Supporting Statement B for
The effectiveness of donor notification, HIV counseling, and linkage of HIV positive donors to health care in Brazil

OMB Number: TBD

March 2015

Sponsored by:

The National Heart, Lung, and Blood Institute
Blood Epidemiology and Clinical Therapeutics Branch
National Institutes of Health

Project Officer/ICD Contact:

Simone Glynn, MD
Blood Epidemiology and Clinical Therapeutics Branch
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
Two Rockledge Center
Suite 9142
6701 Rockledge Drive
Bethesda, MD 20892
Phone: (301) 435-0065
Fax: (301) 480-0868
Email: glynnsa@nhlbi.nih.gov

TABLE OF CONTENTS

Page

B. Collection of Information Employing Statistical Methods

In this study, we will formally measure donor notification rates resulting from the testing of donations for infections (e.g., HIV, Hepatitis B and Hepatitis C) at four major blood centers in Brazil, and enroll a cohort of HIV-positive donors in a follow-up study to assess linkage to health care and risk behaviors following notification of donation testing results. Our findings will yield insights into improved methods for donor selection and qualification that can increase rates of self- and on-site deferral and therefore decrease the frequency that higher-risk persons are accepted as donors in Brazil and other Latin American countries. This will also serve to guide the development of improved notification/counseling strategies in the US and identify potential ways to reduce test seeking.

There are 3 aims for this study:

1. Aim 1 is to conduct an analysis of the proportion of donors who are successfully notified for the infections for which donations are tested in Brazil, and to identify the factors associated with successful notification. In the Brazil context, successful notification means that the donor returns to the blood center for additional testing and results counseling.

2. Aim 2 is to assess whether HIV-positive donors who returned to the blood center for notification and counseling subsequently attend HIV referral centers for additional counseling, treatment and health care follow-up, and to determine self-reported behavioral change among HIV-positive donors using audio computer-assisted structured interviews (ACASI).

3. Aim 3 is to utilize HIV positive blood donors (from Aim 2) as key informants by inquiring through ACASI about ways in which we can improve the disclosure of HIV risks in donors during eligibility assessment.

This study is also a follow-up to previous research conducted on HIV-positive blood donors in Brazil. The four REDS-III Brazil blood centers maintain files which will permit data linkage to the REDS-II and REDS-III HIV participants because each center tracks the number of HIV-positive donors, blood bank registration ID number (donor ID), study ID number from the REDS projects, blood sample ID numbers, date of birth, address and contact phone number. Based on this set of information, we will be able to identify HIV-positive blood donors, the subset who previously returned, and the subset of returning donors who completed the HIV risk factor questionnaire during REDS-II or REDS-III.

B.1. Respondent Universe and Sampling Methods

The study population for Aim 1 will come from the current REDS-III Brazil participating blood centers: Fundação Pró-Sangue (São Paulo), Hemominas (Belo Horizonte), Hemope (Recife), and Hemorio (Rio de Janeiro). The study participants will be Portuguese-literate persons aged 18–69 years who were sent notification letters during the first three years of the REDS-III study consequent to infectious marker repeat reactive or inconclusive results for HIV, HCV, HBV, HTLV, syphilis or *T. cruzi* who did and did not respond or return to the blood centers following receipt of the letter. The blood center notification letters are sent by standard mail with delivery confirmation. Letters that

cannot be delivered are returned to the blood centers. Only donors for whom delivery confirmation to the last known address the donor provided at the time of donation will be included in the study.

There will be no sampling or new data collection for Aim 1 of our study, in which we will analyze results from all of the donors meeting the eligibility criteria using extant data.

Our study's population for Aims 2 and 3 will be HIV-positive Portuguese-speaking persons aged 18–69 years who participated in the REDS-II HIV case-control study, or, the first three years of the ongoing REDS-III HIV case surveillance study. The target enrollment for aims 2 and 3 is 275 blood donors which should be achievable considering the number of HIV-positive donors enrolled in the REDS-II study and the numbers enrolling in the REDS-III study thus far: During the REDS-II case-control study, 341 HIV positive donors were enrolled in the four participating Brazilian blood centers. Further, a subset of enrollees in the REDS-III study (about 120) during 2012 to 2014 will be eligible for this new study (see Sample Size Calculations below).

Aims 2 and 3 will utilize a convenience sample, since we will be recruiting all eligible donors whom we are able to recall as described in the previous paragraph.

Sample Size Calculations:

Aim 1: The overall percentage of discarded blood units for serologic markers varies from 4% in Sao Paulo to 8% in Recife, and in Brazil the great majority of discarded units are attributable to repeat reactive and inconclusive donation testing results**.**

Table 1. Number of delivered notification letters and blood donor returns by blood center* and infectious marker. **

Infectious Marker	Fundação Pro-Sangue		Hemominas		Hemope		Hemorio	
	Delivered Letters n	Returning donors n (%)	Delivered Letters n	Returning Donors n (%)	Delivered Letters n	Returning donors n (%)	Delivered Letters n	Returning donors n (%)
Chagas	10	3 (30%)	29	22 (76%)	1	0 (%)	22	15(68%)
HBsAg	6	5 (83%)	34	28 (82%)	23	9 (39%)	6	2 (33%)
Anti-HBc	88	39 (44%)	326	239 (73%)	236	105 (44%)	52	12 (23%)
HCV	31	9 (29%)	38	27 (71%)	44	17 (38%)	19	6 (31%)
Syphilis	83	34 (41%)	225	165 (73%)	538	244 (45%)	119	21 (18%)
HTLV	2	2 (100%)	20	16 (80%)	36	16 (43%)	6	0
HIV	20	11(55%)	41	31 (76%)	78	34 (43%)	22	3 (14%)
Total	**240**	**103 (43%)**	**713**	**528 (74%)**	**956**	**425 (44%)**	**246**	**59 (24%)**

** Data related to one month period (August 2010 for Hemominas and Hemope, October 2013 for Hemorio, and August 2013 for Fundação Pro-Sangue).*
***Includes repeat reactive and inconclusive results.*

These preliminary data show marked differences in the number of persons who return following receipt of letters by blood center and infectious marker.

Using the data from the one month period described above we estimate that for a 3-year period (36 months) we will have the following total number of letters sent that will be included in our analysis of notification success (Table 2).

Table 2. Estimated number of request for return to the blood center letters delivered for repeat reactive or inconclusive testing results for all infections (HIV, HBV, HCV, HTLV, syphilis, and *T. cruzi*) at each blood center in 2011-2013.

Blood center	Approximatenumber of notification letters in a 3-year period
Fundacao Pro Sangue (Sao Paulo)	8,600
Hemominas (Belo Horizonte	25,600
Hemope (Recife)	34,400
Hemorio (Rio de Janeiro)	8,850
Total	77,450

Aim 2 and 3 Sample Size

The estimated enrollment for these aims is based on the current enrollment rates for the HIV molecular and risk factor surveillance study in REDS-III combined with achieved enrollment from the REDS-II case-control study. For REDS-III, approximately 46% of eligible HIV positive donors have enrolled in the risk factor and molecular case surveillance study. One-hundred-seventy-eight (178) donors have enrolled in the REDS-III study as of May 6, 2014. Because study personnel have recently had contact with these donors, for this notification and HIV follow-up protocol it is expected that 60% to 75% of these 178 participants, or 95 to 119 participants from the REDS-III case surveillance study will enroll, with additional potential eligibles from the period May 7, 2014 – December 2014. With respect to the previous REDS-II case control study, it is assumed that an enrollment rate of 50% for the 341 HIV positives from the REDS-II HIV case-control study will be achieved for the notification and HIV follow-up study, leading to 171 participants from the REDS-II study. Therefore, the overall expected participation in the counseling and follow-up study is 265 to 290 participants. This number has been rounded to a targeted enrollment of 275 participants.

Table 3. Overall REDS-III HIV molecular and risk factor surveillance study enrollment by blood center May 6, 2014.

Blood center	Total enrolled (%)	Study launch
Fundacao Pro-Sangue, Sao Paulo	53/90 (59%)	11/8/2012
Hemominas, Belo Horizonte	22/76 (29%)	12/3/2012
Hemope, Recife	48/121 (39%)	12/4/2012
Hemorio, Rio de Janeiro	55/98 (56%)	12/13/2012
Total	178/385 (46%)	

B.2. Procedure for the Collection of Information

There will be no formal sampling for any of the three aims. We will be recruiting all eligible donors for the Aims 2 and 3.

For Aim 1, we will not be recruiting donors. We will extract data for analysis from extant operational databases.

For Aims 2 and 3, HIV-positive donors who participated in the REDS-II HIV case-control study or from the first three years of the ongoing REDS-III HIV-positive case evaluation study (2012-2014) will be invited to return to the blood center to participate in this additional study. Based on a list of

HIV-positive participants from the previous studies, a phone call will be made to invite them to participate in this new study. If the person agrees to be enrolled, a follow up letter establishing a day and time for the appointment will be sent. We plan up to two phone call attempts followed by two letter attempts to enroll each participant.

No reimbursement will be provided for Aim 1. The project will pay US$ 35.00 (~R$75.00 in Brazil currency) to reimburse participants for transportation expenses to and from the blood center, and time away from other activities to participate in Aims 2 and 3 of this study. This reimbursement is intended to acknowledge the importance of participation (completion of the ACASI interview) in this notification and HIV follow-up study based on previous participation in the related REDS-II and REDS-III Brazil HIV studies. There is no other study population that can be accessed to achieve the objectives of the planned study.

We will also try to obtain with Aim 2 participants' consent the HIV infection status information captured in the State and National databases on HIV progression such as viral load and CD4/CD8 counts. The Brazilian National HIV treatment and progression databases (SI-CTA) were created in 2002 by the Ministry of Health because of the need to register and monitor the care provided by HIV Counseling and Testing services (HCT)/medical staff, obtain demographic, behavioral, and biological information regarding the individuals who attend this service. Each Brazilian HCT provides information on the individuals with HIV/AIDS (based on viral load, CD4 and CD8 information) to a data coordinating center located in Brasília. Some HCTs also provide testing for syphilis and hepatitis B and C (see B3 below and section 4.5.2 of the protocol).

Data Analysis

Aim 1: Analysis of proportions of donors who return by infection type, blood center, and donor demographic characteristics. Depending on the outcome variable, modeling the proportions may require logistic regression (dichotomous outcome) and multinomial logistic regression (polychotomous outcome). In addition, we plan to compare time to return to the blood center using Kaplan-Meier curves to see if there are earlier median return times for some infections compared to others. We may then compare return proportions by center to establish if there are statistical differences between centers in the success in notifying donors.

Aim 2 & 3: *Analysis of Risk Behaviors and Behavior Change*

Primary Predictor Variable. Self-reported attendance to clinics or health care services for HIV infection treatment.

Outcome Variables. Evidence of behavioral risk reduction (change) based on responses to the same HIV risk behavior questions at two time points spaced at least one year apart.

Quantitative Analyses
The demographic characteristics of the participants in the study population will be compared to HIV-positive donors over the same time frame as captured in the REDS-II and REDS-III Brazil donor and donation databases (2008 – 2014). Changes in HIV risk factors ascertained by questionnaire, including male-to-male sex, number of lifetime male and female sexual partners, number of male and female sexual partners within the past year, use of condoms, IDU, sex with an IDU, and age of sexual debut

will be assessed. Secondary predictors will include demographics, socioeconomic status, and other factors such as drug and alcohol use.

A study participant who is enrolled shortly after receiving notification of being HIV-positive by the blood center but has not sought follow up care may be someone who will not seek follow up care or someone who hasn't sought such care yet. We will use time-to-event analysis techniques with seeking follow-up care as the outcome. Elapsed time will be defined as the time from notification to obtaining follow-up care. Persons who have not sought care by the time of the study would be treated as censored observations with respect to analysis of linkage of donors to healthcare. This approach will allow us to account for the differential follow-up times between REDS-II and REDS-III donors who participate in this study.

Bivariate associations of specific categorical risk factors will be assessed using contingency tables with significance tests using Chi squared or Fisher's exact tests. Any risk factors with a continuous distribution or format will be assessed using logistic regression. Variables with significant or borderline bivariate associations ($p<0.15$) with confirmed HIV infection will be entered into a multiple logistic regression, multinomial logistic regression, or Cox proportional hazards regression model to assess independent associations and potential confounding. In additions, variable selection methods, i.e., forward selection, backwards elimination, and stepwise selection, may be used to identify relevant predictor variables. Key variables that will be examined to assess behavioral changes over time will include the use of condoms and the number of sexual partners in the year before the original HIV-positive blood donation and before completion of the new ACASI for this study. In addition, the number of persons with access to public or private HIV health care services will be reported.

Based on results of the HIV case-control study (REDS-II), 70% of the HIV-positive participants reported high-risk behaviors (1); Of those, we presume that as many as 20% will not have changed their risk behaviors, but this type of assessment has not been attempted before and so is highly speculative. Assessment of and understanding lack of risk reduction (behavior change) is important from a public health perspective because it will identify those risk behaviors where additional education efforts to prevent persons from being exposed to multiple strains of HIV are necessary, and also to define characteristics of persons who may further spread infection. We are also interested in assessing if behavior change is the same for donors who gave at each blood center or if regional differences may be evident.

We expect that if persons have records in the Brasilia SI-CTA (Ministry of Health), indicating evidence of ongoing access and use of health care services, risk behaviors may be different than for those donors without any evidence of being under care for HIV infection.

Qualitative Analyses We will group the study participants into two distinct groups: high and low risk behavior, for qualitative analyses. These groupings will be based primarily on number of sexual partners, use of condoms, and whether illegal drug use is reported. Common themes and recommendations for questions to ask prospective blood donors that might help to better identify persons with risk behaviors who should not be allowed to donate will be assessed.

Aim 3 will use mixed methods of qualitative and quantitative analysis of ACASI response data to identify common themes or approaches recommended by HIV-positive donors to help elicit risk behavior disclosure before donation occurs.

B.3. Methods to Maximize Response Rates and Deal with Non-response

During data collection, we will monitor participation and response rates to identify any potential problems that are indicated by differential response rates across sites. We assume that the responses rates of the HIV-positive subjects for the completed REDS-II and REDS-III phases of the study may differ because of the elapsed time from the REDS-II study. We will conduct nonresponse bias analysis to assess the potential for nonresponse bias. If we find that nonresponse bias may exist, we will conduct post-survey weighting based on the information produced during the nonresponse bias analysis to minimize the potential nonresponse bias when the risk behavior frequencies are reported. Variables that may be associated with non-participation are: participation in the previous REDS-II or REDS-III study, the demographic characteristics of the donors (age, gender, race/ethnicity, previous donation history) and also potential participation rate differences by blood center. It is important to note that simple or unadjusted HIV case rates per blood center will not be sufficient to indicate whether there is evidence of bias because the demographic characteristics of blood donors at each of the REDS-III blood centers are not the same. In addition, for Aim 1 we will examine the proportion of letters that are returned as non-deliverable to better inform us about the *potential* differences between the delivered and non-delivered test positive donors for important analytic covariates.

We expect low levels of item nonresponse for this study in Aims 2 and 3. Our use of ACASI was very successful in the previous REDS-II and REDS-III studies with little evidence of nonresponse to any of the questions asked during the interview. For example, we asked a question about whether the donor had ever been tested for HIV outside of blood donation. Only 1 person out of 1,244 (<0.1%) respondents in the REDS-II study refused to answer this question. Similarly, for a clearly social sensitive question in which we asked respondents to classify their sexual orientation 18 out 1,244 respondents (1.4%) refused to answer. These data suggest that the use of ACASI was successful in eliciting responses to stigmatizing or socially sensitive questions, and we expect the same to be true for our use of ACASI in this study. We will monitor item response rates and examine the *potential* nonresponse bias for important analytic variables that have relatively high rates of nonresponse.

Here are some of the specific data collection procedures that will be implemented in Aims 2 and 3 of this study to reduce response burden and increase participation:

1. Written informed consent for participation in the study will only be obtained when the participant returns to the blood center. Thus only those participants who demonstrate a willingness to participate in the study by returning to the blood center will be asked to complete informed consent.

2. ACASI on the topics of access to health care and risk behaviors will be completed. Private locations in each blood center will be made available for the participants to complete the ACASI, helping to increase response rates. Additionally, to support our objectives we will access the responses from the two previous ACASI questionnaires, namely the original HIV-positive case interviews from the REDS-II or REDS-III HIV surveillance studies. The great advantage of the use of ACASI is the ability of respondents to skip irrelevant detailed questions based on initial responses to indicator questions. This creates a lower participation burden in each respondent and also limits exposure to socially sensitive topics if the participant does not have the corresponding risk behavior.

3. Trained counselors will be on site during and after the ACASI interviews should participants want additional counseling. This helps to reduce any potential psychological burden. The knowledge that each participant will have access to additional counseling outside of the study, if desired, may also facilitate increased participation.

4. At the time informed consent is obtained, we will also seek authorization from each participant to obtain HIV infection status information captured in the State and National databases on HIV progression such as viral load and CD4/CD8 counts. The Brazilian National HIV treatment and progression databases (SI-CTA) were created in 2002 by the Ministry of Health because of the need to register and monitor the care provided by HIV Counseling and Testing services (HCT)/medical staff, obtain demographic, behavioral, and biological information regarding the individuals who attend this service. Each Brazilian HCT provides information on the individuals with HIV/AIDS (based on viral load, CD4 and CD8 information) to a data coordinating center located in Brasília. Some HCTs also provide testing for syphilis and hepatitis B and C. This information is essential for health services planning and strategies with a focus on the individual and affected communities to provide indicators of success and to support efforts to manage HIV in Brazil. In addition, this information is also being used to improve research by providing ways to access summary data for research projects. More than half of a million (500,000) records of individuals with HIV, syphilis, and hepatitis B and C are stored in this dataset. There is no time limit on how long this information is housed in databases. By asking participants to allow us to obtain treatment information electronically from these databases, the study participants will not have the burden or potential social discomfort of seeking this information from their treating physician or directly from Brazilian National HIV databases.

B.4. Test of Procedures

The data collection procedures for this study have been successfully implemented in the REDS-II and REDS-III Brazil HIV studies. There are no new procedures or methods planned for this study.

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

We have consulted biostatisticians on statistical aspects of the study design; the blood center researchers responsible for enrollment, administering questionnaires, and collection of samples; as well as, the Coordinating Center staff for protocol development, study monitoring, and data management. Data analysis will be performed by the Coordinating Center analytic staff, which includes epidemiologists and biostatisticians with assistance and oversight provided by the REDS-III International Advisory Committee (IAC) (see *Attachment 3.3* for a complete list of IAC members). The REDS-III OSMB (*Attachment 3.1*) will monitor the study.