Supporting Statement A for
Incident HIV/ Hepatitis B virus infections in South African blood donors: Behavioral risk factors, genotypes and biological characterization of early infection

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Sponsored by:

The National Heart, Lung, and Blood Institute
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SUPPORTING STATEMENT

Introduction and Summary

South Africa has one of the highest burdens for HIV infection in the world. The HIV epidemic in South Africa is largely heterosexual, but risk factors for infections can change and so identifying factors that contribute to the recent spread of HIV in a broad cross-section of the otherwise unselected general population, such as blood donors, is highly important for obtaining a complete picture of the epidemiology of HIV infection in Africa. Small previous studies suggest that the risk factors for HIV among more recently acquired (incident) infections in blood donors may differ from those of more distant (prevalent) infections. Similarly risk factors for recently acquired HBV may be different than for prevalent HBV infections. The demographic and behavioral risks associated with incident HIV and incident HBV infection have, as yet, not been formally assessed in South African blood donors using analytical study designs. Due to the high rates of HIV and HBV infection in South African blood donors, a better understanding of these risk factors can be used to modify donor screening questionnaires so as to more accurately exclude high-risk blood donors and contribute to transfusion safety. Risk factor data from this research may also provide critical information for blood banking screening strategies in other countries.

This study which provides a contemporary understanding of the current risk profiles for HIV and separately for HBV will also prospectively monitor genetic characteristics of recently acquired infections through genotyping and drug resistance profile testing, thus serving a US, South African, and global public health imperative to monitor the genotypes of HIV and HBV that have recently been transmitted. For HIV, the additional monitoring of drug resistance patterns in newly acquired infection is critical to determine if currently available antiretroviral medicines are capable of combating infection. Because the pace of globalization means these infections can cross borders easily, these study objectives have direct relevance for HIV and HBV control in the US and globally. Further, the ability to identify recent HIV infections provides a unique opportunity to study the biology, host response and evolution of HIV disease at time points proximate to virus acquisition. Genotyping and host response information is scientifically important not only to South Africa, but to the US and other nations since it will provide a broader global understanding of how to most effectively manage and potentially prevent HIV (e.g. through vaccine development). Efforts to develop vaccines funded by the National Institutes of Health and other US-based organizations may directly benefit from the findings of this study.

The South African National Blood Service (SANBS) uses both Nucleic Acid Testing (NAT) and serology (antibody or antigen testing) to screen blood donors for Human Immunodeficiency Virus (HIV) and Hepatitis-B Virus (HBV), among other infections. Positive NAT precedes seroconversion by days to weeks in newly acquired HIV and HBV infections; a combined testing strategy using NAT and serology therefore, confers the ability to detect acute infection and discriminate between recent (incident) and more remotely acquired (prevalent) infection. Additional post-seroconversion techniques that exploit antibody maturation kinetics such as Limiting Antigen Avidity assay (LAg Avidity) can further assist to classify HIV seroconverters as recently acquired or prevalent infections. Hepatitis B core antibody (anti-HBc) testing of NAT-positive and NAT and serology (Hepatitis B Virus Surface Antigen HBsAg) concordant positive HBV infections allows further classification of HBV infections as recently acquired or prevalent infections.

Infections that are anti-HBc negative are recently acquired.

Leveraging the ability to classify HIV and HBV infections as incident or prevalent leads to three study objectives, in order to determine risk factors for incident HIV and HBV infections (Objective 1) we will conduct a frequency matched (stratified sample) case-control study with two case groups: incident HIV infected blood donors; and incident HBV infected blood donors. The risk factors in these two case groups will be compared to the risk factors in a group of infectious marker negative control donors. Cases and controls will be accrued from a geographically diverse blood donor pool. We will further characterize HIV clade and drug resistance profiles and determine viral loads in all cases of incident HIV infection, and HBV genotype and viral load in all incident HBV infections (Objective 2), and follow elite controller HIV infections and a subset of HIV incident infections prospectively for three additional visits at 2, 3, and 6 months following index donation (Objective 3).

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

Under Title 42 › Chapter 6A › Subchapter III › Part C › Subpart 2 › § 285b–1 the Director of the National Heart, Lung and Blood Institute (NHLBI) shall conduct and support programs for the prevention and control of heart, blood vessel, lung, and blood diseases. Such programs shall include community-based and population-based programs carried out in cooperation with other Federal agencies, with public health agencies of State or local governments, with nonprofit private entities that are community-based health agencies, or with other appropriate public or nonprofit private entities. The proposed study, Incident HIV/ Hepatitis B virus infections in South African blood donors: Behavioral risk factors, genotypes and biological characterization of early infection, fits within the NHLBI's research agenda as described here and in the other supporting documents.

The significance of this study is related to its three objectives: One, determination of demographic and behavioral risk factors for incident HIV and HBV holds great promise for informing targeted prevention measures by blood banks and public health authorities. The potential for identifying persons who are recently infected with both HIV and HBV also exists. In countries where the two viruses are highly endemic the rate of co-infection can be as high as 25%.[1] In recent years, approximately 2.4 % of those SANBS blood donors with confirmed HIV or HBV infection have been co-infected. Persons with co-infection are known to have up to five-fold faster disease progression[1] and so efforts to understand the epidemiology of both HIV and HBV, among individuals who are co-infected within the SANBS donor population has the potential for direct impact on public health and health care services in South Africa. Additionally, prospective collection of incidence data allows for measurement of secular trends and the methodological approaches of behavioral and molecular surveillance we will use may also be of value to other countries. Two, we will determine the viral subtype and drug resistance profile of all recently acquired HIV infections, and the genotype of recently acquired HBV infections, allowing study of viral evolution, viral fitness and pathogenicity. For HIV, we will be able to determine the frequency at which drug-resistant strains are being transmitted in the population which has clear implications for changing pharmacogenetics and appropriate antiretroviral medicines. Three, evaluation of donors with recently acquired HIV infection

and “elite controllers” [HIV antibody positive, individual donation (ID)-NAT negative infections)] at multiple time points will be valuable to virologists and immunologists studying the natural history of early HIV infection. These studies will be useful in identifying appropriate HIV drug therapy regimens for this condition, as well as strategies for producing an effective HIV vaccine, which has eluded 30 years of HIV research.

The South African National Blood Service (SANBS) uses ID-NAT testing (in contrast, in the US, mini-pool NAT testing is being used). The use of ID-NAT provides a unique opportunity to identify very recent HIV and HBV infections with a high degree of accuracy. Universal screening of donations by parallel testing for nucleic acids and serological assays can accurately gauge incidence given known thresholds of detection by NAT and serology. In the event that HIV is newly acquired, positivity by ID-NAT (5-10 days post-infection) precedes antibody positivity (detectable at about 21 days) by over 10 days; these so-called “NAT-yield” HIV infections refer to incident or recently acquired infections that have not yet stimulated an antibody response. Over more than 5 years (2005-2010), 165 HIV NAT-yield incident positive cases have been identified at SANBS.

Following infection by HIV or Hepatitis B virus there is a time known as the “eclipse” phase when the infection is not widely disseminated and therefore is not detectable in blood. This time period is different for each infection. Once the infection is established, the risk of transmission to another individual increases as plasma viremia increases during the ramp-up phase. After progressing through this stage of infection, the presence of an infection can be determined based on the ability of available methods to identify it. Although ID-NAT testing allows for very early detection of HIV, there remains a narrow “window period” that eludes current laboratory testing. There is an even longer window period for HBV infection. This underscores the importance of donor selection through behavioral risk screening as the primary means to capture the high-risk donor prior to appearance of the first detectable viral marker.

The findings from this project will also complement similarly structured monitoring of HIV and HBV prevalence, incidence, transfusion risk and molecular variants in the US and other funded international REDS-III sites (HIV in Brazil and HIV and HBV in China), thus allowing direct comparisons of these parameters on a global level.

A.2. Purpose and use of the information

The objectives of the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) program is to assure safe and effective blood banking and transfusion medicine practices through a comprehensive, multi-targeted strategy involving basic, translational, and clinical research to improve the benefits of transfusion while reducing its risks. Improving blood component safety and availability in the U.S. and internationally through the conduct of epidemiologic, survey, and laboratory studies is the cornerstone of the REDS program. Transfusion therapy is the most commonly employed, and, arguably, one of the least understood medical procedures in the U.S. affecting about five million recipients annually. This research program is not only critical to public health in the U.S., but also to countries struggling with the HIV epidemic where blood safety and availability are major concerns. Thus, the goal of the REDS-III International Component which is currently being conducted in Brazil, China, and South Africa is to conduct epidemiologic, laboratory, and survey research on blood donors in regions seriously affected by the AIDS epidemic to help increase the global safety and availability of blood for transfusion.

Additionally, research into health outcomes of blood transfusion recipients is of interest to the program.

HIV Infection is presently the foremost public health concern in South Africa owing to a nationwide prevalence of 10.9% in persons over 2 years of age and up to 30% among pregnant women.[2] In this environment of high HIV prevalence, the South African National Blood Services (SANBS) must collect more than 800,000 units of whole blood each year from a pool of more than 350,000 donors in order to contend with the country's growing transfusion need. A number of strategies have been successfully implemented by SANBS in order to protect against HIV in the blood supply. Donor selection is central to this process and is achieved through the exclusive use of voluntary, non-remunerated donors, exclusion of high-risk donors identified through the donor history questionnaire and a product triage policy that excludes use of higher risk, first-time donations for component production. An accurate risk assessment of prospective blood donors is contingent upon contemporary knowledge of behavioral risk factors associated with recent HIV and/or HBV infection, since recent infection is more likely to escape detection by available laboratory tests. The selection process consequently hones in on high-risk behavioral exposure (e.g. multiple sexual partners, sexually transmitted diseases, injection drug use, sexual assault) etc. Failure to capture high-risk donors through this primary interface is in part addressed through universal laboratory screening for antibodies against HIV (HIV-1 and HIV-2) and HBV surface antigen (HBsAg) as well as HIV viral RNA and HBV viral DNA using ID-NAT. Although laboratory testing bolsters the safety net, it should not distract from the importance of donor selection, particularly in view of residual risk such as possible undetectable viral subtypes or very early infection that could escape laboratory capture.[3]

National surveillance of HIV risk in African countries has traditionally focused on prevalent rather than incident infection; this holds implications for prevention planning and evaluation.[4] Prevalent infection, although easier to measure, provides a skewed assessment of disease profile, particularly in view of expanding antiretroviral coverage that prolongs survival. Incidence surveillance reflects a more accurate representation of currently relevant risk factors given the proximity to recent infection. This has consequently been adopted effectively in the United States and other industrialized countries.[5] Unfortunately, there is a lack of HIV or HBV incidence data, particularly in resource-poor settings and specifically in sub-Saharan Africa where these diseases are prominent. The assumption that incident risk factors parallel those of prevalent infection is not necessarily accurate. This was demonstrated in a study by McFarland et al. in Zimbabwe, whereby age and marital status reversed their direction of association with respect to HIV incidence vs. prevalence.[6] This may reflect a shift in the epidemiology of HIV infection.

In addition, evaluation of donors with recently acquired HIV infection and "elite controllers" (HIV antibody positive, ID-NAT negative infections) at multiple time points will be valuable to virologists and immunologists studying the natural history of early HIV infection, and may provide valuable insights into vaccination targets or other research to reduce rates of HIV transmission in the US and elsewhere. Genotyping and host response information is scientifically important not only to the US and South Africa, but to a broader global understanding of how to most effectively manage and potentially prevent HIV (e.g. through vaccine development). Efforts to develop vaccines funded by the National Institutes of Health and other US-based organizations may directly benefit from the findings of our study.

A.3. Use of Information Technology and Burden Reduction

Donors who agree to participate in the study will undergo a written informed consent process in which the requirements of the study will be fully described. Donors who consent will then be enrolled in the study and specimens collected for additional testing of markers of HIV and/or HBV infection. Following sample collection, the participant will complete a risk factor questionnaire, administered using an audio computer-assisted self-interview (ACASI) format. A research assistant or nurse will direct the participant to a private setting where the ACASI computer (including earphones to be able to listen to the questions and responses options confidentially) can be used to complete the interview. The study subject will be shown how to use the computer to complete the interview by entering basic demographic data with the help of the research staff, but will be given privacy to complete the rest of the questionnaire. The research assistant or nurse will remain available to answer questions and provide help as necessary.

We chose ACASI to maximize reporting of stigmatized risk behaviors and to streamline the interview. For example, the ACASI program has built in skip patterns depending on initial responses so that donors are only prompted to answer questions about the details of a specific risk factor or behavior if they report having the risk, thereby reducing participant burden. The ACASI format also uses electronic data capture which reduces data entry errors. The ACASI program has demonstrated very good performance during the previous HIV risk factor study conducted in the Retrovirus Epidemiology Donor Study-II in Brazil, and in the ongoing REDS-III study of HIV in Brazil. Similarly, ACASI has been successfully used in several other NIH-funded studies in South Africa. The questionnaire for the South Africa study is based upon an instrument previously utilized and validated by the US Centers for Disease Control and Prevention (CDC) in its HIV surveillance at U.S. blood banks and on the instrument used in the REDS HIV study conducted in Brazil with modifications appropriate to the South African setting.

In addition, at each of three follow-up visits for Objective 3 participants (n = 70), a short questionnaire will be completed just after collection of the blood samples, using a paper questionnaire (designed to allow electronic data capture by scanning). The content of this questionnaire will assess healthcare-seeking behavior and any medicines or natural remedies the study participant has taken or initiated since the last study visit, possible side effects of these medicines and other exposures that may influence the disease progression dynamics of early HIV infection. Women will also be asked if they are currently pregnant. These questions are necessary as they can influence biological markers of HIV disease progression.

Donors will continue to be assured of the confidentiality of their responses. Use of a Subject ID on the Objective 3 questionnaires will allow for tracking of survey responses without entering any personally identifying information into the study database. For all participants, the link between the Subject ID number and the identity of the donor is only maintained by SANBS. This link is maintained in South Africa so that members of the SANBS study team may recontact study participants with essential information that may affect their clinical care, (e.g., drug resistance test results for HIV-positive participants), or in a case where any donor wishes to withdraw from the study. The US-based Coordinating Center (CC) or other US investigators will not have access to any donor identifying information.

A.4. Efforts to Identify Duplication and Use of Similar Information

This detailed risk factor information is not routinely collected by South African blood collection centers in the course of their routine donor screening operations. Although numerous epidemiologic studies have been conducted in South Africa, there are nevertheless no adequate data related to the blood donor community, especially in view of the evolving nature of the HIV epidemic in the population and ability to identify recently acquired HIV or HBV infection. Blood banks can play an important role in this effort due to HIV and HBV testing of a large number of individuals who otherwise may not access testing services. Regarding clinical relevance of the proposed research, the South African Government and public health authorities have been responsive to the HIV epidemic, with prevention campaigns, provision of condoms, alternative testing sites, and most notably, the implementation of universal access to antiretroviral medicine for individuals meeting National Standards, but infection rates remain very high posing continued risk to persons requiring blood transfusion.

This study will provide a better understanding of the observed epidemiological patterns of recent HIV and HBV infection in this setting, and may help inform public health initiatives seeking to prevent HIV and HBV acquisition. In addition, monitoring HIV and HBV viral subtypes and HIV drug resistance patterns, and identifying risk behaviors for incident infections among donors (NAT yield donors and recent seroconverters) are critical steps to assessing and reducing risk of infection transmission through blood transfusion. In addition, characterizing genotypes of recently infected donors for purposes of blood safety and performing molecular surveillance of HIV infections in blood donors enables documentation of the rates of primary transmission of anti-viral drug resistant strains in the community, and serves a public health role in identifying individuals with acute HIV infection who may be eligible for anti-retroviral treatment.

A.5. Impact on Small Businesses or Other Small Entities

Small businesses or entities are not involved. All respondents are individual blood donors.

A.6. Consequences of Collecting the Information at a Chosen Frequency

For all participants enrolled in this study, the risk factor and behavior questionnaire will be administered only once in an ACASI format on a computer. The content of this interview includes respondent demographics, history of previous donation and HIV testing, motivations for donating, sexual history, risks related to sexual partners, alcohol and drug use, medical history, other potential risk factors, work place exposures, and treatment. In addition to blood saved from their index blood donation, no more than 48 ml of blood will be drawn for study-specific purposes from HIV and HBV cases (not controls) at the time of the enrollment and interview. Data collected from each respondent during the ACASI are essential to understanding the characteristics of this study population; the interview itself constitutes a minimal level of burden on the respondents. For participants enrolled in Objective 3 of this study, no more than 48 ml of blood will be drawn and a short paper questionnaire focused on participants' clinical symptoms and health-seeking behavior will be administered at each follow-up visit. These data will serve several purposes: 1) they will characterize the health-seeking behavior of individuals with acute infection and that of elite controllers; 2) they will provide important data to cross-tabulate with laboratory results;

and 3) will contribute to the understanding of factors that may influence biological markers of early HIV disease progression and seroconversion.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The proposed data collection is consistent with 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

The 60-day Federal Register Notice was published in Volume 78, November 8, 2013, and Page 67175. One public comment was received that was a personal opinion regarding protecting the safety of the American blood donation system. There was consultation outside of NHLBI to conceptualize and design the current, first phase of the study. The final study design was developed, reviewed, and approved by the REDS-III South Africa Steering Committee, the International Advisory Committee (Attachment 3.2) for the overall REDS-III study, and the REDS-III Observational Study Monitoring Board (OSMB) (See Attachment 3.1 for a complete list of members). The OSMB reviewed the final protocol and provided input and comments. Revisions were made to the Informed Consent document incorporating the suggestions of the OSMB to clearly state that strict confidentiality will be maintained throughout the study and to the content of the ACASI questionnaire.

A.9. Explanation of Any Payment or Gifts to Respondents

The project will pay 80 Rand (~$USD 10) to reimburse participants for transportation expenses to and from the study center and for completion of study activities at each visit. The 80 Rand proposed is based on average South African city bus and taxi round trip fares ranging from 4 to 15 RAND. Consequently, 80 RAND are sufficient funds to pay for the full set of costs for blood donor participants during their study involvement.

A.10. Assurance of Confidentiality Provided to Respondents

All respondents will be assured of the actions taken to safeguard their confidentiality and privacy as study participants. They will be shown how to use the computer to complete the interview by entering basic demographic data with the help of the research assistant or nurse, but will be given privacy to complete the rest of the questionnaire. Donors will be assured of the confidentiality of their responses, and will remain private to the extent permitted by law. Use of a Subject ID on the questionnaire will allow for tracking of survey responses without entering identifying information into the study database. The link between the Subject ID number and the identity of the donor is only maintained by the blood centers. This link is maintained so that the study team may recontact donors with essential information that may affect their clinical care, for example drug resistance test results for HIV-positive participants or in a case where any donor wishes to withdraw from the study. The Data Coordinating Center (DCC, RTI) or other US investigators will not have access to any donor identifying information.

A.11. Justification for Sensitive Questions

Special attention has been devoted to carefully designing potentially sensitive questions in a straightforward and non-judgmental way. To assess a donor's level of altruism by determining if the donor exhibits altruistic behaviors in their daily life, we want to correlate their daily behavioral answers to assess how important of a factor altruism is when donating blood. It is already known that donors will give a socially acceptable response rather than the real reason to donate when asked directly about blood donation. There is a major difference between asking a donor whether altruism is a motivation factor and measuring the degree to which donors report engaging in other altruistic behaviors. The survey instrument is comprised of questions designed to determine the donor's intention to get HIV or HBV testing through blood donation (test seeking). Blood bank testing may be attractive to people seeking HIV testing. We intend to ascertain donor's perceptions/confidence related to the HIV and HBV testing performed by the blood bank as well as whether this blood testing was a contributing factor in donating. Sexual lifestyle, including the number of lifetime sexual partners increases the odds of having a sexually transmitted disease, as well as its spread. The sexual history responses will allow us to determine the most prevalent sexual patterns for the South African blood donors and whether this pattern may or may not be correlated with specific laboratory testing markers. In this section we also ask whether the respondent has ever or recently (past 6 months) experienced physical violence from a sexual partner or sexual violence from anyone or an intimate sexual partner. Globally, South Africa has one of the highest rates of physical and sexual violence, and these factors have been associated with HIV risk. As such, the study team and the OSMB felt it was important to measure violence, and provide appropriate referrals for psychosocial support, if needed.

In many countries in sub-Saharan Africa with generalized HIV epidemics, including South Africa, the majority of HIV spread is attributed to heterosexual transmission, and consequently homosexual transmission in this setting is less well understood. A better understanding of sexual risk factors for HIV and HBV may allow us to build more accurate questions at the time of blood donation to improve the donor qualification process. It may also help us to avoid potential discrimination and unnecessary loss of donors if the patterns of HIV and HBV transmission are not shown to be associated with specific sexual activities. The social matrix section is designed to capture detailed sexual information for up to 5 sexual partners in the 6 months before the last blood donation. The questionnaire focuses on this period for two reasons. First, this is the time period that donors are asked about with respect to deferrable behaviors during the donor selection process. Second, this is a window of time that is both short enough to minimize recall bias, and long enough to accommodate a range of behaviors that may be causally associated with incident infection.

In general, persons tend to maintain a particular pattern of sexual behavior in their lifetime (MSM, bisexual, heterosexual) as well as specific sexual practices that are relevant to identify higher risk behaviors for HIV or HBV transmission. We assume, therefore, that asking about more than the last 5 sexual partners will not provide significant valuable supplemental information. We expect that relatively few respondents will have more than a few sexual partners in the preceding six months before donation. These donors will be asked to provide specific information for only the number of sexual partners they have had. Responses from different partners will be combined to determine the frequency with which a donor has engaged in higher risk sexual behaviors. The individual responses are less important than the combined results across all partners that can be used to determine if

specific sexual practices are associated with testing positive for incident HIV or HBV. These questions will guide future efforts to develop donor health history questions that will exclude donors with high risk.

The section on alcohol and drug use was included to evaluate the influence of social lifestyle in terms of alcohol and drug use. Use of mood altering substances may be associated with the risk of HIV or HBV acquisition. However, this association has not been clearly demonstrated in South African blood donors. We also intend to evaluate whether specific serologic markers are related to riskier behaviors or illicit drug use. Several types of illicit drug use may be common in some subpopulations in South Africa and the questionnaire will determine if blood donors have similar exposures.

The medical history section will capture information about exposures that could lead to HIV or HBV transmission. The section on other potential risk factors will obtain data related to potential risk factors that are rare for HIV but potentially more common for HBV infection and includes questions related to tattoos, acupuncture treatment, time spent in jail, prison, or a detention center, body piercings as well as pedicure and manicure treatments at a salon or barber shop. Ritual scarification, ritual piercing and other traditional practices including bloodletting, or subcutaneous treatment from a traditional healer will be explored. The questionnaire will also capture information about potential risk of HIV associated with circumcision and substances inserted into the vagina (for women only) or anus to dry, tighten or prepare for sex. Exposure to bed bugs, lice, or mosquitoes, as well as stab wounds will be ascertained based on recommendations from HBV experts in South Africa. Information from the section on work place exposures will be asked of all participants. However, donors who work in a health care profession or other social settings that could lead to exposure to blood or other body fluids could be at higher risk for disease acquisition. Exposure and treatment questions will be used to ascertain if the blood donor knew of his/her HIV and HBV status at the time of blood donation, self-reported route and time of infection, and past or current anti-retroviral therapy (ART). In South Africa, highly active (HA)ART is available in the public sector for individuals meeting National Standards, and in the private sector; however, there is still a large unmet need for treatment. These questions will be useful for interpreting possible drug resistance patterns in the molecular surveillance component of the study. Please see Attachment 2 for the questionnaires and their justification and goals.

With regard to the race categories provided in the demographic section of the questionnaires, in South Africa the categories that members of society know are those provided in the questionnaire. Study respondents would not understand the racial categories that are used in other countries such as the United States. It is important to note that ‘Coloured’ is its own racial category separate from the category of ‘Black’, specifically referring to a self-defined mixed racial background; this category is currently used by the South African government in its Census Questionnaire, most recently available online for the 2011 Census Questionnaire, the link to which is here: http://www.statssa.gov.za/census2011/documents/CensusQuestionnaires/Census%202011_q_A.pdf

In addition, in awareness of the possible sensitive nature of the questions, the following steps will be taken to ensure the confidentiality of respondents although personal identifiable information is not collected:

- The risk factor and behavior questionnaire is administered using audio computer-administered self interview (ACASI) program. The purpose of using a self-administered instrument is to ensure that potentially stigmatizing behaviors will be

reported as honestly as possible without fear or concern that an interviewer would stand in judgment.

- The clinical follow-up questionnaire will be administered by paper. Only study subject ID will be include on the paper forms. No personal identifiers will be collected on these forms.
- All data will be stored in a secure location, accessible only to authorized study personnel.
- Donors are advised of the voluntary nature of their participation in the study and of the steps taken to ensure the confidentiality of the information collected. See Informed Consent Documents, Attachment 2.

A.12. Estimates of Burden Hours Including Annualized Hourly Costs

We estimate that for Objectives 1 and 2 all subjects will require on average 15 minutes to complete the informed consent including time for research staff to answer any questions participants may have. The time to complete the ACASI questionnaire will be different for persons with limited behavioral exposures compared to those with more extensive behavioral exposures. Approximately 75% of the study population is expected to have limited exposures and will require 0.5 hours to complete the ACASI. The other 25% is expected to require more time, taking 0.75 hours to complete the ACASI. It is estimated that each respondent on average will spend about 15 minutes completing the consent form and 34 minutes completing the questionnaire for a total of 49 minutes. Study enrollment is planned for 3 years and will include 1,450 ACASI interviews in total. Thus on average, there will be 483 subjects completing the ACASI interview every year for an annualized burden hours of 395 hours. The South African average wage exchanges to approximately $3.63/hour, so the annualized cost burden to respondents is estimated at $1,434.[7]

We estimate that the informed consent process for Objective 3 participation, including time for research staff to answer participant questions, will be 15 minutes at the enrollment visit for the study. For Objective 3 the time to complete the initial consent form is 15 minutes and the total time to complete the brief clinical follow-up question is estimated to be 10 minutes each time the questionnaire is completed. This leads to total burden of 55 minutes per Objective 3 participant over the planned 4 follow-up visits. Objective 3 will occur during all 3 years, with an anticipated 70 participants over the course of the 3 years. This translates on average to about 23 individuals each year participating and an annualized burden of 21 hours. All participants in this Objective will have the same burden for participating. The South African average wage exchanges to approximately $3.63/hour, so the annualized cost burden to respondents for Objective 3 is estimated at $77.[7]

The estimated annualized burden hours for all 3 objectives are 416 hours. The South African average wage exchanges to approximately $3.63/hour, so the annualized cost burden to respondents is, $1,511. [7]

A.12.1 – ESTIMATED ANNUALIZED BURDEN HOURS

Form Name	Type of Respondent	Number of Respondents	Number of Responses per Respondent	Average Burden Per Response	Total Annual Burden Hour

				(in hours)	
Objectives 1 and 2 Consent Form	Adult Donors	483	1	15/60	121
Objectives 1 and 2 – ACASI Questionnaire	Adult Donors	483	1	34/60	274
Objective 3 consent form*	Adult Donors	23	1	15/60	6
Objective 3 – Clinical Follow-up Questionnaire *	Adult Donors	23	4	10/60	15
Total for All Objectives		483			416

* These objective 3 respondents are a subset of the respondents included in Objectives 1 and 2.

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A.12 - 2 ANNUALIZED COST TO RESPONDENTS

Form Name	Type of Respondent	Number of Respondents	Number of Responses per Respondent	Average Time per Respondent	Hourly Wage Rate	Respondent Cost – all respondents
Objectives 1 and 2 Consent From	Adult Donors	483	1	15/60	$3.63	$439
Objectives 1 and 2 – ACASI Questionnaire	Adult Donors	483	1	34/60	$3.63	$995
Objective 3 consent form*	Adult Donors	23	1	15/60	$3.63	$22
Objective 3 – Clinical Follow-up Questionnaire *	Adult Donors	23	4	10/60	$3.63	$55
Total for All Objectives		483				$1,511

* These objective 3 respondents are a subset of the respondents included in Objectives 1 and 2.

A.13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no capital or start-up costs, and no maintenance or service cost components to report.

A.14. Annualized Cost to the Federal Government

The annualized cost to the Federal Government for the proposed data collection effort is estimated to be approximately $213,373 for activities in South Africa.

Item	Salary	Fringe Rate	% Effort	Annualized Cost
NIH Project Oversight Officer - GS15-10	157,100	20%	1.5%	23,565
6 in-house contractor staff	205,714	39%	38%	78,171
4 field contractor staff	37,708	27%	50%	75,416
Operational Costs for Data Collection Activities – Printing, equipment, overhead), non-labor				12,961
Other Contractual costs for data collection, non-labor				5,673
Travel costs associated with data collection				12,387
Other costs, non-labor				5,200
Total				213,373

A.15. Explanation for Program Changes or Adjustments

This is a new collection.

A.16. Plans for Tabulation and Publication and Project Time Schedule

The schedule for study activities

Activity	Time Schedule
Initiate Study Recruitment Activities	April 2014
Participant Enrollment and Data Collection (3 years)	April 2014 to March 31, 2017
Data Management and Analysis	Ongoing through March 31, 2018

Data will be disseminated after review by the NHLBI REDS-III Publication Committee

and NHLBI following the REDS-III Publication Guideline Manual (Attachment 5) to the scientific and blood banking community and others through peer-review journal publications, and presentations at government (e.g. FDA Blood Products Advisory Committee) and professional meetings (e.g. American Association of Blood Banks and the International Society for Blood Transfusion). Individual data will not be presented.

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate

The OMB expiration date will be displayed in the upper right-hand corner of the first screen of the ACASI questionnaire for Objectives 1 and 2, and in the upper right-hand on all pages of the paper questionnaire for Objective 3.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification statement of OMB Form 83-I.

References

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