TO: Ms. Mikia Currie April 4, 2011

FROM: Simone Glynn

SUBJECT: Response to OMB comments for Transfusion-transmitted retrovirus and hepatitis virus rates and risk factors: Improving the safety of the US blood supply through hemovigilance (NHLBI)

Dear Ms. Currie,

In response to the OMB comments regarding the REDS-II protocol entitled "Response to OMB comments for Transfusion-transmitted retrovirus and hepatitis virus rates and risk factors: Improving the safety of the US blood supply through hemovigilance (NHLBI)", we have made the following modifications:

1) Study design

- ***Listed as one of the Specific Aims of the project is to "Determine nationally representative infectious disease marker prevalence and incidence for HIV, HCV, HBV, and HTLV overall and by demographic characteristics of donors." Please explain how the sample allows NIH to make conclusions that are nationally representative?***

Aim 3 of the project will create a database representing 60% of all blood donations collected in the country from blood donors in most but not all of the 50 States. The database will capture basic demographic information (age, gender, race, first time or repeat donor status) for all blood donors from the American Red Cross, New York Blood Center, and Blood Systems, Inc. blood centers during the time period of the study (2011 through part of 2012). This database will include all infectious marker positive donations for HIV, HCV, HBV, and HTLV permitting us to report on the prevalence of these infections in a very large sample of all blood donors. The participating blood centers collect blood in all or part of 45 of the 48 contiguous United States including large metropolitan and more rural areas of the country, providing a geographically distributed sample of the United States donor population.

- ***On page 5 of Part B, NIH states that controls "for the study are intended to reflect the population of eligible blood donors". Do you mean eligible blood donors or active blood donors?***

We recognize that different word choices may convey different meaning. Our intent is for the controls to reflect the population of eligible blood donors who have successfully donated blood. In other words, the controls will represent all persons who have been determined eligible to donate in the same time frame as cases and who have donated blood that has been tested for infectious disease markers. In blood banking, "active donors" generally refers to highly engaged repeat donors who donate frequently. Supporting Statement Part B has been revised with this additional text.

- ***Why did NIH decide to make the control group false positive donors and not just donors?***

Donations from donors that test initially repeat reactive that ultimately cannot be confirmed by supplemental testing are thought to be random events and therefore they represent an appropriate random sample of blood donors. Studies of confirmed infected and confirmed uninfected blood donors have previously used this strategy to identify controls for case-case control studies and research has shown that donors with false positive results on the initial screening tests are not infected. Robust confirmation procedures are used to ensure false positive donors are indeed false positive. There is virtually no chance that a false positive donor will be a true positive donor that has been misclassified. Donors with indeterminate confirmation results will not be eligible controls for this study.

False positive donors are notified of the testing results according to standard operational procedures. The operational processes that are used for blood test results notification for these donors represent an opportunity to sample an informative control group that has interacted with each blood center in a largely similar manner to that of cases. These donors are contacted by mail informing them of the results of testing and their false positive status. They represent appropriate controls because they have gone through confirmatory testing procedures that unambiguously establish they are not infected with one of the four viral infections of interest in this study. In addition because they have to be contacted and provided the results which include the false positive screening tests, these donors may be interested and motivated to complete the questionnaire as part of the counseling process. All controls will be serving as the comparison population for each confirmed positive infection the ratio of controls to cases will vary according to each viral infection.

- ***Please explain how each participating organization will "ensure that the controls in the study are similar to the population of eligible donors" and how the organization will monitor this. (Part B, page 6)***

Each participating organization will have to ensure that the controls in the study are similar to population of eligible donors according to age, gender, race, and first time donor status. To accomplish this each organization will monitor the demographic characteristics of control donors so that study participants resemble the eligible donor population for that blood collection organization while the study is being conducted. For example we will select controls in bins that largely resemble the eligible donor population with respect to gender, age group, race/ethnicity, and first time or repeat donor status. Procedures to be used at each blood center for the ongoing monitoring will be developed during the ramp-up phase of the study. It should be noted that, as a result of the low positive predictive value of these tests when used for blood donors, many false positive results are found for each true positive.

- ***Will 80% power to detect a 5-fold increased prevalence of risk will be sufficient for how NIH plans to use the results of this study?***

The results of the study will be informative for scientific, regulatory and policy reasons. For each infection specific viral infection power calculations were performed to determine what the power would be for the expected sample size. Given that we are inquiring about the possible behaviors or exposures that are associated with infection acquisition, we expect that for many risk factors the true positive donors will have notably higher prevalence of the risk factors than the control donors. For that reason the power calculations allow us to say that even if the difference in the prevalence of specific risk factors is as low as only 5-fold higher for HIV or HTLV and 3-fold higher for HBV and HCV in cases compared to controls we will have sufficient ability to detect statistically significant differences. In fact the difference

in the prevalence of risk factors may be much higher in cases than 3 or 5-fold when compared to controls.

A balance must be struck in donor eligibility that meets the simultaneous goals of achieving the safest blood supply possible while still ensuring that an adequate quantity of blood in the supply is available to meet transfusion needs. A difference of 3 to 5-fold in relative risk of infected donations among subsets of donors (differentiated based on donation type, demographic or behavioral risk factors) is generally accepted as the level of relative risk that drives policy decisions regarding blood donor eligibility criteria and content of the donor history questionnaire. For example there is a >20-fold difference in prevalence and an approximately 3-fold difference in incidence for major transfusion transmitted viral infections (TTVIs) among first time donors (which represent ~20% of donations but nearly 50% of donors each year) relative to repeat donors. There are also approximately 3 to 5-fold differences in prevalence and incidence of TTVIs when donors are sorted by demographic characteristics such as gender, race/ethnicity, country of birth or region of residence in the US. Consequently this level of relative risk is deemed acceptable, whereas higher relative risks for groups such as persons with histories of injection drug users or high risk sexual exposures have led to explicit questions and FDA-sanctioned deferral criteria. One goal of our study is to establish if there are additional behavioral risk factors that exceed this tolerable level that should result in consideration of new deferral criteria (e.g., # of recent heterosexual partners).

- ***You assumed a 75% participation rate for confirmed positive donors. Please explain the basis for that assumption.***

We assumed this participation proportion because previous *retrospective* studies of risk factors for confirmed positive blood donors had participation rates of 56% (See Orton and colleagues HCV NAT risk factor study.) In that study donors who donated up to 4 years before were contacted, in our study we will be contacting donors in essentially real time leading us to believe we will be able to obtain higher participation rates. Plus we are leveraging the communication skills of trained donor counselors and physicians to enroll donors in the study. Donor counselors and blood bank physicians have expertise and training in empathetic communication which should help in to obtain the expected participation proportion. We acknowledge the participation proportion we plan to achieve is relatively high for interview studies.

2) <u>Incentive Scheme</u>

- ***The factors that justify the incentives must be outlined.***

The incentives used for the study are justified on the basis of three considerations.

First, the majority of interviews will be conducted by telephone at the time of first voice contact with the donors. It is very important that we seize upon this opportunity to enroll the potential participants in the study and we believe that offering incentives will help the donor counselors and physicians to gain consent for participation in the study. From our experience in previous studies of infectious markers in blood donors, it is best to complete interviews of risks factors during the first voice contact. Incentives can help to facilitate the willingness to complete the risk factor questionnaire

Second, we will be seeking verbal consent to ask the study participants sensitive questions regarding private and personal behaviors. The incentives are intended to recognize and thank each subject for taking the time to answer the questions as honestly as possible.

Third, the two-tiered incentive schedule has been guided by the following factor. The risk factor questionnaire is designed with skip patterns consisting of initial screening questions that ask if the participant has a specific risk behavior or exposure. If the participant says yes, then additional questions are asked to get more specific details. It is expected that cases will have more risk factors and so it will take longer for cases to complete the questionnaire.

To more closely parallel other government funded interview studies we have decided to modify the incentive amounts. We will pay each case $75 incentive for a completed interview and will pay each control $35 for a completed interview. The two tiered incentive schedule remains in place because of the expected time difference to the complete the interview.

- ***Why the large difference in incentives for positive and false positive donors when positive donors only have two additional questions to answer? Wouldn't false positive donors require more of an incentive since they likely would not be seeking counseling otherwise?***

The incentive for participation is structured so that the expected amount of time necessary to complete the risk factor questionnaire is commensurate with the incentive amount. While it appears that cases and controls will be answering nearly the same number of questions, the questionnaire is designed with skip patterns. With the expectation that cases will have more risk behaviors or exposures to report, it will take longer for cases on average to complete the questionnaire than it will for controls. The reimbursement schedule is designed to reflect this difference. Our goal is to reimburse participants for total time it will take to complete the risk factor interview because complete answers for all questions on the questionnaire are critical for the success of the research project.

- ***Page 6 in Part A states "compensate for the study subject's time spent" and page 7 states "reimburse participants for their time." Our understanding is that this is an incentive for participation, not compensation or reimbursement. Please clarify that language.***

Please see the initial response in this section.

- ***Page 7 in Part A states that the $100 participation incentive would "encourage the honest reporting of risk behaviors". Is there any research that supports the idea that larger incentives cause more honest reporting?***

The two-tiered reimbursement is intended to function in a way that is commensurate with the amount of time necessary to complete the risk factor interview. In the protocol we may have erred in indicating that higher reimbursement may lead to more honest reporting of risk behaviors. We are unaware of studies that demonstrate more honest reporting when larger reimbursement is provided.

3) Privacy Issues

- ***When a donor receives the notification letter with positive results and counseling materials, does he/she know that the results are positive or false positive—or do the results just say positive?***

According to standard operating procedures each donor is notified of the exact testing results and their meaning – either by letter or in person (for HIV infection). Letters do not just say positive.

- Explain the procedures that NIH will follow to ensure that the information will be kept "as confidentially as possible" as stated on page 7 in Part A.

The study procedures are designed to protect the privacy of the study participants. Each participating blood center has obtained human subjects approval from relevant IRBs to conduct all aspects of the study. Each IRB has approved the privacy procedures we have built into the study design. The only persons who will have access to personally identifying information are the donor counselors and physicians within in each blood collection organization. The personally identifying information will be used to properly identify each donor according to standard operation procedures and to provide the reimbursement for participation. The information collected in the research databases will include unique study identification numbers. The data transferred to the researchers in this project will not include personally identifying information and from this data it will not be possible to trace back to personally identifying information. In addition, by specific addendum this study is covered by the Certificate of Confidentiality covering all of the Retrovirus Epidemiology Donor Study – II project thus preventing the researchers from being legally compelled to release information reported by the study participants.

- ***Please provide the Privacy Impact Assessment.***

NIH will not hold or receive databases from this project.