Nurse Delivered Sexual Risk Reduction Intervention for HIV-Positive Women in the South

Supporting Statement
Part B

0920-XXXX

Contact Information

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B. Statistical Methods

1. Respondent Universe and Sampling Methods

HIV-positive women 18 to 69 years (average 42 years), from several clinics in North Carolina will be screened for participation in this study. The facilities that will serve as the respondent universe, are: Early Intervention Clinic, Durham County Health Department (Durham NC); the Positive Active Women Center, an HIV-related community based organizations (Durham, NC); the Carolina Medical Center HIV Clinic (Charlotte NC); the Mecklenburg County Health Department (Charlotte, NC), the Moses Cone Hospital (Greensboro NC) and the HealthServe Clinic, an HIV community based organization (Greensboro NC). The catchment areas for these sites are Durham County, Mecklenburg County and Guilford County in North Carolina. Women served by these sites are predominantly African-American (~96%) with a much smaller number of Caucasian (~3%) and Hispanic (~1%) women receiving care.

An estimated 550 HIV- positive women will be screened using a Screener Form (Attachment 3a) to determine eligibility for study participation. The Screener Form will collect information to ascertain if the potential participant meets the following eligibility criteria: 1) female, 2) HIV-positive, 3) 18 years of age and older, 4) reside within the geographic boundaries of the catchment areas (i.e., Durham County, Mecklenburg County and Guilford County in North Carolina), 5) speak and read English, 6) have been sexually active with a man in the past 3 months, and 7) does not intend to get pregnant in the next 3 months.

The full intervention trial will be conducted with a total of 330 HIV Positive women with a projected sample size of 165 each, for the intervention group and the wait list/comparison group. A subset of 25-30 women who participated in the Sister to Sister Positive HOPE intervention condition will be recruited following their completion of the trial. Participants will be drawn from the participants in the intervention condition of the trial.

Sampling Procedures: The current study is a randomized controlled trial of HIV-positive women in the southeastern United States. Power and sample size calculations for this study were performed using two outcome measures:

- Frequency of unprotected sexual acts in the past 3 months.
- An HIV preventive psychosocial factor (i.e., condom use self-efficacy).

Estimates of these outcome measures were obtained from the WiLLOW Program (Wingood et al., 2004) which evaluated the efficacy of an intervention to reduce HIV transmission risk behaviors and enhance HIV-preventive psychosocial factors in women living with HIV. For the purpose of these calculations, frequency of unprotected sexual intercourse (UPS) is defined as the number of reported unprotected sexual acts in the past 3 months. Data are assumed to follow a normal distribution. The estimated variability used in these calculations is the pooled variance of estimated UPS at baseline. The sample size calculations presented are the number of participants needed for 80% power to detect various differences between the treatment condition and the control condition with a two-sided test and α=.05. Using estimates similar to those reported in the Sister to Sister Study, Table 1 contains the sample size calculations.

Table 1. Participants per condition needed for 80% power to detect a difference in number of unprotected vaginal sex acts in the past 3 months (α=.05).

Control Condition	Treatment Condition	Difference in Means	N per Condition for 80% Power	N per Condition for 80% Power (15% attrition)	N per Condition for 80% Power (20% attrition)
7.5	4.5	3.0	159	183	210
	4.0	3.5	117	135	155
	3.5	4.5	90	104	119
8.7	5.5	3.2	140	161	185
	5.0	3.7	108	124	130
	4.3	4.0	125	144	150

Table 1 contains sample size calculations for various levels of UPS, treatment differences, and attrition. According to these results, the factor which has the greatest impact on sample size is the difference in the mean UPS between the treatment and control condition. The Willow Study reported a rate difference of approximately 3.9 acts. Using this as a gauge, the projected sample size per condition of approximately 165 is adequate relative to the goals of this study.

2. Procedures for the Collection of Information

Project staff at the University of North Carolina, Chapel Hill includes a Project Manager, Data Collectors, and the Data Manager. The Project Manager will coordinate all aspects of the project, including screening, enrollment, baseline and follow-up assessments, and in-depth interviews. The Project Manager will also be responsible for coordinating all tracking and contact activities including using contact information to locate participants and schedule follow-up visits and will interact as necessary with other staff assisting with maintaining contact with participants.

Prior to beginning data collection, study staff at UNC, Chapel Hill will receive training on confidentiality and scientific ethics, recruitment and facilitation skills, referral resources, and managing adverse events, among other important issues. Data Collectors will be trained to administer the assessment instrument (Attachment 5) using CAPI and A-CASI. The Data Collector will remain accessible to the participant during the ACASI portion in case she needs help or has any questions. Strict ethical guidelines regarding professional conduct will be enforced and signed by all research team members.

Potential participants will be screened for eligibility using the Screener Form (Attachment 3a). If potential participants are not able to complete screening when they are first approached in the clinic or community based organization, but are willing to be contacted by recruitment staff for screening, they will be asked to provide their name and telephone numbers. She will be asked to indicate whether a message may be left. She will also be asked if it is okay to identify the caller as from the Sister-to-Sister Positive HOPE Project. If it is not, she will be asked how she would like the caller to identify herself. This information will be

documented on the Screener Contact Form (Attachment 3b). After eligibility is verified, and during the baseline visit, the Data Collectors will explain the study to the potential participant, review the Consent Form (Attachment 7a), and have the participant sign the form. After consent is obtained, the Data Collector will collect basic contact information from the participant using the Locator Form
(Attachment 4). The purpose of collecting this information is to aid the study staff in locating participants for follow-up visits.

After the screening and study enrollment, participants who meet eligibility requirements will begin baseline procedures: (1) The Data Collector will conduct the combination CAPI (Computer Assisted Personal Interviewing) /ACASI (Audio-Computer Assisted Self-Interviewing) baseline assessment (Attachment 5) with the participant; (2). Following the baseline assessment, participants will be randomly assigned to the intervention or the comparison condition (projected sample size per condition N = 165).The assignment to a condition will occur by computer. Participants enrolled in the intervention condition will then be scheduled to complete the single session, "Sister to Sister Positive HOPE" intervention, a brief, nurse delivered one on one counseling session, will last approximately 45 minutes. No data will be collected from participants during the "Sister to Sister Positive HOPE" one on one intervention counseling session. Three months after completing the intervention, intervention condition participants will complete the follow up assessment (Attachment 5). The follow-up assessment will cover virtually the same content as the baseline assessment with a few additional questions regarding use of ACASI. Participants assigned to the wait list/comparison condition will return for the follow up assessment three months after completing the baseline assessment. The follow up assessment will also take approximately 45 minutes to complete (Attachment 5).

The wait list/comparison group (= control) will be offered the opportunity to participate in the intervention session after completing the follow up assessment, however no data will be collected on this group beyond the three month follow-up assessment. For each condition, participants will be reminded that they have to complete a three month follow up assessment and that they will be sent a card (Attachment 7f) with the date/time of the follow up assessment appointment. Participants will also be reminded that they will receive a reminder phone call (Attachment 7g) the day before their scheduled follow up assessment reminding them of their appointment. Participants will be given a specific "target date" for the follow-up visit (at the baseline visit for the wait list/comparison group and at the intervention visit for the intervention group). All follow-up visits will be scheduled within a two-week target window (i.e., visits may be scheduled either up to one week before or up to 1 week after the target follow-up date). Participants who miss an appointment within the target window or cannot complete the assessment at that time will be scheduled for an appointment outside of the target window, but within the acceptable window period. For the 3-month visit, the acceptable window period will be one week before the start of the target window and two weeks after the target window.

The baseline and follow-up assessment (Attachment 5) will be administered in private offices at all sites. The assessment instrument contains questions about participants' socio-demographic information, health and health care, sexual activity, drug use, and other psychosocial issues. Sensitive questions on the assessments (e.g., sexual activity, drug use) will be asked using A-

CASI. The A-CASI system displays each assessment question on a computer monitor while simultaneously playing an audio recording of the question through headphones. Participants enter their responses to the assessment questions directly on the computer. Use of this method allows not only for direct entry of data into the computer, but this method has also been shown to result in participants reporting higher rates of sensitive behavior than from other survey methods (Turner, Forsyth. O'Reilly et al, 1998). Data Collectors who have been trained in the use of A-CASI will prepare a new data record for the participant. Data Collectors will demonstrate the A-CASI system to each participant and answer any questions about its use. Questions determined not to be sensitive (e.g., socio-demographic information, health care) will be asked using CAPI, where a Data Collector will ask respondents questions face-to-face while inputting the responses into the computer. The CAPI portions of the assessment will be completed by participants at the beginning and the end of the assessment. During administration of the assessment, the Data Collector will remain on-site to answer any additional questions or address any problems.

For the in-depth individual interviews (Attachment 6), a subset of 25-30 women who participated in the intervention condition will be recruited following their completion of the three-month follow-up assessment. Participants will be identified by a random numbers table (generated from a pool of women who were randomized into the intervention arm) prior to the 3-month follow-up assessment. Data collectors will be blinded to who is selected for the in-depth interviews prior to conducting the follow up assessment. Once the follow up assessment is complete, the data collector will open an envelope to determine if the participant has been selected to participate in the in-depth interview (Attachment 6). If yes, then the data collector will read the script describing the qualitative study to determine if participant is interested in participating. If the woman agrees to participate, informed consent (Attachment 7b) will be obtained. After informed consent is obtained, the in-depth interview will be conducted or scheduled. Participants will complete in-depth interviews within 30 days of the follow-up assessment. After 10 interviews, the study investigators will assess this demographic pool of subjects interviewed to see if there is a need to target specific demographic characteristics (e.g. age, race, geography) in subsequent interviews in order to ensure a representative sample. In-depth interviews will be conducted by a trained data collector in a private room in the clinic, agency, or community AIDS organization in which the follow-up assessment took place.

Data quality is ensured by use of computer-assisted interviewing, data collector training and monitoring, site visits, and data editing. Computer-assisted interviewing improves data quality in several ways. Data Collector errors are reduced because interviewers do not have to follow complex routing instructions; the computer does it for them. Respondent errors are also reduced. Consistency checks are programmed into the assessments so that inconsistent answers or out of range values can be corrected or explained while the interview is in progress. Use of computer-assisted interviewing also reduces coding and coding errors, which makes it possible to prepare the data for analysis faster and more accurately. A two-day training of local field staff will occur prior to implementation of data collection. This training will cover general interviewing skills, the sampling and recruitment protocol, and a question-by-question review of data collections forms to ensure data collectors understand the purpose of each question and how data collected should be entered on forms and in the computer. Data collectors will have opportunities to practice administering the eligibility screener (Attachment 3a), as well as going through the CAPI/ACASI assessment. The training will also address data collector integrity, underscoring

the importance of collecting quality data and the consequences of inappropriate behaviors, including falsification of data. The training will cover how to provide technical assistance to respondents who have problems with the CAPI/ACASI assessment. During the data collection period, field staff will be monitored by their Principal Investigator or other management staff. Feedback will be provided for areas of improvement or incorrect implementation of the protocol. Supervisors will provide feedback on ways to help improve response rates. CDC will conduct at least one site visit per year. The purpose of the site visit is to monitor adherence to the study protocol and to obtain feedback on study procedures. In addition to the checks provided through the computer-assisted interview program, editing of the data will be performed by CDC, performing extensive checks of the quality of the files and identification of errors in programs or procedures.

HIV preventive psychosocial factors (or mediators) are defined as intermediate factors specifically targeted by the intervention to bring about a change in behavior. Condom use self-efficacy is a common mediator in HIV intervention studies which measures a participant's self-perceived effectiveness at using a condom. In this study, condom use self-efficacy was measured using a 9-item scale that assessed participants' confidence in their ability to use condoms properly (Cronbach's α=0.90). Data are assumed to follow a normal distribution. As with the previous analysis, the sample size calculations presented are the number of participants needed for 80% power to detect differences of varying size between the treatment condition and the control condition with a two-sided test and α=.05. Using estimates similar to those reported in the WiLLOW Study, Table 3 contains the sample size calculations.

Table 3. Participants needed for 80% power to detect a difference in condom use self-efficacy (α=.05)

Rate: Control Condition	Rate: Treatment Condition	Difference in Rates	N per Condition for 80% Power	N per Condition for 80% Power (15% attrition)	N per Condition for 80% Power (20% attrition)
12.5	14.0	1.5	274	315	362
	14.5	2.0	154	177	204
	15.0	2.5	100	115	132

Due to the size of the variability in this estimate, we need a slightly larger sample size than the anticipated 165 per treatment arm in order to detect the one percentage point difference reported in the WiLLOW Study. However, the current study, which aims to recruit approximately 165 participants per condition, has sufficient power to detect a two percentage point difference or greater.

The Sister to Sister study reported approximately 8% attrition among an HIV seronegative population. The WiLLOW Program examined the effectiveness of an intervention on transmission risk among HIV seropositive women and also reported an attrition rate of approximately 8%. For this sample size calculation, we are assuming a 15-20% rate of attrition,

thus our sample sizes are very conservative. If the actual rate of attrition is lower than we assume, the sample size needed to detect the specified difference will be smaller.

3. Methods to Maximize Response Rates and Deal with Nonresponse

Participant retention during the intervention trial will be enhanced in several ways. This is particularly important in an intervention trial, where high-levels of follow-up are required for an intervention study to be deemed scientifically rigorous.

In order to reach the number of women needed to participate in the study, we will monitor closely recruitment and retention throughout the course of the study. If we are not reaching the number of women needed, we will expand recruitment efforts by doing the following: 1) locating additional clinics and community based organizations serving HIV-positive women, 2) determining ideal times for recruitment to occur (i.e., when patient flow is maximal), and 3) maximizing study staff available during patient peak periods to increase opportunities to recruit participants for the study. Study staff will also remind participants of follow-up visits and attempt to locate participants who cannot be found. Participants will also receive a phone call (Attachment 7e) the day prior to a scheduled visit (i.e., baseline assessment, intervention and 3 month follow-up) using a reminder script (Attachment 7g). If a participant misses a scheduled visit without prior notification to staff, she will be contacted the day following the missed appointment to try and reschedule the visit.

Another important method for retention is the use of reimbursements for participation. As described in Section A.9, the use of monetary incentives has previously been shown to improve retention of participants in projects similar to this (Kamb et al., 1998; Greenberg et al., 1998). In addition, many of our potential study participants live in rural areas of North Carolina; therefore monetary incentives are necessary, in part, as a token of appreciation for their interest in assisting UNC and CDC. They will also be provided with bus passes to assist with transportation costs.

To maximize reporting of sensitive behaviors in the baseline and follow-up assessments (Attachment 5), we will use ACASI for sensitive portions of the questionnaire (i.e., questions asking about participants' sexual and drug using behaviors and traumatic life events. Research suggests that the A-CASI technology improves reporting of sensitive behaviors (Des Jarlais et al., 1999; Turner et al.). For relatively non-sensitive questions, CAPI will be used where the Data Collector administers the instrument face-to-face and enters responses directly into a computer. As described in the previous section, the Data Collectors will receive extensive training on how to administer CAPI/ACASI assessment. Participants will also receive a mini-practice session from the Data Collector before she starts the ACASI portion of the assessment. The Data Collector will be available to the participant during the ACASI portion in case she needs help or has any questions.

Since this study is a randomized controlled trial of an intervention, the following measures will be taken to minimize potential biases that could be threats to the study's internal validity: 1) use of a computerized randomization program to allocate participants into the immediate

intervention group or the wait list comparison group; 2) examination of baseline participants' characteristics (e.g., demographic and risk behavior data) to ensure that the two groups are equal; if not, make statistical adjustment in the analyses; 3) aim to achieve equal follow-up rates between the two groups; if not, examine potential reasons for differences in follow-up rates.

The Data Manager will develop and maintain databases to track and monitor data collection, enter data and produce reports on the status of data collection. Monitoring of response rates will be done through conference calls on a weekly basis with CDC, offering the opportunity to share strategies for improving response rates.

Non-response bias is certainly an issue of concern for any research study, ranging from cross-sectional surveys to observational cohorts to experimental trials. In our experience with conducting experimental trials to evaluate an HIV behavioral intervention, however, we have been extremely successful in achieving extremely high retention rates (and, thus, low rates of non-response) across a wide variety of populations and risk groups, resulting in retention rates over 80% in both treatment arms in most studies, and particularly achieving almost 90% in both treatment arms in two recently concluded intervention trials. In addition, the original research trial of the nurse-delivered intervention that is being adapted in this study successfully retained over 90% of subjects in each of 5 treatment arms.

These extremely high retention rates as observed in these intervention trials are in stark contrast to the typically low response rates as seen in most survey research. In survey research, where the primary purpose of the study is to provide an unbiased population-based estimate of an underlying parameter of interest, non-response bias can significantly impact the accuracy of that estimate. In survey research non-response bias resulting in either over- or under-estimating the true parameter of interest are equally problematic. With response rates as low as those normally seen, non-response bias is a huge concern and is most likely always affecting the validity of the results to some degree.

In intervention research trials, non-response bias can certainly play a significant role in the accuracy of the intervention effect estimate; however, if the non-response is non-differential, this results in a conservative bias (bias towards the null; greater likelihood of non rejecting the null hypothesis of no treatment difference). So, differential non-response bias is of greatest concern in intervention research trials. With the high retention rates that we have successfully achieved in our research studies, and equally high retention rates across treatment arms (non-differential rates), there is a much smaller likelihood that differential non-response bias actually occur at the level of significantly affecting the validity of our results (as compared to typical survey research studies).

Despite having a history of successful retention in previous studies, we certainly will assess whether non-response bias, and more importantly differential non-response bias, exists in our data and is affecting our findings. We will go about that using the following strategies:

- Assess the extent of overall non-response and differential non-response rates across treatment arms

- Assess potential causes for overall non-response and differential non-response by testing whether any background factors, demographics, or other individual characteristics are associated with non-response, and particularly whether these factors are significantly differentially associated with non-response across treatment arms.
- If differential non-response exists, and particularly if differential underlying factors appear to be related to non-response, then we will employ statistical analyses to attempt to address this bias. First, we will conduct simple data imputation methods such as the "missing equals failure" assumption approach and "last observation carried forward" (i.e., "no change" assumption) approach. Second, we will consider employing regression model techniques for predicting missingness and imputing missing data. Finally, we will consider conducting Bootstrap methods to account for the missingness and improve upon the estimated standard error and confidence interval of the intervention effect estimate for this study.

4. Test of Procedures or Methods to be Undertaken

Individuals who were knowledgeable about the study population (i.e., Principal Investigators and their staff, CDC investigators) and those who shared sociodemographic characteristics similar to the study population (i.e., near peers identified by the Principal Investigators, Community Advisory Board Members) reviewed the data collection instrument and provided verbal feedback on the length of the data collection instruments and readability and comprehension of each question. Based on the feedback, the instruments were further revised and shortened

Participants will be randomly allocated to one of two study conditions following baseline data collection, with follow-up measurements at 3 months after intervention (if intervention condition) or baseline (if comparison condition).

The proposed study presents a number of challenges that must be addressed in the primary and secondary analyses. First, as with any longitudinal cohort study, there is potential for attrition over the course of the study and differential attrition between treatment conditions. Second, many of the outcome measures used to assess the impact of the intervention will be non-normally distributed, including dichotomous indicators for whether risky sexual behaviors occurred and frequency variables indicating how often behaviors occurred.

Prior to beginning analyses to evaluate treatment effects, preliminary analyses will be conducted to determine whether randomization was successful in creating equivalent groups of participants across study conditions at baseline. Any differences between treatment and comparison conditions at baseline will be controlled for in subsequent evaluations of the treatment effect. Analyses will also be conducted for the purpose of describing the baseline sample and examining the distributions of each of the outcome variables (unprotected sex acts - i.e., vaginal, anal, oral). Further analyses will explore distributional assumptions related to each outcome measure.

The preliminary analysis will also include a test for differential attrition across condition. This test will be conducted using a chi-square test of a 2 treatment (intervention vs. control) by 2 attrition (lost vs. retained) contingency table analysis. A significant attrition effect would indicate a differential loss across treatment conditions which might result from there being some

underlying difference between those who were lost and those retained and/or a breakdown in randomization. All analyses will be conducted on an Intent to Treat (ITT) basis in which no randomized subjects are excluded and all subjects are analyzed according their randomly assigned treatment group regardless of actual treatment or dose received. In addition, data imputation methods will be used to include all subjects lost to follow up and thus missing 3 month data. Simple imputation methods, regression methods and bootstrap methods will be used to account for missingness in the analsyses.

The main study outcome analysis will be guided by the following hypothesis (which centers on the primary study objective): HIV+ women in the intervention group, when compared to those in the comparison group, will, on average, report greater reductions in unprotected sex acts at follow-up. The primary analysis of treatment effect on reducing unprotected sex acts will be conducted using logistic regression for dichotomous outcomes, generalized linear model-based analysis for continuous, normally-distributed outcomes and zero-inflated Poisson or Negative – Binomial regression models for zero-inflated highly skewed frequency data.

To investigate various pathways of intervention effectiveness, we will also conduct a mediation analysis of the secondary study objective, and examine the mediating effect of the condom use self-efficacy on reduction of unprotected sexual acts. The approach that we will use is described in MacKinnon et al. (2004). Under simulation studies, this approach proved to be the most powerful test of mediation. This approach also, unlike the standard approach, does not require a significant treatment effect on the outcome. The results of the mediation analysis will test the magnitude of the effect of the intervention on the outcome through various mediating pathways and thus inform the design of future interventions.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

The primary persons consulted on statistical aspects of this project and who will be responsible for analyzing the data are Ms. Felicia Hardnett of the CDC and Dr. Michael Weaver of the University of North Carolina-Chapel Hill. The study design and data collection instruments were a collaborative effort between CDC and University of North Carolina-Chapel Hill. UNC-Chapel Hill will be responsible for data collection activities.

Statisticians assigned to the project are as follows:

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