

Supporting Statement A for

Characterization of risk of HIV and HIV outcomes in the Brazilian Sickle Cell Disease (SCD) population and comparison of SCD outcomes between HIV sero-positive and negative SCD patients

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ATTACHMENTS

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SUPPORTING STATEMENT

Introduction and Summary

The Retrovirus Epidemiology Donor Study (REDS) program and successor programs, REDS-II and the current Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) program have conducted research focused on the safety of the blood supply and the epidemiology of human immunodeficiency virus (HIV). REDS-III which is currently conducted in the United States, Brazil, China and South Africa, has continued to perform research related to HIV and blood safety and has expanded to include a focus on the recipients of blood products. Sickle cell disease (SCD) is a blood disorder that affects thousands of people in the United States and Brazil. Patients with SCD are high utilizers of blood both domestically and internationally and one component of the REDS-III research program in Brazil is to establish a cohort of SCD subjects that would provide the infrastructure to study transfusion outcomes and infectious diseases such as HIV in the SCD population.

Sickle cell disease predominantly affects persons with ancestry of sub-Saharan Africa and other malaria-endemic regions as the heterozygous carrier state confers a survival advantage for malaria. Sub-Saharan Africa, where most people with SCD in the world live, remains one of the regions most severely affected by HIV, with nearly 1 in every 20 adults living with the virus. In the United States, HIV disproportionately affects persons with African ancestry. Despite the diseases' occurrence in similar populations and the fact that both HIV and SCD are independent predictors of outcomes such as stroke, there is a paucity of data to elucidate how interaction between the two may alter clinical outcomes in patients with co-existing disease. The proposed study will seek to understand the risk of HIV in the Brazilian SCD population, describe HIV outcomes in SCD in Brazil, and compare SCD outcomes between HIV positive and HIV negative SCD patients in Brazil using the infrastructure established by the REDS-III SCD Cohort in Brazil.

The limited studies focused on HIV in SCD have suggested a lower prevalence of HIV in SCD compared to a non-SCD population. While some investigators have suggested that perhaps SCD pathophysiology has a unique effect on HIV infection or replication, none of the studies adequately measured risk of HIV in SCD. The study has two main objectives:

Objective 1 of the proposed study is to compare HIV risk factors between 150 patients with SCD (cases) randomly selected from the REDS-III Cohort and 150 age matched controls from a demographically similar population. An assessment that has been well validated in previous REDS/REDS-II HIV studies has been modified for the SCD population and will be used to collect data regarding HIV risk behaviors. Blood samples will be tested to confirm HIV status in all participants.

Objective 2 will seek to enroll approximately 25 SCD patients diagnosed with HIV infection as part of routine clinical care at REDS-III participating centers in the previous 10 years and abstract detailed information regarding the HIV infection and SCD outcomes from medical records. This will allow a detailed case series description of HIV outcomes in this population (Objective 2a). Finally, HIV negative controls matched in a 2:1 ratio on age (± 2 years), gender, SCD type and Hemocenter to the identified objective 2 HIV sero-positive SCD patients will be selected from the REDS-III cohort to compare SCD outcomes between HIV positive and HIV negative subjects (Objective 2b). The

HIV negative controls to be included in the Objective 2b analysis have already consented to participate in REDS-III research; therefore, their SCD outcomes will be extracted from the REDS-III SCD database. No re-contact will be required, and no assessment will be administered to this group of HIV negative controls selected from the REDS-III SCD database. This study will provide critical information to guide the management and future research for patients with HIV and SCD in Brazil, the United States, and worldwide.

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

As noted in Worksheet Part 1, 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, “Characterization of risk of HIV and HIV outcomes in the Brazilian SCD population and comparison of SCD outcomes between HIV seropositive and negative SCD patients”, fits within the NHLBI’s research agenda as described here and in the other supporting documents.

There are limited data regarding the interaction between HIV and SCD, therefore this will be the first large study to provide answers to open questions regarding the risk, outcomes and management of these patients. A few studies have compared the prevalence of HIV in SCD to a non-SCD population and have suggested a lower prevalence of HIV in SCD. This has led to speculation that SCD pathophysiology may have some unique ability to inhibit HIV infection and/or replication. This would be incredibly important to explore in order to shed light on potential mechanisms of resistance to HIV infection that may have implications for new therapeutic targets. However, no studies have adequately investigated the risk of HIV in SCD; therefore, it is unknown if the suggested lower prevalence of HIV is simply due to lower risk of acquisition rather than an impact of SCD pathophysiology on the virus. This study will administer a detailed HIV risk assessment to 150 SCD patient cases randomly selected from the REDS-III SCD Cohort (Establishing a Brazilian SCD Cohort and Identifying Molecular Determinants of Response to Transfusions, and Genetic Determinants of Alloimmunization, clinical exemption number 2013-03-001) and 150 frequency matched controls selected from SCD patient advocacy associations at each Hemocenter. Selection of cases and controls will be stratified on Hemocenter and age, with age divided into 5-year intervals. The goal is to have the number of controls in a stratum match the number of cases. These data regarding risk of HIV will provide important context to the reported prevalence of HIV in SCD. If similar risk behaviors exist between SCD and a well-matched population without SCD, this would lend support to the hypothesis of an interaction between SCD pathophysiology and viral infectivity/replication and help drive the direction of future research in this area.

While objective 1 will measure risk of HIV in SCD and non-SCD controls in a sampled population within Brazil, objective 2 of this study will enroll a different study population: all SCD patients diagnosed with HIV through routine clinical care in the 10

years prior to study initiation at the REDS-III Brazil participating centers: Hemorio in Rio de Janeiro, Hemominas in Belo Horizonte, Juiz de Fora and Montes Claros and Hemope in Recife, Brazil. A detailed medical record review to capture HIV and SCD outcomes and laboratory assessments relevant for HIV outcomes will be performed. The goal of objective 2a is to describe outcomes of HIV in the SCD population. In order to limit survival bias in the analysis that would suggest improved outcomes in HIV in SCD simply if all patients with poor outcomes were deceased and not included in the analysis, we will seek ethical committee approval to perform a medical record review of all HIV positive SCD patients deceased or lost to follow up at the time of study start in addition to recruiting all HIV positive SCD patients followed by the Hemocenters. Therefore this will likely be the largest, and most comprehensive, case series description of HIV in SCD to date, contributing significantly to the current lack of understanding regarding HIV outcomes in this population.

The final objective (objective 2b) of the study is to compare key SCD outcomes between HIV positive and HIV negative SCD patients in Brazil. We will select HIV negative controls from the REDS-III SCD Cohort database who are matched in a 2:1 ratio for age (± 2 years), gender, SCD type and hemocenter to the identified HIV positive SCD patients enrolled in objective 2. Both HIV and SCD are known to be independent predictors of stroke, pulmonary hypertension, avascular necrosis and other outcomes. It is presumed HIV and SCD may interact to increase the odds of these complications, but no studies have specifically investigated this. Understanding the odds of these outcomes in patients with co-existing disease has important implications for the management and monitoring of patients. Therefore collecting all information required for this research is necessary to provide important data to guide future treatment strategies for this group of patients.

A.2. Purpose and use of the information

The specific objectives of this research are to 1) measure the risk of HIV in the Brazilian SCD population, 2a) characterize HIV outcomes in SCD in Brazil and 2b) compare SCD outcomes between HIV positive and HIV negative SCD patients in Brazil.

The information collected to achieve objective 1 will include answers to an assessment designed to measure HIV risk behaviors. The assessment 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 has been modified for use in this Study's Brazilian setting for the REDS study "Prevalence, Incidence, Epidemiology and Molecular Variants of HIV in Blood Donors in Brazil" (OMB control number 0925-0597). The assessment was further modified for the Brazilian SCD population with input from Brazilian physicians, nurses and research assistants familiar with the population. Questions will capture data regarding known HIV risk factors such as number of sexual partners (lifetime and previous 12 months), intravenous drug use (IVDU), sex with known HIV positive persons, men who have sex with men (MSM) and other risk factors. The prevalence of the risk factors in the SCD population will be compared to a frequency matched population of similar age and coming from a similar region. The purpose of the information is to allow a comparison of the prevalence of HIV risk factors in the two populations, thereby providing an assessment of the risk of HIV in the SCD population.

The information collected to achieve objective 2 will include outcomes relevant

for SCD and HIV. The medical record of each participant enrolled in objective 2a (HIV sero-positive SCD patients) will be reviewed to abstract these outcomes. Key clinical and laboratory outcomes related to HIV will include method of HIV acquisition, prevalence of AIDS defining illnesses, CD4 count at time of diagnosis and most recent contact and details of HIV therapy. The purpose of this information is to provide a detailed, comprehensive description of HIV outcomes in SCD. The information collected regarding SCD will include presence of stroke, avascular necrosis, pulmonary hypertension and frequency of pain episodes and acute chest syndrome as well as other key indicators of disease severity. SCD outcomes in HIV sero-positive Objective 2 participants will be compared to HIV negative SCD subjects from the REDS-III SCD cohort for the purpose of understanding how HIV and SCD interact to alter odds of key outcomes. Current guidelines exist for monitoring and treatment of various SCD complications. However, there are no data to support how these guidelines might be modified to optimize patient care for persons with comorbidities such as HIV. The information collected for this research used to analyze both HIV outcomes in SCD (Objective 2a) and SCD outcomes with co-existing HIV (Objective 2b) will provide critical data to help guide management for monitoring and treatment of this patient population.

All SCD cases and non-SCD controls enrolled in Objective 1 will have blood collected to confirm HIV status at time of enrollment. Any subjects found to be HIV sero-positive will be called to return to the Hemocenter for the same repeat confirmatory testing and counseling that is provided to SCD patients or blood donors with a positive HIV screening test at the Hemocenter. Blood from all non-SCD controls enrolled in Objective 1 will also be tested for hemoglobin S by electrophoresis to confirm subjects do not have sickle cell disease. All HIV sero-positive SCD cases enrolled in Objective 2 will have blood collected to determine the viral load of HIV in addition to the genotype and drug resistance patterns and CD4 count.

A.3. Use of Information Technology and Burden Reduction

The detailed HIV risk factor assessment will be administered to all Objective 1 subjects (SCD cases and non-SCD controls) and consenting HIV positive objective 2 subjects (See Attachment 1) at the 5 Brazilian hemocenters in Recife, Belo Horizonte, Montes Claros, Juiz de Fora and Rio de Janeiro. The assessment will be administered to respondents using a self-administered audio computer-assisted self-interview (ACASI). We chose the ACASI to maximize reporting of stigmatized risk behaviors and to streamline the interview. The ACASI has built in skip patterns depending on initial responses so that participants are only prompted to answer questions about the details of a specific risk factor if they report having the risk. The ACASI format also uses electronic data capture which reduces data entry errors. The ACASI program demonstrated very good performance in previous REDS-II research. These studies demonstrated that young Brazilian subjects adapted easily to the computer interview, while older or illiterate subjects relied more heavily on the audio component. A research assistant or nurse will direct the participant to a private room where the ACASI computer with headphones is located at each blood center. The study subject will be shown how to use the computer to complete the assessment by entering basic demographic data with the help of the research staff, but will be given privacy to complete the rest of the assessment. The research

assistant or nurse will remain available to answer questions and provide help as necessary.

Subject will be assured of the privacy of their responses. Use of a Subject ID on the assessment will allow for tracking of survey responses without entering any personally identifying information into the study database. The link between the Subject ID number and the identity of the subject is only maintained by the lead investigator and designated key personnel at each center. The US-based Coordinating Center (CC) will not have access to any patient identifying information.

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

The detailed risk factor assessment information to be used in objective 1 is not routinely collected by treating centers. While some physicians may ask a few questions regarding HIV risk, this is highly physician-specific and if information is collected, it is typically limited in scope and not collected in a standardized way. A thorough review of the literature revealed no other publications reporting comprehensive assessment of HIV risk in the SCD population. A 1984 survey administered to 52 females with SCD and 80 controls demonstrated 39% of SCD subjects were sexually active compared to 81% of controls, and the mean age at first sexual encounter was 17.7 years in the SCD group vs. 17.0 years in the control population¹. Updated and more comprehensive assessments of HIV risk in this population have not been performed.

The information regarding HIV and SCD outcomes has already been recorded in the medical record and will be abstracted from this primary source, no additional information will be collected. Only two previous studies have reported HIV outcomes in SCD patients. Godeau et al identified 8 HIV+ of 283 (2.8%) screened adults with SCD and reported 0 of 8 had progressed to AIDS, even without antiretroviral therapy (ART), with a mean follow up of 4.6 years.² Bagasra et al compared 18 HIV+ SCD patients (all HIV+ patients identified at 5 US SCD Centers) to 36 HIV+ non-SCD controls matched for age, race/ethnicity and gender. They reported 8 of 18 (44%) SCD cases were long-term non-progressors (LTNP= asymptomatic with low viral load and CD4>500/mm without ART for at least 10 years) compared to 5 of 36 (13.9%) LTNP in controls with an average follow up of 10 years (p=0.0193). Death due to AIDS occurred in 5 of 18 (23%) HIV+ SCD patients vs. 22 of 36 (61%) of HIV+ controls³. No studies have reported impact of HIV status on odds of SCD complications.

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

Small businesses or entities are not involved. All respondents are individuals with SCD or non-SCD controls.

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

The risk factor assessments will be administered only once to all subjects in an ACASI format on a computer. The content of this interview includes respondent demographics, history of previous HIV testing, sexual history, risks related to sexual partners, alcohol and drug use, medical history, other potential risk factors, work place exposures, and treatment. A total of 12ml of blood will be drawn at the time of the enrollment and interview. Data collected from each respondent during this interview are

essential to understanding the risk of HIV in the study population; the interview itself constitutes a minimal level of burden on the respondents.

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

As noted in Worksheet Part II, the 60-day Federal Register Notice was published in Volume 80 page, 32388 on June 8, 2015. There were no public comments. There was consultation outside of NHLBI to conceptualize and design this study. The final study design was developed, reviewed, and approved by the REDS-III investigators, the REDS-III International Advisory Committee (IAC) (See Attachment 3.3 for a complete list of members) and the Observational Study Monitoring Board (OSMB) (See Attachment 3.1 for a complete list of members).

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

The project will pay R\$60.00 (~US\$20) to each study participant. It is estimated that the majority of SCD patients or non-SCD controls recruited from similar communities would earn minimum wage in Brazil (R\$4/hour). It is estimated approximately 1 hour would be required to complete study activities (informed consent and completion of assessment) in addition to 1.5 hour travel time to/from Hemocenter. Therefore total time lost from work is estimated at 2.5 hour = R\$10. The estimated cost of travel to/from Hemocenter is R\$30 and estimated cost of 1 meal during this time is R\$20. Total payment to be provided to respondents is therefore R\$60 (~US\$20).

A.10. Assurance of Confidentiality Provided to Respondents

All respondents will be assured of the actions taken to safeguard their privacy and all efforts will be made to secure the privacy of respondent patients to the extent permitted by law. 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 assessment. Use of a Subject ID on the assessment 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 patients is only maintained by the blood centers. The link is maintained so any HIV positive participants can be re-contacted to return to the Hemocenter for appropriate counseling and referral. Patient identifying information is already collected by the Hemocenters as part of regular procedures and routine care of SCD patients. However, the Coordinating Center (RTI, US) will not have access to any patient identifying information.

A.11. Justification for Sensitive Questions

The primary goal of objective 1 of this research is to determine the risk of HIV in SCD, necessitating the inclusion of sensitive questions. Therefore, special attention has been devoted to carefully designing these questions in a straightforward and non-judgmental way. In many countries including Brazil, the path of HIV spread has moved from homosexual to heterosexual transmission. Sexual lifestyle, including the lifetime number of sexual partners and sex without condoms, increases the odds of having HIV, as well as its spread. Therefore questions regarding sexual history are critical to understanding the risk of HIV. The section on drug use was included as this is also a known risk factor for HIV.

The section on other potential risk factors will obtain data related to rare risk factors for HIV infection and includes questions related to tattoos, acupuncture treatment, time spent in jail, prison, or a detention center and body piercings or work place exposures for patients/controls who may work in professions that could lead to exposure to blood or body fluids.

In addition to specific HIV risk behaviors, other potentially sensitive questions include questions regarding race/ethnicity and income of participants. These data are included to allow a comparison of the demographics of the SCD and control population to determine if the study populations are relatively similar, except for SCD status. Note that the race/ethnicity categories asked of respondents in the assessment are consistent with the Federal Government of Brazil Census categories (IBGE).

http://www.ibge.gov.br/home/estatistica/populacao/caracteristicas_raciais/default_raciais.shtm

Please see Attachment 3.2 for a detailed justification for each question.

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

- The assessment 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.
- All data will be stored on password protected computers and in a secure location, accessible only to authorized study personnel. One designated research assistant in Hemominas Belo Horizonte will be responsible for up load of files to the DCC through a secure, encrypted FTP site on the private REDS-III website. No personal identifying information is included in files transferred to the DCC.
- Participants are advised of the voluntary nature of their participation in the study and of the steps taken to ensure the privacy of the information collected. See Informed Consent, Attachments 2.1 and 2.2.

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

The annualized burden hours for all respondents are 325. The annualized cost to all respondents is estimated at \$432 based on \$1.33 per hour. It is estimated that each respondent will spend about 15 minutes completing the consent and about 45 minutes completing the assessment. The Brazilian average minimum wage \$R4/hour translates to

approximately \$1.33/hour. Physicians and nurses familiar with the study population estimate the majority of SCD patients will earn minimum wage.

A.12.1 – ANNUALIZED BURDEN HOURS TO RESPONDENTS

Form Name	Type of Respondents	Number of Respondents	Number of Responses per Respondent	Average Burden Per Response (in hours)	Total Annual Burden Hours
Objective 1 Risk Factor Informed Consents	Adult SCD cases and non-SCD controls	300	1	15/60	75
Objective 2 Risk Factor Informed Consent	Adult HIV-positive SCD patients	25	1	15/60	6
Objectives 1 and 2 Risk Factor Assessment	Adult SCD cases and controls (Objective 1), and Adult HIV positive SCD patients (Objective 2)	325	1	45/60	244
					325

A.12.2 ANNUALIZED COST TO RESPONDENTS

Form Name	Number of Respondents	Frequency of Response	Average Time per Respondent	Hourly Wage Rate *	Respondent Costs
Objective 1 Risk Factor Informed Consents	300	1	15/60	\$1.33	\$100

Objective 2 Risk Factor Informed Consent	25	1	15/60	\$1.33	\$8
Objectives 1 and 2 Risk Factor Assessment	325	1	45/60	\$1.33	\$324
					\$432

<http://thebrazilbusiness.com/article/minimum-wage-in-brazil>

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 study is estimated to be approximately \$38,114 for activities in Brazil.

Item	Salary	Fringe Rate (%)	% Effort	Annualized Data Collection Cost
NIH Project Oversight Officer - GS15-10	157,100	20	1.5	2,357
1 in-house contractor staff (RTI Staff)	141,296	39	2.6	3,674
5 In – house contractor staff (Brazil)	45,867	0	11.25	5160
4 Field contractor staff (Brazil)	39,024	0	25	9756
Operational Costs for Data Collection Activities –Printing, equipment, overhead, respondent reimbursement,, non-labor				15509
Other Contractual costs for data collection, non-labor				351
Travel costs associated with data collection and study launch				1,307
Other costs, non-labor				0
Total				\$38,114

A.15. Explanation for Program Changes or Adjustments

This is an initial application.

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

The schedule for study activities

Activity	Time Schedule
Initiate Study Recruitment Activities	Immediately following OMB approval
Participant Enrollment and Data Collection (2 years)	Two years from OMB approval.
Data Management and Analysis	Ongoing through December 2018

Subject to NHLBI review, data will be disseminated to the scientific 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 Society of Hematology).

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 assessment.

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

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

REFERENCES

1. Samuels-Reid JH, Scott RB, Brown WE. Contraceptive practices and reproductive patterns in sickle cell disease. *Journal of the National Medical Association* 1984;76:879-83.
2. Godeau B, Bachir D, Schaeffer A, et al. Severe pneumococcal sepsis and meningitis in human immunodeficiency virus-infected adults with sickle cell disease. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 1992;15:327-9.
3. Bagasra O, Steiner RM, Ballas SK, et al. Viral burden and disease progression in HIV-1-infected patients with sickle cell anemia. *American journal of hematology* 1998;59:199-207.