DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

November 16, 2010

Mr. Robert Reinhard,
Public/ Global Health Consultant
68 Yukon Street San Francisco, CA 94114

Dear Mr. Reinhard:

Thank you for providing detailed comments in your letter of October 28 on the study entitled, Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factors: Improving the Safety of the US Blood Supply through Hemovigilance. For the purpose of brevity throughout the remainder of this response, the study will be referred to as the US Risk Factor study. Your thoughtful comments show your commitment and high level of interest in blood safety issues and the topic of donor eligibility, and are much appreciated. As you know, the National Heart, Lung, and Blood Institute (NHLBI) has primary responsibility at the National Institutes of Health (NIH) for supporting research studies to improve the safety and availability of the Nation's blood supply.

We have addressed each of your comments in the order you provided them beginning with your overall comments.

The proposed study is not designed to address all individual recommendations of the June 2010 Advisory Committee on Blood Safety and Availability (ACBSA) meeting. However, we believe that the proposed study does meet part of the objectives of the 2nd recommendation of the Committee, namely:

> "To develop and validate candidate alternative policies, we recommend research in the following areas:
>
> 2- Establish ongoing national hemovigilance program for TTID markers in blood donors linked to analysis of demographic, behavioral, and other risk factors:
>
> a. Obtain a baseline on prevalence and incidence of TTIDs,
> b. Characterize risk in different donor subgroups (e.g., younger age), and
> c. Use above characteristics for continuous quality improvement of the donor deferral process;"

This research study will represent approximately 60% of the nation's blood supply, and serves as *a pilot* for an expanded initiative that could include a larger proportion of the blood supply. The intended study population for this project is not restricted in any way to specific donors according to gender, race or ethnicity, age, or any other demographic characteristic.

We will seek to obtain risk factor information from all persons who have donated a viral disease marker positive donation and an appropriate comparison population of control donors at the three participating blood collection agencies.

Unfortunately, it is not possible to address the June 2010 recommendations of ACBSA in one study. The recommendations require a wide-ranging set of studies, many of which will depend on other methodologies entirely different than those we propose to use in our study. To achieve further important insights into the issue of lower risk men who have sex with men (MSM), different study designs are necessary. We are aware of other studies that are being planned that may more directly address the specific questions regarding MSM by stratification of risk as related to possible blood donation.

With respect to your numbered comments:

1. **Improved Characterization of Populations and Risks.**We agree with your assessment of the infectious disease trends from the recently published paper by Dr. Zou and colleagues from the American Red Cross (Transfusion 2010;50:1487-94). The US Risk Factor study does not make any hypotheses regarding HIV risk and specific race or ethnic backgrounds. The purpose in providing this information was to indicate that continued vigilance coupled with compilation of additional data are necessary to understand whether any significant trends are present. The US Risk Factor study hypotheses are focused on the need to determine whether risk factors for infections in blood donors today are different than those previously reported, and if modifications to the donor health history questionnaire are needed. No assumption has been made about what the results will show. This study will be able to partly assess your point regarding blanket MSM risk versus assumed risks related to the number of sexual partners for heterosexuals because identical risk behavior information will be collected from all participants regardless of sexual identity.

   We agree with your assessment that the US Risk Factor study will not be informative with regard to lower risk MSM who might potentially be eligible to donate. The investigators will not over-interpret the findings of this study or make any conclusions outside of the population of persons who did not disclose risk factors at the time of blood donation. The primary goal of the US Risk Factor study is to catalog risk factors associated with disease marker-positive blood donations and to report on the rates of disease marker-positive donations in more than 50% of the overall US blood supply.

2. **Additional Population Study.** The US Risk Factor study will take place in almost every state in the contiguous US. The study proposal does not target San Francisco or New York. Some of the investigators for the study are based in these locations, but the study itself will seek to enroll blood donors in all of the areas in which the American Red Cross, Blood Systems, Inc. and New York Blood Center collect blood. The US Risk Factor study supplements existing operational procedures that are used by blood centers.

US blood centers conduct all eligibility assessment procedures in English and occasionally in Spanish. Donors must be able to understand, communicate, and provide informed consent for blood donation and testing in English or Spanish to be eligible to donate. Except in unique circumstances, and for donors in Puerto Rico, donor notification is conducted in English. The US Risk Factor study will be relying on these standard procedures, and operational languages. In addition, persons who will conduct the telephone interviews are highly trained donor counselors at each blood center and quickly will be able to identify language comprehension issues.

3. **Questionnaire Administration Techniques.** We agree with your comment that ACASI is a useful tool for obtaining socially sensitive or personal information. The researchers in this study are familiar with and use ACASI in other studies. However, because this study of blood donors is relying upon the current notification procedures used at each participating blood collection agency, the use of telephone administered questionnaires is more appropriate for the study design. Study participants will come from virtually every location in the contiguous US and thus, ACASI cannot be deployed in a controlled manner that ensures protection of confidentiality. As technology advances, future studies may permit the use of secure, web-based ACASI interviews. Please note that part of the ability to achieve risk behavior disclosure in this study relies on the expertise of highly trained and empathetic donor counselors who will be conducting the interviews.

4. **Payment Incentives.** First we would like to acknowledge a limitation of the language that was used in the protocol; the term "incentives" is incorrect and the term "reimbursement" should have been used. That is because the aim is to reimburse participants for the time it takes to complete the study. The two-tiered approach to reimbursement has been guided by the following primary consideration. The reimbursement is intended to appropriately compensate each participant for the expected time it will take to complete the study. It will take longer for disease marker-positive donors to complete the questionnaire than for control donors. Furthermore, disease marker-positive donors have no compelling reason to maintain a relationship with the blood center since they cannot donate blood again. This study design of including a two-tiered payment between confirmed-positive (case) and false-positive (control) donors has been successfully used previously in several studies conducted by blood centers investigating undisclosed donor risk or symptomatic infection outcome following donation. Each study was approved by an institutional review board and appears in the peer-reviewed literature. Examples include:
    - Orton SL et al., Risk factors for HCV infection among blood donors confirmed to be positive for the presence of HCV RNA and not reactive for the presence of anti-HCV. Transfusion 2004;44:275-81.
    - Orton SL et al., Self-reported symptoms associated with West Nile virus infection in RNA-positive blood donors. Transfusion 2006;46:272-7.

- Custer B et al., Association between West Nile virus infection and symptoms reported by blood donors identified through nucleic acid test screening. Transfusion 2009;49:278-8.
- Zou et al., West Nile fever characteristics among viremic persons identified through blood donor screening. Journal of Infectious Diseases 2010;202:1354-61.

5. **Informed Consent/Protection of Confidentiality.** First, blood centers are explicitly not covered entities under HIPAA, so law enforcement cannot compel the disclosure of any information by blood centers using HIPAA. Blood centers must deal with protection of confidentiality every day and the researchers have tried to build in protections into the study design that will further reduce the chances that individuals can be identified. For example, the donor counselors or doctors who conduct the interviews will be the only persons in the study who will have access to personally identifying information, which of course is required for results notification. The study investigators will receive information such as the study questionnaire form number and blood unit number so that laboratory testing results can be traced if necessary. However, they will not receive personally identifying information. In a further effort to protect confidentiality, the investigators have obtained a Certificate of Confidentiality (see page 13 of protocol). This provides enhanced protection for participants. The investigators are compelled to release information only if a study subject indicates an intention for personal harm or harm to another person. No other reason is permitted.

   The current versions of the informed consent and description of study objectives have been approved by three separate Institutional Review Boards (IRBs) that independently cover the activities of the three participating blood collection agencies. For this reason, the current language for the informed consent and description of study objectives appears to have been adequately vetted.

6. **RFQ Question 13.**We concur with your interpretation that the content of the questionnaire covered in Question 13 is subjective. The purpose in asking the three parts of question 13 is to investigate the subjective opinion of the study participants. No donor is required to complete any specific question and may decline to respond. The content of question 13 is general in nature and does not imply that current donor selection procedures are either "fair" or "unfair"; instead, this question aims at learning what donors think. Again, the Certificate of Confidentiality will protect the disclosure of any responses on this question.

7. **RFQ Questions 19 and 20.** We agree that the results, whatever they turn out to be, cannot and should not be over interpreted and stress again that this study is not intended to provide specific data on the topic of lower risk MSM and blood donation. This study is a preliminary evaluation of all risk behaviors associated with disease marker-positive donations.

In questions 19 & 20, the different time periods that are being inquired about are not presumed to be the optimal time periods with regard to any possible blood donation policy changes. However, while these time periods have been discussed, there are no data to know the frequency with which donors will fit within each of the time periods. This information will be useful because identical questions are being used for male and female donors regardless of sexual identity, and for cases and controls; therefore, new results that have not previously been determined for US blood donors will be obtained.

Thank you again for your comments and we are hopeful that our responses directly address the issues you raised. Please be assured that the NHLBI is firmly committed to the continued support of research to ensure the safety and availability of our valuable blood supply.

Sincerely yours,

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