verbal abuse, relationship break-up, and relationship strain.
4) Using safer sexual behavior and safer sexual negotiation vignettes women will: a) observe behavioral modeling of a range of action options including planned passivity, cajoling, assertiveness, frank withdrawal and other options; b) brainstorm pros and cons of these options; c) problem-solve courses of action for these options; and d) rehearse these skills in role plays. Women will identify adverse effects posed by safer sexual behavior and negotiation for them. Particular emphasis will be placed on risk of partner violence, sexual abuse and verbal abuse, relationship break-up, and relationship strain.
5) Using flipchart visual materials and "take home message" worksheets, women will wrap up and summarize the major action options they have identified during the intervention. Through the use of unsafe sexual behavior vignettes, women will become familiar with cognitive-behavioral techniques for "breaking" drug and alcohol use and/or unsafe sexual behavior slips before they become full-blown relapses. Resource handouts, especially for dealing with partner violence, seeking HIV/STD testing and counseling, and seeking women's activism organizations will be reviewed. A graduation ceremony will be held, and certificates will be given.

6.2 Selection and Training of Therapists

Therapists will be recruited from the counseling staff of the CTP sites to deliver both study interventions. Priority will be given to counselors with group therapy and/or HIV education experience. Two therapists will be trained in each site. If there are less than two interested and available counselors, the CTP Study Coordinator will recruit therapists from the community. As described in section 6.3.3, procedures for training and administration of both study interventions will maximize adherence to each therapy, respectively. Using the intervention manuals, the therapists will receive 20 hours of training. Training will also include self-observation and self-restraint in limiting discussion of SSB intervention material strictly to the intervention sessions for which it is intended. HIV safer skills building group intervention training will be conducted by the Lead Investigator and a member of the intervention author's (Nabila El-Bassel, Ph.D.) team. Training for therapists unable to attend the Lead Investigator training will be conducted at each local site in consultation with the Lead Node.

We acknowledge the possible advantage, to protect the discreteness of each condition, of using distinct facilitators. Nevertheless, we judge the advantages of using same facilitators to outweigh those. We propose that, in using same facilitators, we: (1) reduce the possibility of confounding intervention with facilitator effect; (2) deliver training in two interventions rather then one, to CTP facilitators; and (3) increase the range of CTPs who could participate –particularly small-staff programs.

6.3 Administration of Study Therapies

The SSB intervention will be delivered in 5-1 ½ hour group sessions, on a twice-weekly basis, over a consecutive 3-week period. The HE intervention will be delivered in 1 hour group session.

6.3.1 Randomization

The randomization will be within strata (CTP site). According to CTN coding, each site is a separate program or location. Separate block randomization schedules will be

developed for each CTP. This randomization scheme was chosen over individual randomization in order to hold the waiting time to group intervention to 4 weeks post baseline assessment. Under an individual randomization plan, excessive waiting periods might be necessary in order to accumulate enough subjects to conduct an intervention group. It should be noted that this randomization scheme poses the potential problem of imbalance between intervention conditions – in the event that a CTN sample (N = 40) is fulfilled by 5 cohorts of 8 subjects.

In each participating CTP clinic site, we will initially use block randomization to randomly assign our target (N=40) subjects to our intervention conditions in 6 cohorts. After baseline assessment, subjects will be placed into an open cohort awaiting randomization to one of the two intervention conditions. Randomization will be carried out either: when a cohort of 8 women has been recruited; or 4 weeks has passed since the first subject was placed in the cohort, whichever comes first. In the event that 3 participants have not been recruited in four weeks, the window will stay open until at least 3 participants have been recruited. Once closed, the cohort will be randomly assigned to one of the two intervention conditions – either the one receiving SSB intervention or the other receiving HE. If recruitment is rapid, a site may exceed the target of N=40 in 6 cohorts, up to approximately 48 subjects. If recruitment is slow, and <40 subjects have been randomized, we will initiate a second block randomization. If < 29 subjects (or an average of <5 subjects/group) have been recruited, a block randomization schedule for 4 more cohorts will be used. If 29 – 34 subjects have been recruited in the initial 6 cohorts, a block randomization schedule for 2 more cohorts will be used. If 35 – 39 subjects have been recruited in the initial 6 cohorts, 1 additional cohort will be randomly assigned.

Randomization will be managed through an outside independent randomization service provided by the Perry Point Cooperative Studies Coordinating Center (PPCSPCC). The PPCSPCC has designed and developed a centralized, automated telephone system to randomize subjects into clinical trials. Study sites access the system using a pre-specified phone number and respond to a series of prompts regarding the subjects' eligibility. After the system verifies subject eligibility, it assigns each subject a treatment assignment. Randomization can be done 24 hours a day, 7 days a week. Following each randomization, a fax notification is automatically sent to the site and others as needed. The system has also been programmed to send summary reports on a weekly basis.

6.3.2 Blinding

Both therapist and subject blinding to intervention condition is not feasible. An effort will be made to keep research assistants conducting assessments blind to intervention condition and the plan for balancing number of cohorts assigned to each intervention condition within each CTP site.

6.3.3 Quality Control of Therapies Administered

Quality control of both interventions will be maintained through 4 procedures. These include: 1) Interventions guided by detailed, written intervention manuals – on which training and ongoing administration will be based; 2) Audiotaping of intervention sessions (audiotapes will be reviewed by the Study Counselor Supervisor and/or the CTP Study Site Coordinator or designee; adherence or deviation from manual will be documented and discussed with the therapist during supervision); 3) Completion of fidelity questionnaires by subjects at each follow up assessment interview – to document

exposure to elements of either intervention condition; and 4) Completion of questionnaires by therapists about content covered and activities conducted – to compare to intervention manual specifications.

It should be noted that the risk of contamination of HE sessions from the therapist's SSB training is also minimized by the lack of time in the HE session to include any activities other than the curriculum provided for this session.

7.0 Concomitant Therapy

7.1 General Considerations

During part or all of subjects' participation in the study, they will be participants in their substance abuse treatment. This may include discussion of HIV risk and/or preventive behavior. Subjects 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. In order to account for these activities, they will be documented through fidelity measures administered to subjects at each follow up assessment interview.

7.2 Therapies Prohibited During The Study

No concomitant therapies are prohibited during the study. Therapists providing the SSB intervention will be instructed to not bring the techniques unique to it into individual sessions during the trial. Subjects will be asked about such exposures on the fidelity measure.

8.0 Measurements, Evaluations and Analytical Methods

Table 1 presents a schema for key study procedures. Study assessments will be conducted at: 1) screening; 2) baseline; 3) immediate post-intervention follow-up; 4) three-month post-intervention follow-up*;* and 5) six-month post-intervention follow-up. Table 2, at the end of this section, presents a schedule for assessment. Subjects will be informed and assured that data collected from research assessments will not be shared with treatment staff. Prior research has indicated substance abusers are more likely to self-disclose substance use behaviors when there are no legal or clinical contingencies tied to that self-report.

Biologic measures, including urine screens for illicit substance and breathalyzer screens for alcohol use, will be used to substantiate self report data. The inclusion of objective measurements increase the validity of self report assessments.

At the same time, we maintain that there is persuasive empirical evidence of the improved validity of self-report risk assessment, conferred by the ACASI method. For instance, Metzger et al. (2000) has demonstrated higher levels of reported risk behavior by ACASI than by face-to-face interview assessment. In choosing ACASI, we propose that we are using a state-of-the-art, feasible method of reducing social desirability effects.

A major consideration in planning treatment outcome research involves formulation of an effective plan to ensure follow-up data are obtained. To encourage participation in follow-up, the length of each visit has been kept as short as possible. Participants will be paid in cash or vouchers for completion of follow-up assessments. Reasonable and non-coercive reimbursement sums will be determined on a site-by-site basis. If necessary, on a case-by-case basis, study staff will provide childcare during follow-up assessment, if CTP policy permits. It is anticipated that follow-up rates for subjects while they are still in treatment will be extremely high. Subjects who have left the area will be interviewed by phone. A paper/pencil version of the SERBAS (usually administered via ACASI) will be created so as to be able to collect data on subjects who have left the area or are unable to be interviewed in person. All subjects will complete a locator sheet that identifies stable individuals who are likely to know of the subjects' whereabouts in the future. On the regular, study-wide conference calls, study staff will brainstorm solutions to attendance problems, when they emerge.

8.1 Informed Consent

At both screening and entry into the main intervention trial, study staff will obtain informed consent for study participation. Sample consent forms for obtaining written informed consent are provided in the appendix. Consent procedures are described in section 5.3.

8.2 Inclusion/Exclusion Criteria Review

8.2.1 Screening Assessment

Screening interviews will consist of three steps: (1) Eligibility on the unprotected penetrative sexual activity and ineligibility on pregnancy intention, will be determined; (2) Basic demographic and HIV risk behavior information, including ineligibility due to age < 18, will be determined; and (3) Ineligibility due to gross mental status impairment or incapacity to give informed consent will be determined, from all women who are eligible on behavioral screening. Participants will be paid in cash or vouchers for completion of the screening assessment. Reasonable and non-coercive reimbursement sums will be determined on a site-by-site basis. The screening assessment will not be audiotaped.

The screening assessments include:

Demographic Form: A CTN created form collecting basic descriptive data, including age, gender, ethnicity, years of education, occupation, and drug use history.

Risk Behavior Survey: The RBS is part of the CTN common assessment battery. It is a brief interview assessing HIV drug use and sexual risk behavior, chiefly during the prior 30 days. Questions C1 – C3 will be repeated for the prior 3 and 6 months. If the client indicates no unprotected heterosexual vaginal or anal sex in the prior 6 months, she will be ineligible for the study.

Mini-Mental Status Exam (MMSE): The MMSE (Folstein, Folstein & McHugh, 1975; Cockrell & Folstein, 1988) will be used to identify potential subjects who are too cognitively impaired to engage in the study. Individuals with scores less than 25 will be excluded from the study. MMSE has the advantage of being: 1) widely used in research

protocols for this purpose, 2) relatively easy to administer and score; 3) relatively short; 4) and extremely inclusionary, in that only the most grossly cognitively impaired individuals will be excluded. This instrument will only be administered at the time of screening.

Basic Data and Locator Questionnaire: locator information, including home address and phone number, will be collected and kept confidential in the subject's record. Data collected on the Basic Data and Locator Questionnaire will be used to contact the patient for assessment and follow-up and in emergencies. Patients will be asked to provide locator information including their residential street address and a working telephone number, or an address of a relative if they are homeless, as well as the address and telephone number of a non-drug abusing relative or friend who can reach the client in emergencies.

Subjects excluded from study during the screening assessment will not be informed of the reason for exclusion, so as to not bias screening assessments of other potential subjects with whom they may come in contact. Excluded subjects will be told that several criteria must be met before a subject can be enrolled into study, and that, unfortunately, they did not meet one. We do not disclose to subjects the criterion that was not met, so as to limit other potential subjects from being able to misrepresent themselves if they did not meet similar criteria. The screening instruments will only be administered at time of screening.

8.3 Baseline and Follow-Up Assessment Battery

Participants will be paid in cash or vouchers for completion of the baseline and follow-up assessments. Reasonable and non-coercive reimbursement sums will be determined on a site-by-site basis. All randomized participants will be followed throughout the study in order to maximize follow up rates. If possible, participants should be interviewed in person, including participants who might be incarcerated. The protocol specific assessments (not the Common Assessment Battery or ACASI administered SERBAS) within the Baseline and Follow Up Assessment should be audiotaped. The following instruments will be used at baseline and follow-up:

8.3.1 Composite International Diagnostic Interview (CIDI): The substance abuse subsections of the Composite International Diagnostic Interview, Version 2.1 (CIDI-2.1), part of the CTN common assessment battery, will be used to determine whether participants meet DSM-IV criteria for substance abuse or dependence. This is administered at the baseline only.

8.3.2 Addiction Severity Index-Lite: The ASI, also included in the CTN common assessment battery, is a standardized, multidimensional, semi-structured, comprehensive clinical interview that provides problem severity profiles and treatment planning information in 6 problem domains commonly affected by substance abuse. These problem domains are: alcohol and substance abuse; medical; psychiatric; legal; family/social; and employment/support. Composite scores for each domain are derived mathematically. A revised version of the 1997 ASI Lite 5th Edition, limited to the items used in the composite scores and some demographic information, will be administered by a research staff member. The full ASI-Lite will be administered at the baseline only.

At the 3-month and 6-month assessment, only the drug and alcohol section will be administered.

8.3.3 Biologic Measures: Urine and alcohol screens will be done at the Baseline assessment to substantiate self-report data. The urine drug screen will occur onsite and test for 10 illicit substances. A breathalyzer will be used to screen for blood alcohol concentration (BAC).

8.3.4 Drug Use and Drug Injection Risk Behavior Assessment: The RBS drug use and injection practice items will be repeated at the 3 and 6 month follow-up visits.

8.3.5 Eating Disorder Examination Questionnaire (EDE-Q): Thirty-eight item self report assessing the frequency of key behavioral features, such as binge eating, self-induced vomiting, and associating eating disorder pathology. The instrument includes four sub-scales: restraint, weight concern, shape concern, and eating concern. Focuses on a 28-day time period and uses 7 point rating scale. The scale has good psychometric properties (Cronbach's alphas ranging from .67 to .90). **(optional assessment)**

8.4 HIV Risk Assessment

8.4.1 Sexual and Sexual Risk Behavior Assessment: The SERBAS (Sexual Experiences and Risk Behavior Assessment Schedule)(Meyer-Bahlburg et al., 1991; Sohler et al., 2000), a psychometrically sound, longstanding, extensively used instrument of the Columbia University HIV Center For Clinical and Behavioral Studies will be the source of our primary outcome measure, number of unprotected (vaginal and anal) penetrative intercourse occasions, as well as other secondary sexual and sexual risk behavior outcomes for the time period of the past 3 months. SERBAS items will include: 1) number of unprotected penetrative intercourse occasions and number of unprotected penetrative intercourse occasions by (main versus casual) partner type; 2) number of partners, gender of partners, HIV serostatus and HIV risk characteristics of partners; and 3) pursuit of HIV testing and counseling. The SADAR (Sex and drug abuse relationship interview) (Calsyn et al., 2000) will be the source of the secondary outcome measure, proportion of drug or alcohol with sex occasions of all sex occasions; and proportion of unprotected occasions of all sex occasions. It should be noted that the use of these items will permit the comparison of results from the women's and men's studies. All items will be administered using the ACASI method. SERBAS items are currently being used in ACASI format in a 1200-person NIMH multi-site intervention study with HIV seropositive IDUs, female sexual partners of IDUs, and men who have sex with men.

We acknowledge the potential for compromised recall posed by our primary outcome assessment of number of unprotected penetrative intercourse occasions during the past 3 months. We acknowledge that this is particularly true if alcohol and drugs are used before sex. However, we maintain that there are compelling precedents for using this outcome and time frame in HIV risk behavior intervention studies with comparable populations. These include: (1) samples of men and women in community-based STD or health clinics in 5 urban areas--including substantial proportions of drug-users (NIMH Multi-site HIV Prevention Trial Group, 1998; Pinkerton et al., 2002); and (2) a sample of

women in an inner-city family planning clinic--including a substantial proportion of women with recent drug use (Ehrhardt et al., 2002). We also maintain that there is considerable quantitative evidence of the reliability and validity of both the SERBAS (Sexual Experiences and Risk Behavior Assessment) (for example, MacKinnon et al., 1993; Meyer-Bahlburg et al., 1997; Sohler et al., 2000; Ehrhardt et al., 2002) and RBS (Risk Behavior Survey) (for example, Simpson et al.,1994) instruments—that are the basis of our proposed study assessment. We offer a more explicit description of administration procedures to demonstrate the feasibility of the time frame. In particular, we clarify that, in quantifying occasions of (general and unprotected) sexual behavior during the past 3 months, the participant is advised about strategies to improve recall. These include: using smaller units of time (i.e. a week) to construct the past 3 months; identifying critical events during this period, relative to which she might more readily recall her behavior; identifying atypical times during this period, when her behavior digressed dramatically from her usual behavior over this period and others.

8.4.2 Perceived self-efficacy to carry out safer sex

Following El-Bassel and colleagues, the Condom Use Self-Efficacy Scale (Marin, Tschann, Gomez and Gregorich, 1998) will be used to measure a participant's belief in her ability to protect herself during sex and to negotiate safer sex. This 11 (5 point Likert) item scale has been used with 1600 unmarried Latino adults in 10 U.S. states. Perceived self-efficacy is the sum of the 11 items (range: 0-44). Factor analyses revealed 5 correlated factors: regular partner, impulse control, partner resistance, STD ideas, and condom discussion. Preliminary psychometrics indicate good reliability (Cronbach's alpha = .86) and good concurrent validity.

8.4.3 Perceived barriers to safer sex

The Condom Barriers Scale (ST. Lawrence, Chapdelaine, Devieux et al., 1999), will be used to assess 4 domains of reluctance to use male condoms. This is a 29 (5 point Likert) item scale, with demonstrated reliability and validity, from which a total score is obtained. Domains include: access/availability; partner barriers; effect on sexual experience; and motivational barriers. The Attitude Toward The Female Condom Scale will be used to assess reluctance to use female condoms.

8.4.4 Condom use skill behavior assessment

Condom use skill is measured, separately, for male and female condoms using checklists of necessary actions. It is measured by (dichotomous) observer ratings of the presence or absence of basic skills for use of each. For each, a total count of number of skills observed is obtained. The following skills for putting a male condom on a penis model are observed: Expiration date on package is checked; package is opened carefully; condom checked for damage; condom rolled correctly downward; condom rolled to base of penis; air removed from condom; space left at tip of condom; lubricant added to condom or penis; withdrew condom and moved away from mode; took care to avoid spilling; and tied off condom and disposed of in trash. The following skills for putting a female condom in a vagina model are observed: expiration date checked; the package is opened carefully; condom checked for damage; condom unrolled and two rings separated; condom rubbed gently to evenly spread lubricant; inner ring squeezed between finger; inner ring pushed into vaginal canal while squeezed; inner ring placed against cervix; outer ring covers outside of vagina; after used condom is twisted and removed taking care not spill contents; and condom disposed of in trash can.

8.4.5 Negotiation skill behavior assessment

Negotiation skill is measured by (4-point Likert scale) assessor ratings of the extent of 4 basic negotiation skills demonstrated in participants' completion of sexual risk vignettes. These skills are: assertiveness (in demanding safer sex from partners); informativeness (about the need for safer sex); ability to anticipate high-risk situations (demonstrated by mention of carrying condoms); and implementation (of safer sex skills). A total skill score can be obtained by summing these. A count of number of alternative solutions is generated. A count of number of obstacles identified is generated.

8.4.6 Bem Sex Role Inventory

The Bem Sex Role Inventory-Short Form (BSRI) (Bem, 1981) will be used to assess degree of masculine and/or feminine gender role attitude. One focus of the SSB intervention is to empower women to adopt more active, less stereotypically feminine gender role behavior in their sexual relationships. It consists of 11 7-point Likert scale items – on which the subject can be categorized as masculine, feminine, or gender-neutral. Mean scores ranging from 1 - 7 for feminine, masculine, and neutral gender role items, are obtained from the mean ratings for each category. In order to reduce respondent burden, 'filler' items, which do not load on to either the femininity or masculinity scales, were eliminated in the short form (Bem, 1981).

8.4.7 Past and current abuse experience assessment

This assessment includes physical, sexual and emotional abuse items. In each domain the participant is asked to report: lifetime occurrence (YES/NO); lifetime frequency (4-point scale from once to regularly); need for medical treatment (YES/NO); use of medical treatment (YES/NO); length of time since last occurrence; occurrence with main partner (YES/NO); occurrence with other than main partner (YES/NO); and past 3 month frequency (on a 1 – 6 scale of daily to no occurrence). Participants are also asked age of first sexual abuse and description of perpetrator (e.g. different family members, strangers, etc). It has been shown that abuse is positively associated with sexual risk behavior.

8.4.8 Attitudes Toward Female Condoms

This assessment measures participants' attitudes toward the use of the female condom. It consists of 18 items scored on a 5-point Likert scale (strongly disagree to strongly agree). Five additional questions ask about intent to use the female condom, with what kind of partner, and whether this will be in the next 3-month period of time.

8.4.9 Gender Specific Questionnaire

This measure contains questions related to contraception, pregnancy, and STDs that are not found elsewhere in the assessment battery. The participant is asked to provide a brief history of pregnancies she might have had, her use of contraception, and a history of STD prevalence. This measure will be administered at baseline and updated at the 3 and 6 month follow up point.

8.4.10 Sexual Relationship Power Scale

The Sexual Relationship Power Scale (SRPS) (Pulerwitz, Gortmaker, & DeJong, 2000) measures power dynamics in relationships using two subscales: Relationship Control and Decision-Making Dominance. The scale was shown to be inversely related to

physical violence and related to consistent condom use. It consists of 23 items scored on a 4-point Likert scale (strongly agree to strongly disagree). The measure will be administered at baseline, immediate post treatment, 3, and 6 month follow up points.

8.5 Adverse Event Evaluation

An adverse event (AE) is defined as any reaction, side effect or untoward event that occurs during the course of the clinical trial. The possibility of abusive partner behavior and/or a marked increase in emotional distress (defined as an increase in depression and/or anxiety symptoms) are the foreseeable adverse effects of participation. Possible triggers for these effects could be: introduction of (male or female) condoms or other methods of protection; introduction of safer sex negotiation; refusal of unprotected sex; or partner knowledge of the woman's participation in a woman's intervention. Subjects are advised to observe any signs of anger in their partners, and any of these problems in themselves, and to discuss this with study staff immediately. Study staff will be trained to provide crisis intervention and referral for clinical emergency situations. In addition, all study assessments contain modules concerning abuse that can alert study staff to evolving risk. The occurrence of AEs will be determined through the use of an AE Worksheet (consisting of one general AE question and a follow up question to gather more information) filled out by the RA at baseline, immediate post treatment, 3 and 6 month follow up assessments. All SAEs will be recorded, respectively, on the AE Case Report Form (CRF) and SAE Form and SAE Summary Report. The procedures for detecting, reporting and monitoring SAEs are described in section 9.0.

8.6 Treatment Compliance

Subjects will be asked to complete an intervention exposure checklist -- designed to measure whether the participant has been exposed to the interventions provided in both the intensive gender specific SSB intervention and the HE comparison condition. The participant checks the interventions she has been exposed to during the assessment period, and identifies the source of exposure. Therapists will be asked to complete an intervention fidelity questionnaire after each intervention session – to document the content and the activities of the sessions they conducted.

Table 2

Schedule of assessment collection

Assessment Measures	Screen Visit 0	Baseline Visit 1	Immediate Post Intervention Visit 2	3 month follow up Visit 3	6 month follow up Visit 4
Addiction Severity Index-Lite (CAB)		X			
Addiction Severity Index-Lite (Drug and Alcohol Only) (CAB)				X	X
Adverse Events		X	X	X	X
Alcohol Breathalyzer (CAB)		X			
Attitudes Towards the Female Condom		X	X	X	X
Bem Sex Role Inventory		X	X	X	X
CIDI (CAB)		X			
Condom Barriers Scale		X	X	X	X
Condom Use Self-Efficacy Scale		X	X	X	X
Condom Use Skills Assessment		X	X	X	X
Demographic (CAB)	X				
Drug Use Screening (CAB)	X				
Eating Disorder Examination Questionnaire (EDE-Q)			X	X	
Gender Specific Questionnaire		X		X	X
Inclusion/Exclusion Form	X				
Injection Risk Assessment (from RBS)				X	X
Intervention Exposure Checklist			X	X	X
Mini-Mental Status Exam	X				
Negotiation Skills Behavior Assessment		X	X	X	X
Past and current abuse experience Assessment		X		Current Only	Current Only
RBS (CAB)	X				
Sexual Relationship Power Scale		X	X	X	X
Sexual Risk Assessment (SERBAS)		X		X	X
Sexual Risk Assessment-post treatment (SERBAS)			X		
Study Termination – Treatment			X		
Study Termination – Follow Up					X
Urine Drug Screen (CAB)		X			

9.0 DATA SAFETY AND MONITORING PLAN

The data safety monitoring plan consists of three components: safety; trial performance; and efficacy. Procedures for monitoring and assuring these components will be

presented here, or references to other sections of the protocol where these procedures are detailed will be provided.

9.1 Safety

9.1.1 Definition of Adverse and Serious Adverse Events

Adverse events will be categorized as serious or non-serious, as related or not related to the study, and as expected or unexpected. An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial. Stable chronic conditions which do not worsen are not considered AEs. Clinically insignificant events will be excluded from any type of documentation. These may include: colds, flus, cuts, scrapes, coughs, headaches, stomach complaints, general fatigue and mild symptoms or problems associated with medical conditions not related to drug use.

A serious adverse event (SAE) is defined as: any fatal event; any immediately life-threatening event; any permanent or substantially disabling event; any event that requires initial hospitalization or prolongs hospitalization (excluding normal childbirth and pre-planned or elective procedures); any event causing congenital anomaly or birth defect; or any event requiring intervention to prevent any of these problems. Hospital visits that do not result in admittance are not considered SAEs (e.g. emergency room visit that does not result in admittance).

Risks from behavioral intervention trials may be expected to be minimal relative to those from pharmacologic interventions. The possibility of abusive partner behavior and/or a marked increase in emotional distress (defined as an increase in depression and/or anxiety symptoms) are the foreseeable adverse effects of participation.

9.1.2 Assessment, Reporting and Monitoring of Adverse and Serious Adverse Events

AEs and SAEs will be elicited by research assistants at each assessment (baseline through follow up). The RA will ask the subject whether she has experienced any new problems or a worsening of existing problems since her last assessment using the AE Worksheet. The RA should be focused on gathering data to aid the Study Clinician in determining study relatedness. Assessment of depression must include an assessment of suicidal ideation, as suicidal ideation may require immediate clinical assistance and qualify as an SAE. All clinically significant AEs will be captured on a standardized AE Log, with immediate assessment for whether or not the AE is serious, and whether or not the AE is study-related, in consultation with the site coordinator or Study Clinician (PhD, MD, PI). Study-relatedness will ultimately be determined by the Study Clinician following discussion with the staff member reporting the AE. AEs that are not serious or study related do not require any further paperwork documentation besides the AE Log. AEs and SAEs could also be spontaneously disclosed by the subject during intervention sessions. In this case, the therapist will record and report them, as described here.

Study staff will be trained to provide crisis intervention and referral for clinical emergency situations. Standard CTP procedures for handling crisis situations should be used. The Site Coordinator and/or Study Clinician will be available by beeper (or other similar method), within 24-hours for consultation and crisis intervention for problems.

From baseline informed consent discussion onward, subjects are advised that conversation about HIV or STDs, introduction of (male or female) condoms or other methods of protection, safer sex negotiation, refusal of unprotected sex, or, even their participation in a women's intervention may anger their male partners. This anger may put them at risk for emotional, physical and/or sexual abuse. Subjects are also advised that emotional distress could develop or increase in response to these problems. For this reason, subjects are advised to observe any signs of such anger in their partners, or such problems in themselves, and to discuss them with study staff immediately. In addition, study assessments contain modules concerning abuse, which can alert the study staff to evolving risk.

All study related AEs and SAEs will be followed until resolution. Monitoring and reporting of SAEs will be maintained by the: CTP staff members (e.g. research assistants, therapists, etc.); CTP Site Coordinator; Protocol PI; Study Project Manager; Lead Investigator; and NIDA Medical Monitor.

Figure 3 presents a flow chart for AE and SAE reporting. Only SAEs and related AEs will be recorded and entered into the study database (via the AE CRF). All SAEs will be recorded on the AE CRF, the SAE Form, and a summary narrative provided via the SAE Summary Report. The AE CRF is a form that will be used to document any adverse event that is thought to be serious or study related. The AE CRF is completed at each assessment point and on an as needed basis. If the adverse event is found to be serious, then a SAE Form and SAE Summary Report must be completed. The SAE Form should be completed by or in consultation with the Study Clinician. The SAE Summary Report contains demographic information and an event narrative and should be completed by the Study Clinician.

All SAEs must be reported by fax of the AE CRF, within 24 hours to the Lead Investigator, Protocol PI, Node PI, NIDA Medical Monitor, and to IRBs in accordance with their guidelines. The Study Clinician will be responsible for reviewing the AE CRF and SAE Form, querying the staff as needed, and completing an SAE Summary Report, to be co-signed by the Lead Investigator. Within 14 days, the AE CRF and the SAE Form and the signed SAE Case Summary are forwarded to the NIDA Medical Monitor, Protocol PI, and Node PI. At the same time, reports will be submitted to all involved IRBs per reporting requirements.

All study staff – including research assistants, therapists, CTP Site Coordinator, Protocol PI, Lead Investigator, and Study Project Manager, will receive common training for AE and SAE detection, monitoring and reporting. Training will include: definition of AEs; definition and grading of SAEs; indications and procedures for completing the AE log; indications and procedures for completing AE CRFs; indications and procedures for completing SAE Forms and SAE Summary Reports; and procedures for reporting SAEs.

9.1.3 Procedures For Human Subject Protection

The Lead Investigator and Protocol PIs will obtain IRB approval to conduct the study. Any amendments must also receive IRB approval. IRB approval must also be obtained for recruitment, advertising or educational materials. The NIDA CTN DSMB, Long Island Node Quality Assurance Committee representatives, and the participating Node Quality

Assurance representatives will have access to facilities and records for review and verification. For additional protection of confidentiality, the Long Island Node will apply for a NIH Certificate of Confidentiality for the study.

The study assessments and interventions consist of techniques that have been widely used in similar forms with comparable populations with minimal problems for the subjects. Previous research experience suggests that subjects generally perceive these discussions positively. There is, however, some risk that discussing sensitive topics, especially HIV risk behaviors, drug use, sexuality, and intimate relationships, will cause distress or emotional fatigue in some subjects. Yet, these risks do not exceed those that are a normal part of any clinical interview or treatment session. The use of individual assessment procedures has not been shown to be either harmful or directly helpful to substance using/psychiatric patients. Appropriate breaks will be given in the interview or session; if necessary, support will be provided during, or at the end of the interview or session.

All research assistants and therapists will be trained to identify signs of emotional distress, partner abuse, and crisis, and to provide crisis intervention and referral for such situations. A detailed manual will provide ongoing guidance in the standard crisis intervention practices of the CTP. The Site Coordinator and/or Study Clinician will be available by beeper (or other similar method), within 24-hours for consultation and crisis intervention. Should this be needed, he/she will notify the CTP staff members and initiate the clinical procedures that constitute the standard crisis intervention practices of the CTP.

During the course of assessment or intervention, it is possible that a subject may report unprotected (sexual or drug use) risk behavior with an HIV serodiscordant partner. For the protection of the health of the subject and/or her partner, HIV risk and prevention education must be provided to the subject, in accord with both CTP standard practice and local public health law. It is also possible that a subject may newly report HIV seropositivity. We will refer the subject for immediate counseling with the CTP staff member responsible for providing HIV education, making HIV service referrals and satisfying HIV public health policy requirements, in accord with CTP standard practice; through this person, responsibilities for HIV disclosure to state registries and/or partner notification will be met. It is also possible that a subject may report pregnancy. Referrals to appropriate local HIV testing and counseling, partner notification, primary care and/or obstetrical/gynecologic services, in accord with CTP standard practice will be provided.

9.1.4 Data Safety and Monitoring Board

The CTN DSMB will monitor this trial, in accord with its SOP. The CTN DSMB will conduct adverse event analyses to determine the acceptability of the safety of the trial. Analyses will be conducted for the total population, total Node population, and total CTP population. All informed consent forms and inclusion/exclusion criteria for all subjects will be reviewed. All research records (e.g. case report forms, source documents, etc.) for subjects experiencing SAEs will be reviewed. Per QAS policy, 100% of the research records for the first 10 subjects and a random 10% of the remaining subjects will be reviewed. At each monitoring visit to a CTP, the randomization process will be reviewed to ensure that the randomization is occurring according to protocol procedures.

The CTN DSMB will review demographic characteristics of subjects in each intervention condition – to determine the efficacy of the randomization procedures. The CTN DSMB will review recruitment and retention data to determine the feasibility of the trial. Interim analyses of primary and secondary outcome data will be conducted for the purpose of determining futility of continuing the study, as planned. Our proposed plan for interim analysis is described in section 11.8.

9.2 Trial Performance

9.2.1 Intervention Integrity

There are two major threats to the integrity of the interventions. First, counselors may not deliver the interventions as intended. As described in sections 6.2. and 6.3.3, two procedures will be used to minimize this threat. Both interventions will be manual driven, and the therapists will receive 20 hours of training in conducting the interventions. All intervention sessions will be audiotaped. The Lead Investigator (or designee), Study Project Manager, clinical supervisor, and/or the CTP Site Coordinator will review a portion of each counselor's audiotapes. Therapists will receive regular supervision, including feedback on deviations from the manual.

Second, there is a potential threat of contamination between the interventions. Since HE is a component of the SSB intervention, contamination from HE to SSB is not an issue. However, there are 3 potential sources of contamination from SSB to HE. First, the study intervention counselors, trained in both interventions, may deviate from training guidelines, to refrain from introducing SSB material in HE sessions, and do so. In order to minimize this deviation, HE has been designed with ample didactic material that there is little time to introduce SSB problem-solving or role play. In addition, as described in section 6.3.3, rigorous procedures for intervention supervision, including audiotape review and feedback, will serve to minimize this threat. Second, subjects in SSB intervention may share SSB material with HE subjects. Third, HE subjects may be exposed to SSB material through non-study-related sources – like street outreach workers or media campaigns. To monitor these potential sources of contamination, subjects will be asked to complete an intervention fidelity questionnaire at each follow up assessment -- to determine if they have been exposed to elements of either intervention. Counselors will be asked to complete an intervention fidelity questionnaire after each intervention session – to document the content and the activities of the sessions they conducted.

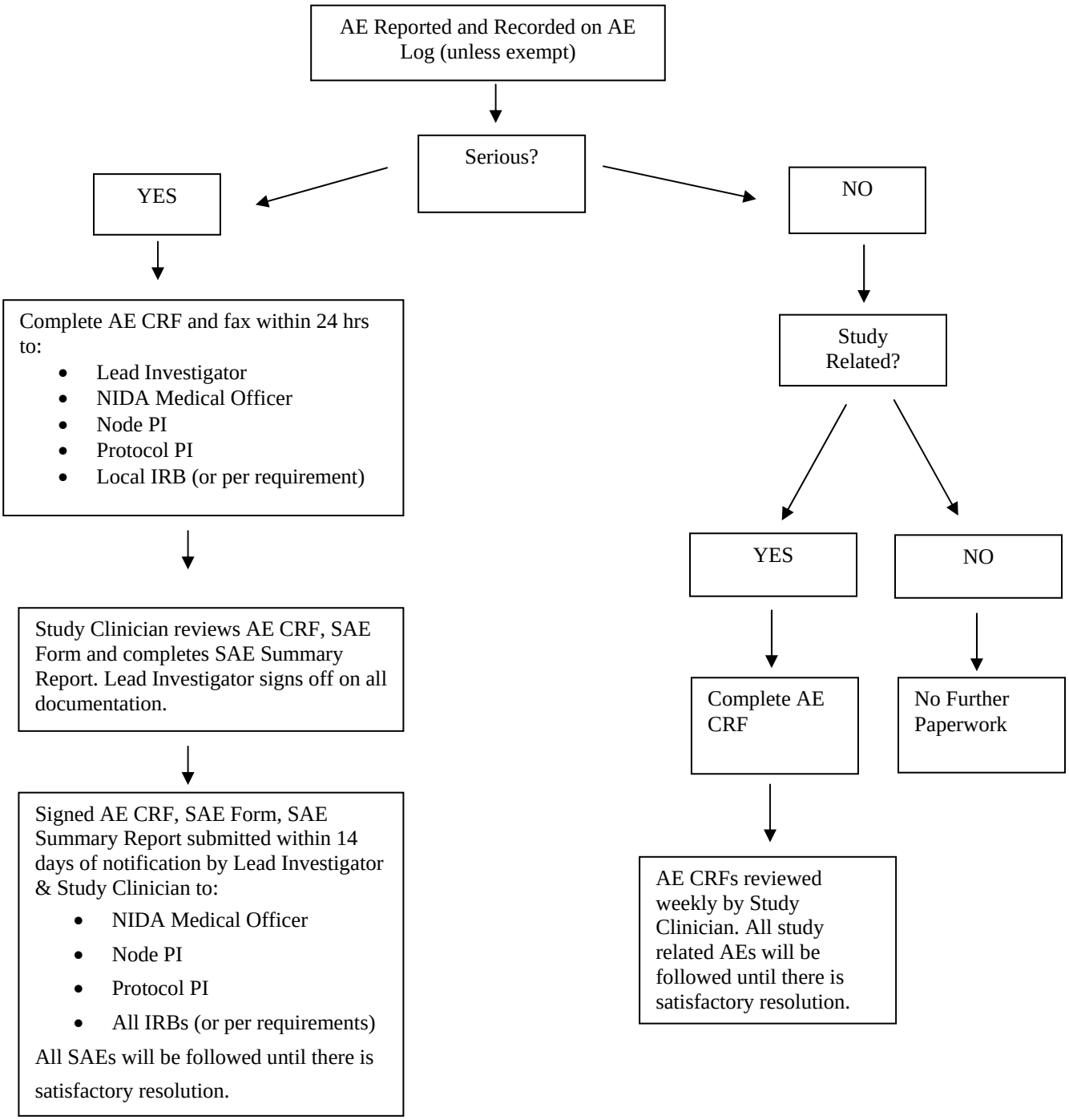
9.2.2 Data integrity

The Long Island Node Data Management Center (DMC) will coordinate data management activities and be responsible for oversight of data integrity. Rigorous procedures for assuring data integrity are detailed in Sections 15.0 to 15.5.

9.3 Trial Efficacy

In view of the limited (i.e. single-study) evidence of the efficacy of this intervention, only within a methadone maintenance treatment program, we plan to conduct an interim analysis, primarily for futility. This plan is described in Section 11.8.

Figure 3
AE / SAE Reporting Flow Chart


AE Reported and Recorded on AE Log (unless exempt)
Serious?
YES
NO
Complete AE CRF and fax within 24 hrs to:
Lead Investigator
NIDA Medical Officer
Node PI
Protocol PI
Local IRB (or per requirement)
Study Related?
YES
NO
Study Clinician reviews AE CRF, SAE Form and completes SAE Summary Report. Lead Investigator signs off on all documentation.
Complete AE CRF
No Further Paperwork
Signed AE CRF, SAE Form, SAE Summary Report submitted within 14 days of notification by Lead Investigator & Study Clinician to:
NIDA Medical Officer
Node PI
Protocol PI
All IRBs (or per requirements)
All SAEs will be followed until there is satisfactory resolution.
AE CRFs reviewed weekly by Study Clinician. All study related AEs will be followed until there is satisfactory resolution.

10.0 Departure From Protocol

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

11.0 Statistical Analyses

11.1 Objectives of Analysis

The proposed trial is intended to test the effectiveness of SSB intervention, as compared to that of single-session HIV education. There will be one primary outcome: number of unprotected penetrative (vaginal or anal) intercourse occasions during the 3-month and 6-month follow-up periods. Secondary outcomes will include: proportion of drugs or alcohol with sex occasions (of all sex occasions); proportion of unprotected sex occasions (of all sex occasions); perceived self-efficacy to carry out safer sex; carrying condoms; and gender role beliefs.

11.2 Sample Size and Statistical Power

The sample size is determined to ensure sufficient power (at least 80%) of a significance test (with level of significance α=0.05) to detect a clinically meaningful intervention effect with respect to the primary outcome measure (number of unprotected penetrative sex occasions).

The study design is a stratified cluster randomization trial (Donner and Klar, 2000). The intervention groups constitute the clusters. Each intervention group will consist of approximately 3 to 8 women depending on the number of eligible subjects recruited in the fixed time interval of 4 weeks. The strata are the 12 CTP sites – in which 40 participants per stratum will be enrolled. Thus, within each stratum, 5 to 10 clusters will be randomized in a balanced fashion to the two interventions. Below is presented the power of the test for comparison of the two interventions subject to these design and recruitment restrictions. Tables 1 and 2 were developed for different counts of CTPs (with the number of subjects per CTP fixed at 40). The two tables corresponding to 12 CTPs (and shown in the protocol) resulted in power values that were closest to our goals.

The power analysis for the stratified cluster randomization trial is based on a test statistic proposed by Liu & Liang (1997). The test statistic is based on generalized estimating equation (GEE). The power analysis takes into account the fact that data are correlated (repeated observations on a subject, the measurements of subjects belonging to the same intervention group (cluster) and from the same CTP (strata) and that the outcome follows a non-normal distribution.

The test statistic is actually a quasi-score statistic based on the generalized estimating equation. The asymptotic distributions of the test statistic under H0 and H1 are both known. In the analysis we assume the outcome (the number of unprotected sex occasions) follows a Poisson distribution with the marginal mean being a function of the intervention. In this case, under the null hypothesis the test statistic converges to Chi-square distribution with 1 degree of freedom. Under the H1, the test statistic converges to non-central Chi-square distribution with 1 degree of freedom. After we specify the parameters in the linear predictor for the mean and in the covariance matrix of the outcome (that is, the working correlation matrix which does not have to be necessarily

exactly correct), we can compute the non-central parameter and thus determine the power of the test.

Power of the test for difference between the two interventions with respect to number of unprotected sex occasions is computed for a range a values of the difference and the associated covariance parameters. As described in Section 8.4.2: Sexual and Sexual Risk Behavior Assessment, following state-of-the-art practices in HIV risk behavior intervention research, our primary outcome variable is number of unprotected sex occasions in the past 3 months. For purposes of our sample size and statistical power considerations, we have drawn on the HIV prevention intervention findings, among a comparable population of at-risk-for-HIV, inner city women, of Ehrhardt et. al. (2002). They reported an average of 17 unprotected sexual occasions in the 3 months prior to intervention in their sample. In our examination of differences between the two intervention conditions of our study, we have considered 3 levels of differences from this average. In particular, we have considered: (1) A difference of 2 unprotected sex occasions, or 15 versus 17; (2) A difference of 1.5, of 15.5 versus 17; and (3) a difference of 1, or 16 versus 17. In as much as a single occasion of unprotected sex can result in HIV infection, these differences are considered clinically significant. It should be noted that Ehrhardt et al. (2002) article did not present actual averages for their 3 intervention conditions. We have obtained unpublished averages from the authors, as follows: (1) Baseline: Control (0 intervention sessions):17.4; 4-session intervention: 13.7; 8-session intervention: 20.9; and (2) Three-month follow-up: Control: 19.5; 4-session intervention: 13.17; 8-session: 11.23.

Difference in the number of the of unprotected sex occasions:

1) Experimental intervention mean=15, control intervention mean=17
2) Experimental intervention mean=15.5, control intervention mean=17
3) Experimental intervention mean=16, control intervention mean=17

Parameters related to the covariance:

The correlation between repeated observations on a subject is rho1. The correlation between subjects in the same therapeutic group (cluster) is rho2 and rho2 $\leq$ rho1. The correlation between subjects from different therapeutic groups within the same CTP (strata) is rho3 and rho3 $\leq$ rho2.

1) within subject correlation: rho1 = 0.4, 0.6, 0.8
2) within therapeutic group (cluster) correlation: rho2 = 0.15, 0.1
3) within site (strata) correlation: rho3 = 0.1, 0.05

The variance parameters are determined by the means described above, since the outcomes are Poisson random variables. When specifying the variances, there are two choices:

1) just Poisson variance, and
2) extra variation due to the effect of cluster and strata, i.e. over-dispersion.

Suppose that conditional on cluster and strata the variance of the outcome is a Poisson variance, for example, the variance of the outcome (X) in the control intervention with mean 17 is Var(X|cluster, strata)=17. Then the marginal variance of the outcome is over-dispersed to Var(X)=17/(1-rho2-rho3). For the experimental intervention group with mean 15 the over-dispersion is 15/(1-rho2-rho3). Presented are results for Poisson and for over-dispersed Poisson variation.

As explained above, the intervention groups' size will vary between 3 and 8; and therefore the number of clusters (intervention groups) within strata (CTP) will be between 10 and 5. From a statistical perspective it is advantageous to have small clusters (intervention groups of size 4) and many clusters per strata (here 10 clusters for a total of 40 subjects per strata (CTP)); such design will have higher power than a design where the clusters will be large but the number of clusters per strata will be small as it is when there are 8 subjects per intervention group for a total of 5 intervention groups per CTP. We present the power computations for these two extreme cases.

The tables below give the power of the test as a function of rho1, rho2, rho3 and mean number of unprotected penetrative sex occasions in the two intervention groups.

Table 1.
Power of a test for comparison of the two experimental interventions: 12 CTP sites with 10 intervention groups per site, each intervention group is of size 4. p = .05

Rho1	Rho2	Rho3	No over-dispersion			Over-dispersion		
			Mean in HE –Mean of SSB			Mean in HE –Mean of SSB		
			17-15	17-15.5	17-16	17-15	17-15.5	17-16
0.40	0.10	0.05	1.00	1.00	0.85	1.00	0.98	0.77
0.60	0.10	0.05	1.00	0.99	0.81	1.00	0.97	0.72
0.80	0.10	0.05	1.00	0.98	0.77	1.00	0.96	0.68
0.40	0.15	0.05	1.00	0.99	0.79	1.00	0.96	0.70
0.60	0.15	0.05	1.00	0.98	0.75	1.00	0.95	0.65
0.80	0.15	0.05	1.00	0.97	0.71	1.00	0.93	0.62
0.40	0.10	0.10	1.00	1.00	0.94	1.00	1.00	0.88
0.60	0.10	0.10	1.00	1.00	0.90	1.00	0.99	0.82
0.80	0.10	0.10	1.00	1.00	0.85	1.00	0.98	0.77
0.40	0.15	0.10	1.00	1.00	0.88	1.00	0.99	0.80
0.60	0.15	0.10	1.00	0.99	0.83	1.00	0.98	0.75
0.80	0.15	0.10	1.00	0.99	0.79	1.00	0.96	0.70

Table 2
Power of a test for comparison of the two experimental interventions: 12 CTP sites with 5 intervention groups per site, each intervention group is of size 8; 2 intervention groups are assigned to SSB and 3 intervention groups are assigned to HE. p =.05

Rho1	Rho2	Rho3	No over-dispersion			Over-dispersion		
			Mean in HE –Mean of SSB			Mean in HE –Mean of SSB		
			17-15	17-15.5	17-16	17-15	17-15.5	17-16
0.40	0.10	0.05	1.00	0.98	0.75	1.00	0.95	0.66
0.60	0.10	0.05	1.00	0.97	0.71	1.00	0.93	0.62
0.80	0.10	0.05	1.00	0.96	0.68	0.99	0.91	0.59
0.40	0.15	0.05	1.00	0.93	0.63	0.99	0.87	0.53
0.60	0.15	0.05	0.99	0.91	0.60	0.98	0.85	0.51
0.80	0.15	0.05	0.99	0.90	0.57	0.97	0.83	0.48
0.40	0.10	0.10	1.00	1.00	0.93	1.00	1.00	0.86

0.60	0.10	0.10	1.00	1.00	0.89	1.00	0.99	0.81
0.80	0.10	0.10	1.00	0.99	0.84	1.00	0.98	0.76
0.40	0.15	0.10	1.00	0.98	0.78	1.00	0.96	0.68
0.60	0.15	0.10	1.00	0.97	0.73	1.00	0.94	0.64
0.80	0.15	0.10	1.00	0.96	0.70	0.99	0.92	0.60

From Tables 1 and 2 above it is evident that there is sufficient power (at least 80%) to detect clinically meaningful differences between the two intervention groups with respect to number of unprotected penetrative sex occasions (difference of 17 in HE and 15 or 15.5 in the SSB) with the two extreme design situations: 10 intervention groups with 4 subjects per group and 5 intervention groups with 8 subjects per group. There is somewhat limited power when a difference of only 1 unprotected sex occasion is expected between the two interventions (17 vs. 16); although even in that case there is sufficient power when no over-dispersion is present or when the within site correlation is larger (0.1 as opposed to 0.05) and when the intervention groups are of size 4.

Notice that the higher correlation due to same CTP site (rho3) the better the power. The reason for this is that the benefit of the stratification (comparing the two interventions within each CTP) offsets the negative effect of decreased number of effective degrees of freedom due to this correlation. The effect of the correlation due to same therapeutic group (rho2) is only negative because the comparison of interest is not performed within a therapeutic group – this is equivalent to the detrimental effect of cluster randomization on the power. Thus, because we have each of the two treatments offered in each of the sites, the correlation due to site actually works to benefit the power. If only one of the interventions was offered in each of the CTNs, the correlation due to site would have only affected negatively the power, just as now the correlation due to therapeutic group (cluster) decreases the power.

11.3 Efficacy Measures and Statistical Analyses

There will be one primary efficacy measure: number of unprotected penetrative (vaginal or anal) intercourse occasions during the past 3 months. This will be computed at the following assessment time points: 1) baseline; 2) 3-month post-intervention follow-up; and 3) 6-month post-intervention follow-up. The primary analysis will test the hypothesis that SSB intervention will significantly exceed HIV education in decreasing number of unprotected occasions from baseline to follow-up assessments. Possible SSB intervention effects on secondary efficacy measures will also be tested over the same time periods. These include hypothesized greater gains in self-efficacy to carry out safer sex, decrements in proportion of drugs or alcohol with sex occasions, gains in condom carrying, and change towards more egalitarian gender role beliefs in the SSB intervention condition, as compared to the HE condition.

The efficacy measures will be defined as:

<u>Primary measure</u>

Number of unprotected penetrative intercourse occasions in the last 3 months is derived from 4 questions on the SERBAS – reflecting 2 penetrative (i.e. vaginal, anal) intercourse type X partner (i.e. main male, other male) type combinations occurring during the past 3 months. That is, the (respective) number of unprotected vaginal intercourse occasions with main partner, number of unprotected vaginal intercourse

occasions with main partner, number of unprotected vaginal intercourse with other-than-main partners, and number of unprotected anal intercourse occasions with other-than-main partners will be summed to produce a total number of unprotected penetrative intercourse occasions. It should be noted that, for any of the above behaviors, the SERBAS directly asks the number of times the type of intercourse occurred and the number of times it was protected. Thus, to obtain the number of unprotected occasions of a behavior, the number of times it occurred with protection (i.e. by either male or female condoms) must be subtracted from the number of times it occurred at all.

Secondary measures

Proportion of drugs (or alcohol)-with-sex occasions (of all sex occasions) during the past 3 months is derived from the SERBAS and 8 sets of SADAR questions that have been incorporated into it. These sets reflect 8 type-of-sexual-behavior (i.e. vaginal, anal, oral passive, oral active) X partner (i.e. main, other-than-main) type combinations occurring during this time period. Each question within a set directly asks for the number of behavior type X partner type combinations that occurred under the influence of 10 different types of drugs or alcohol, as well as the total number of time the behavior type X partner type combination occurred (in general). Thus, to obtain the proportion of drugs-or-alcohol-with-sex, 2 different operations must be carried out. First, for each of the 8 (behavior type X partner type combination) sets of questions, the number of times the behavior occurred under the influence of the certain drugs (including alcohol) is summed. Second, this sum is divided by the total number of times the behavior X partner type combination occurred (in general) to obtain the proportion of time this combination occurred under the influence of drugs or alcohol. To obtain an overall proportion of all drugs-or-alcohol-with sex occasions of all sex occasions, the overall total number of times all behavior type X partner type combinations occurred under the influence of drugs or alcohol is divided by the overall total number of times that all behavior type X partner type combinations occurred (in general).

Proportion of unprotected sex occasions (of all sex occasions) during the past 3 months is derived from the studies reporting the efficacy of our study intervention (Schilling, El-Bassel, Schinke, Gordon and Nichols, 1991; El-Bassel and Schilling, 1992).

Perceived self-efficacy to carry out safer sex will be measured by the Condom Use Self-Efficacy Scale. This consists of 11 5-point Likert scale items that measure the participant's belief in her ability to protect herself during sex and to negotiate safer sex. Perceived Self-efficacy is the total of the 11 questions; it can range from 0 – 44.

Carrying condom: Dichotomous rating of whether or not the participant is carrying condoms – assessed at 3-month and 6-month post-intervention. This is a simple dichotomous (Yes/No) rating of whether or not the subject produces condoms from his/her pockets or handbags, when asked to do so by the research assistant.

Gender role beliefs will be measured by the Bem Sex Role Inventory-Short Form (BSRI) (Bem, 1981). It consists of 30 7-point items – on which the participant can be characterized as masculine, feminine, or gender-neutral. Means scores, ranging from 1-7, are obtained for each of these categories.

Additional Predictors

The following variables will be examined for their effect on the relationship between intervention and the primary and secondary outcome measures:

Perceived Self-Efficacy To Carry Out Safer Sex – described above;

Condom Use Skill is measured, separately, for male and female condoms. For each, a total count of number of basic skills observed by a rater is obtained.

Negotiation Skill is measured by (4-point Likert scale) assessor ratings of the extent of 4 basic negotiation skills demonstrated in participants' completion of sexual risk vignettes. A total skill score can be obtained by summing these. A count of # of alternative solutions is generated. A count of # of obstacles identified is generated.

The Condom Barriers Scale (St .Lawrence, Chapdelaine, Devieux et al., 1999) is a 29-item scale with demonstrated reliability and validity. A 5-point Likert scale is used to answer each item. A total score is obtained. The Attitude Toward The Female Condom Scale will be used to assess reluctance to use female condoms.

Monogamy status will be dichotomously rated as Yes/No. It is well established that condom use is more problematic in monogamous relationships; therefore, the association between monogamy status and unprotected penetrative sex will be examined in study analyses.

Frequency of drug use will be measured on the Risk Behavior Survey (RBS). Since drug use affects libido, arousal, self-control, judgment, agility, emotional lability and other functions that influence sexual behavior, it is conceptualized as an impediment to safer sex.

Past and current abuse experience will be assessed. This assessment includes physical, sexual and emotional abuse.

11.4 Study Population

The study will be carried out at approximately 6 MMTP and 6 ODF who can each provide an average of 40 women who have had recent unprotected, heterosexual penetrative sex, within a recruitment period of about 6 months.

11.5 Analytic Plan

11.5.1 Testing and estimation

All testing will be two-sided and significance will be judged at level α=0.05. Effects will be reported with point estimate and 95% confidence intervals in addition to p-values.

11.5.2 Preliminary analysis

Prior to the analysis of the primary hypothesis, we will examine the distributions of the outcome measures and identify possible outliers. Outliers will be thoroughly checked for collection or entry errors and will not be used in the analysis unless confirmed as correct and valid data. The confirmation will be by an independent evaluator, in consultation

with the principal investigators. The data managers will not have the authority to correct such values without instructions from the principal investigators.

11.5.3 Demographic and Baseline Characteristics

The number of participants enrolled into the study will be summarized by CTP site and by intervention group. For participants who are screened but not randomized, a distribution of the reasons for non-randomization will be provided for each site separately and overall. Intervention groups will be described with regard to baseline characteristics, using proportions when the data are categorical, or means and standard deviations when the data are quantitative.

11.5.4 Mixed Effects Models

Mixed Effects Models (MEMs) will be used to analyze continuous outcome measures. The statistical issues arising from clustering of subjects within therapeutic group and within sites requires appropriate statistical methods for analysis of clustered data, namely Mixed Effects Models (MEM). Mixed effects models are sometimes referred to as hierarchical models (Brown & Prescott, 1999; Bryk & Raudenbush, 1992). MEMs are also used to analyze repeated measurements of data over time (Diggle, Liang & Zeger, 1994). In addition, the repeated measurement on an individual over time are usually correlated and thus represent another cluster in addition to the clustering of subjects within a therapeutic group and clustering of therapeutic groups within a site.

The use of MEMs allows us to estimate the random effects corresponding to the participating sites and to explore the relationship between these random effects and site-specific characteristics. In addition, MEMs do not require complete repeated measurements data on all subjects when used to estimate the course of the outcome variable over time. Incomplete or missing data are handled by the model, providing that the missing data are assumed to be “missing at random” [Little and Rubin, 1987].

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

The design of our study – to conduct each intervention within each CTP site – makes stratification by CTP a significant source of benefit to power. This benefit strongly offsets the detrimental effect of within CTN correlation. We have a made adjustments for the fact that within CTP correlation has a detrimental effect on power – by decreasing the effective degrees of freedom associated with an intervention. For example, our design calls for 20 subjects within each CTP to be assigned to each of the two interventions; the within CTP correlation decreases the 40 degrees of freedom to a number that depends on the size of the correlation. (Please note that the group nature of the intervention is another source of decrease in degrees of effective freedom – due to correlation within group). These conditions have been taken into account in the sample size computations. In fact, the larger the within CTP correlation, the better the power is. Stratification by CTP results in a more powerful test – much like the paired t-

test is more powerful then the two-sample t-test when pairs of observations are known to be associated. (The pairs of observations in this study are the means of the outcome for the experimental and control interventions within CTP site). Sample size computations are performed using the exact model that will be used in the analysis. These computations take into account both the (relatively small) detrimental effect of within CTP correlation and its (relatively large) beneficial effect. The interaction between site and intervention effect is treated as random effect with variance sigma st.

The covariance structure for any particular model will be determined by modeling a variety of possible covariance structures. For example, the correlations between repeated measures on an efficacy measure over time will be modeled as auto-regressive correlation of order one or, compound symmetry or, unstructured correlation. Selection of which structure to be used will be based upon review of both Akaike's Information Criteria and Schwarz's Bayesian Criteria. An auto-regressive covariance structure has the property that observations taken close in time are more correlated than observations taken further apart in time. This correlation structure can be combined with either homogeneous or heterogeneous variances of the observations at different times. A compound symmetric covariance structure has the property that all observations are equally correlated, no matter how much time has elapsed between observations. Compound symmetry covariance structure is appropriate for modeling the correlation between subjects within sites and corresponds to a random effect for site. An unstructured covariance has no restrictions on the correlation and the variances of the repeated measurements; however, it does estimate many more parameters than the other two-covariance structures and is often inefficient.

11.5.5 **Methods for Categorical and Count Data**

Generalized estimating equations (GEEs) (Diggle, Liang, and Zeger, 1994) will be used to analyze categorical (binary, ordinal, nominal) and count outcome measures. The statistical issues arising from clustering of subjects within a site requires appropriate statistical methods for analysis of clustered binary data just as it is for continuous normal data. The GEE model is appropriate for the Poisson distribution of our primary outcome number of occasions. The GEE methodology allow for the analysis of categorical and count data which may be missing for some subjects either because of a missed week or due to drop-out, thus complete information for all subjects is not needed. The PROC GENMOD in SAS® [SAS Institute Inc. Cary, NC] will be used to carry out these analyses.

11.5.6 **Intention to Treat Analysis**

The primary analysis will be in the intent-to treat (ITT) sample, consisting of all randomized subjects.

11.5.7 Missing data and dropout

We will make any effort to assess all subjects at both follow-up times (3- and 6-months post-intervention). Despite our thorough and proactive approach to taking complete measurements on all randomized study subjects at all time points, we expect that there will be cases when assessments will be incomplete or missing. The analytic strategy in such cases will depend on the nature of the missing pattern and missing data. For example if at a given assessment time a subject has all but a few items of a questionnaire, a prorated score based on the available items will be computed. As another example, when data on a subject are available only at baseline, such subject

cannot be included in the analysis since even the modern statistical methods like Longitudinal Models (described above) require observations on at least two occasions; in such case some imputation is needed for values of the outcome at follow-up. In general, we will use multiple imputation approach based on propensity scores (Lavori et al., 1995). However, for some outcome measures alternative imputation methods might be more appropriate; for example, for the dichotomous secondary outcome measure 'taking condoms from open clinic supplies' it will be more appropriate to impute 'no' for the missing value of subjects who can not be brought to the clinic for assessment.

In the analysis, we plan to use statistical models that do not require complete observations on all subjects (MEM, GEE). However, the validity of the inference based on these models still depends on whether or not the assumptions on which these models are based are satisfied in our data. One important assumption in all these models is that the missing data is missing 'at random', i.e. the missing mechanism does not depend on the value of the unobserved outcome. Unfortunately, this assumption is un-testable in most medical research and in our study as well. One approach to this problem is to assume a model for the missingness mechanism that does depend on the unobserved outcome value and to do the analysis (i.e. estimate the treatment effect) incorporating the assumed model for the missingness. There are parametric and semi-parametric methods for doing so (Diggle et al., 1994; Kenward, 1998; Rotnitzky et al. 1998, Scharfstein et al. 1999; Liu et al. 1999). Comparison of the inferences from assuming various models for the missingness provides a measure of the validity of the efficacy estimate from the model that assumes missing 'at random'. Another approach to sensitivity analysis is based on the computation of a local sensitivity index which measures the change in the estimated intervention effect in a neighborhood of the 'missing at random' model for missingness (Rotnitzky et al. 2001; Ma and Heitjan (in press). We plan to perform a sensitivity analysis based on these two approaches in order to assess the effect of the assumption of missing 'at random' being violated on the inference regarding the treatment efficacy.

11.6 Analysis of specific hypotheses

11.6.1 Primary hypothesis

Hypothesis 1: SSB intervention will significantly outperform the HE condition with respect to decreasing the number of penetrative intercourse occasions that are unprotected.

The following marginal model for outcome of count will be used to test this hypothesis:

(1) $$\log E(Y_{ijkt}) = \beta_0 + \beta_1 X_{ijk} + \beta_2 t + \beta_3 X_{ijk} t + \gamma_1 Z_{1ijk} + \gamma_2 Z_{2ijk}$$

where Y_{ijkt} is the value of the primary outcome measure at time *t, t=0* for 3 months post intervention and *t=1* for 6 months post-intervention, for the i^{th} subject in the j^{th} intervention group (cluster) in the k^{th} CTP site (strata); X_{ijk} is intervention indicator ($X_{ijk}=1$ for the experimental intervention and $X_{ijk}=0$ for the control intervention); Z_{1ijk} is the value of the outcome measure prior to intervention; Z_{2ijk} is the monogamy status prior to intervention. The model parameters will be estimated by GEE (generalized estimating equation) approach that makes use of all available data and takes into account the within site, within treatment group, and within subject correlations in the way insensitive to the specification of correlations.

The regression parameters in this model correspond to intervention effects of interest. For example, statistically significant from 0 parameter β_3 indicates that over time the effects of the two study interventions are different; $\beta_3<0$ corresponds to the effect of the experimental intervention increasing over time faster than the effect of the experimental intervention; $\beta_3=0$ corresponds to no difference in the effectiveness of the interventions over time. If $\beta_3=0$, the parameter β_2 estimates the rate of change in the outcome measure from 3 to 6 months post-intervention in the two intervention groups, and the parameter β_1 estimates the difference between the experimental and control intervention, which is the same at the two follow-up assessment times.

We clarify that each parameter in the model corresponds to a distinct question. A statistically significant coefficient for the interaction term (β_3) will indicate that the intervention effect is different at 3 and 6 months; in this case, different intervention effects will be estimated for 3 and 6 months post intervention. If the interaction term is not significant, the intervention effect will be estimated with the coefficient for the main effect of the intervention, β_1. The coefficient for monogamy status will be used to assess the effect of monogamy, etc. We maintain that no multiple testing adjustment is necessary – with the proposed strategy for testing the hypothesis that the experimental intervention will be superior to the control intervention with respect to number of unprotected sex occasions.

11.6.2 Secondary hypotheses

Hypothesis 2: SSB intervention will significantly outperform HE intervention with respect to decreasing the proportion of drugs-or-alcohol-with-sex occasions (of all sex occasions).

Hypothesis 3: SSB intervention will significantly outperform HE intervention with respect to decreasing the proportion of unprotected sex occasions (of all sex occasions).

Hypothesis 4: SSB intervention will significantly outperform HE intervention with respect to increasing perceived self-efficacy to carry out safer sex.

Hypothesis 5: SSB intervention will significantly outperform HE intervention with respect to increasing condom carrying.

Hypothesis 6: SSB intervention will significantly outperform HE intervention with respect to increasing the magnitude of egalitarian gender role beliefs.

Some of these outcome measures could be assumed to follow normal distribution and for them linear mixed effects models will be used test the respective hypotheses. Linear Mixed Effects Models for continuous outcome Y will be employed:

(2) $$Y_{ijkt} = \beta_0 + \beta_1 X_{ijk} + \beta_2 t + \beta_3 X_{ijk} t + \gamma_1 Z_{1ijk} + \gamma_2 Z_{2ijk} + s_k + s_{kt} + c_j + \varepsilon_{it},$$

Here the variables X, Z and t are defined the same as in (1), s_k is a random effect for strata, s_{kt} is a random effect for strata by intervention interaction, c_j is a random effect for cluster and ε_{it} is an individual error term and the two error terms associated with the two measurements on the same individual will be correlated. The following assumptions

about the random terms are made: $s_k \sim N(0,\sigma_s^2), s_{kt} \sim N(0,\sigma_{st}^2),\ c_j \sim N(0,\sigma_c^2)$, $\varepsilon_{it} \sim N(0,\Sigma)$ and all random terms are independent of each other and Σ is homoskedastic. The estimated variance of the random effects of sites by intervention (s_{kt}) will give a measure of the variability of the intervention effects between sites. This can be compared with the estimated variance of the random site effects (s_{kt}), which estimates the variability between sites with respect to the efficacy of the control treatment. The estimated variance of the random effects associated with cluster (c_j) will be a measure of the variability in the outcome measure associated with intervention group within a CTP site. We anticipate that this variance will be small compared with the between CTP sites variance.

Binary outcome will be analyzed with marginal logistic regression and outcome of count will be analyzed with the marginal model similar to (1). The covariates in these regression models will be specified in the same way as in testing the primary hypothesis. GEE will be used to estimate the parameters in the marginal models.

11.6.3 Exploratory Analyses

This study offers the opportunity to explore several important questions related to the delivery and the efficacy of HIV prevention intervention for women. We will explore characteristics of site related to the delivery and potential effect on effectiveness. Site characteristics that will be studied include: individual clinic; MMTP versus drug-free outpatient treatment program; and Node. Hierarchical models (Bryk and Raudenbush, 1992), a special case of MEMs, will be used to study these characteristics. In addition, in an exploratory fashion we will study the effect of individual characteristics, by including these factors in the models described above. Factors to be studied especially include: (1) putative mediators, especially perceived self-efficacy variables and the observable skills variables; and (2) putative moderators, especially frequency of drug use, proportion of drugs or alcohol with sex occasions of all sexual occasions, extent of abuse, extent of perceived barriers to safer sex (especially fear of partner abuse) and monogamy status.

11.7 Analysis of Safety Measures

For each individual adverse experience, each participant will be categorized by the maximal severity reported during the intervention phase. Adverse experiences occurring during screening but ending prior to randomization, or those starting during screening and continuing into the randomization phase with the same or less severity will be excluded. The severity categories are: none (if the participant never had the adverse experience), mild, moderate, severe, life threatening and lethal. If a participant has an adverse experience more than once, then the adverse effect with most severe rating will be used in the analysis. It may be necessary to group the individual adverse experiences before any analysis can be performed. If this is necessary, then the coding will be performed centrally by Long Island node personnel.

11.8 Interim Analysis

We propose an interim analysis of data of baseline and 3-month follow-up assessment of ½ of the study sample. We will use the method of stochastic curtailment, with conditional power analysis (Lan and Wittes, 1982; Lan and Wittes, 1988; Jennison and Turnbull, 1989), to examine the possibility of early stopping. Accordingly, our analyses will proceed from the following rationale:T will be the test statistics for testing the primary

null hypothesis for the primary outcome Ho:B1>0. D(1) will be the interim analysis data. The examination of early stopping will be based on the conditional power analysis, whereby: P(0)=P(T will reject Ho at the end of the study/D(1), B1=0). If 1-P(0)≥ 0.8, stopping will be recommended due to futility. If 1-P(0)<0.8, continuation will be recommended.

12.0 Study Timetable

Estimated study start date	4/1/04
Estimated date when 50% of subjects will be completed	4/1/05
Estimated study end date	7/1/06

13.0 Disclosure of Data

The data and information in this protocol may be disclosed to staff as required to conduct this study.

14.0 Adherence to Ethical, Regulatory and Administrative Considerations

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

14.1 IRB Approval

Prior to initiating the study, the Principal Investigator at each study site will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the Principal Investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject.

14.2 Informed Consent

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

14.3 Health Insurance Portability and Accountability Act (HIPAA)

Authorization for use of Protected Health Information (PHI) will be obtained at each site prior to initiating the study. Principal Investigators at study sites will ensure that the

length of authorization extends throughout the study period. Study participants will need to sign an authorization agreement or a consent form with the appropriate authorization language, as specified by the local IRBs.

14.4 Investigator Assurances

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

14.5 Outside Monitoring

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

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

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

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

15.0 Disposition of Data

The Long Island Node Data Management Center (LIDMC) will coordinate data management activities and provide ongoing consultation and assistance to participating nodes throughout the study. All procedures will be in accordance with the Standard Operating Procedures (SOPs) developed by the CTN Data Management and Analysis Subcommittee (DMAS). The DMAS SOPs are in accordance with the Food and Drug

Administration regulations, which NIDA has adopted as the data collection and management standards for all CTN studies.

15. 1 Lead Node Responsibilities

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

15.2 Data Collection

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

15.3 Data Submission, Editing and Monitoring

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

15.4 Automated Data Acquisition and Management Systems

Each node is responsible for the development of a comprehensive automated data acquisition and management system in accordance with guidelines and SOPs published by NIDA and DMAS. The Long Island Node DMC is willing to discuss the use of the

Long Island automated data acquisition and management system if it is not desirable or cost effective for a node to develop an independent data acquisition and management system.

15.5 Central Data Repository

Data will be transmitted by the participating node DMC to the NIDA central data repository on the 10th of every month. The Long Island Node DMC will receive aggregated data from the NIDA central data repository on a monthly basis for data completeness, timeliness and accuracy quality assurance review. At the completion of the study, all data will be transmitted from the NIDA central data repository to the Long Island Node DMC for data analysis and the development of the final study report. The Long Island DMC will conduct final data quality assurance checks and "lock" the study database from further modification in accordance with the Database Lock SOP developed by the DMAS. The Long Island DMC will send the final analysis data setback to NIDA for storage and archive.

PROTOCOL SIGNATURE PAGE

SPONSOR

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

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

LEAD INVESTIGATOR(S)

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

_____ _____
Susan Tross, Ph.D. Date

_____ _____
Don Calsyn, Ph.D. Date

NODE PRINCIPAL INVESTIGATOR

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

_____ _____
Name/Signature Date

INVESTIGATOR(S)

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

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

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

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

- I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others,

following reporting requirements of the local IRB. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

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

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

_____ _____
Protocol Principal Investigator Name/Signature Date

Additional Investigators

_____ _____
Name/Signature Date

_____ _____
Name/Signature Date

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