Program Responses to DHHS OMB Comments/Questions Regarding the ***Nurse Delivered Sexual Risk Reduction Intervention for HIV-Positive Women in the South*** Information Collection Request (CDC ICR 0920-05CS)

Thank you very much for such a thoughtful review. Please find below the responses to reviewer comments/questions below. Also please note that the pages referenced correspond to page numbers for the entire ICR (total pages =144) and not to the individual sections. The information included in the responses has also been inserted in the Information Collection Request where indicated.

Reviewer: How will effectiveness be determined?
Response: 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 (i.e., vaginal, anal, oral) 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. The data analysis plan is included in greater detail in the section entitled, *"Test of Procedures or Methods to be Undertaken."* (pg. 9 – Purpose and Use of Information Collection)

Reviewer: Will [locator data] data be retained in any form?
Response: The paper copies of the Locator Form will be destroyed immediately after the information is entered (on a daily basis) into the computer file on an encrypted and password protected computer in the research office with access only to the Principal Investigator, Project Manager and Research Data Manager. The computer file will be destroyed within 6 months after the end of the intervention trial. No locator information, in any form, will be retained after this period. (pg. 15 – Privacy Impact Assessment Information)

Reviewer: What does this pledge include?
Response: By signing the pledge, staff acknowledge that they have read, received and had all their questions answered regarding the document entitled, *"Ethical Guidelines for Project Staff*." This document outlines ethical guidelines for staff working with the project, specifically as related to maintaining professional boundaries in staff-participant relationships and general rules of conduct, including demeanor, dress and prohibiting drug and alcohol use. Staff also agree to keep all information regarding study participants as secure as possible, to the extent permitted by law, and not to disclose the names of participants, information about their personal lives, or the fact that they are study participants to anyone who is not a member of the research staff. (pg. 15 – Privacy Impact Assessment)

Reviewer: How were these estimates determined?
Response: These estimates were derived from pilot testing the assessment with 9 HIV+ women. (pg. 17 – Estimates of Annualized Burden Hours)

Reviewer: How will potential non-response bias be analyzed?
Response: 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 *(References are available upon request)*. 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. (pgs. 28-30 - Methods to Maximize Response Rates and Deal with Nonresponse)

Reviewer: Please describe all statistical analyses to be used. Also, clearly state under what circumstances this intervention will be determined "effective." (If there is a statistically significant decrease in risky behaviors? A statistically significant increase in protective behaviors? How many significant improvements, and on what items, will be needed to deem the intervention successful?)
Response: 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 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). *(See Assessment – pg. 72 (for main partner), page 87 (for HIV+ other partners), pgs. 95-96 (HIV- other partners) and pgs. 104-105 (Unknown status other partners)*. 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 analyses.

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. (pgs. 30-31 Test of Procedures or Methods to be Undertaken)

Reviewer: Why is this information being collected? Will participants be contacted or searched for at these locations?
Response: It is optional for a participant to provide information on "hang outs." Staff will inform participants of the purpose for collecting this information and that it will helpful in locating them if needed. Participants will be informed that it is optional to provide this information. (pg. 44 Appendix 4 - Locator Information Form)

Reviewer: Perhaps provide examples/more description to distinguish Treatment Agencies from Health Care Providers
Response: We added the following examples of treatment agencies: substance use, mental health and case management. (pg. 44 Appendix 4 - Locator Information Form)

Reviewer: Perhaps include suggestions of what to include here (e.g. times available?).
Response: This item is an optional field for staff to complete if any additional information relevant to contacting a participant is needed. We have accepted the reviewer's recommendation to add "times available." (pg. 44 Appendix 4 - Locator Information Form)

Reviewer: Delete this choice – "Other" category for race.
Response: The "other" category for race has been deleted. (pg. 47 – Assessment)

Reviewer: Are you planning to get pregnant in the future? Should there be space to include number of months (greater than 3)?
Response: The intent of this question is to determine if a participant plans to ever get pregnant. Also, participants indicating that they planned to get pregnant in the next 3 months (at screening) would have been determined to be "ineligible" and excluded from participation in the study. (pg. 49 – Assessment)

Response to Additional Reviewer Comments:
Per the email dated 10/7/09, we have made the requested revisions throughout the ICR in deleting references to the term "confidentiality" and replacing it with "secure" where indicated.