Transfusion-Transmissible Infections Monitoring System (TTIMS)
Laboratory and Risk Factor Database Coordinating Center (LRCC)

Risk Factor Assessment in Blood Donors

Protocol 1

11 July 2017

Protocol Synopsis

The Transfusion-Transmissible Infections Monitoring System (TTIMS) Laboratory and Risk Factor Database Coordinating Center (LRCC) project has two primary responsibilities in TTIMS. The first responsibility is to lead the collection, evaluation and analysis of risk factors in blood donors who have HIV (NAT yield and seropositive), HCV (NAT yield) and HBV (NAT yield) positive blood donors (Protocol 1). The second responsibility is to establish a biospecimen repository, conduct laboratory analyses of HIV seroprevalent infections to be able to classify them as newly acquired or long standing, and to determine genotypes and, where applicable, drug resistance profiles for HIV (NAT yield and seropositive), HCV (NAT yield) and HBV (NAT yield) infections (these activities are described in a separate Protocol 2 document).

The overall objectives of Protocol 1 procedures are to: a.) Coordinate the collection of risk factor data by the participating blood centers from enrolled donors meeting consensus definitions, b.) Combine risk factor data and disease marker surveillance information across different blood collection organizations; c.) Evaluate and monitor risk factor data of donors and their donations confirmed to be positive for transfusion-transmissible viral infections; and d.) Compare/analyze risk factor data to those obtained in the REDS-II TTI Marker Prevalence and Donor Risk Factor Study. The specific aim of this part of LRCC activities is to catalog contemporary risk factors for the purpose of understanding how blood donors became infected with a transfusion-transmissible virus. While the likely risk factors for acquisition of HIV, HCV, and HBV are known, the relative frequency of such risk factors in US blood donors is not well known, and could change over time as blood donor eligibility criteria are modified. Blood donors with infections that meet the study consensus case definitions as well as false-positive control donors at the American Red Cross, Blood Systems, Inc., New York Blood Center, and OneBlood will be asked to complete a risk factor questionnaire following notification of their test results via routine blood center procedures. Each organization will interview its own blood donors. Consent and interview responses will be captured electronically. A participation incentive linked to completion of the risk factor interview will be provided to each participant. Data analysts at the LRCC will generate monthly, quarterly, and annual reports of risk factors. Analyses will be stratified by infection, donor demographics, and US Department of Health and Human Services Public Health Service region so that the relative proportion of specific risk behaviors such as men having sex with men (MSM), multiple heterosexual partners (MHP), and injection drug use (IDU) can be monitored for proportional changes over time. In addition, research publications will be developed to more completely describe the risk factor findings reported by blood donors who have HIV (NAT yield and seropositive), HCV (NAT yield) or HBV (NAT yield) infections in combination with other results from the TTIMS program.

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Protocol 1 – Risk Factor Assessment and Analysis

Background and Significance

Approximately 4.5 million US patients receive red cell transfusions each year and millions of other patients receive platelets and/or plasma.[1] Preventing the transmission of infections to persons requiring transfusion is of paramount importance. Information on current risk factors for viral infections in blood donors was largely unavailable in the US until the REDS-II Marker Rates and Donor Risk Factor Study (DRFS) was completed.[2] Blood donors from four large blood centers were included in a case-control study of donors with confirmed infections (cases) and a comparison population of donors with repeat reactive unconfirmed infections (false positive donors, classified as controls).

American Red Cross (ARC), Blood Systems, Inc. (BSI), New York Blood Center (NYBC), and OneBlood participated in the case-control study from 2010 to 2013. Donors with serologic and nucleic acid testing (NAT) or NAT-only confirmed human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) infections (cases) and donors with false-positive results (controls) were interviewed for putative behavioral and demographic risks.

Frequencies of putative risk factors from that study are provided separately for males and females with regard to sexual exposures and grouped together for other exposures (Appendix 2 Table 1). Male HIV and HBV cases had similar numbers of female sexual partners as did controls (median 4 and 6, respectively), but male HCV and HTLV cases reported higher numbers of female partners (median 15 and 10, respectively). Over 60% of male HIV cases reported MSM behavior, including over 50% in the last 12 months; this was not common for HBV, HCV or controls. For females, higher numbers of sexual partners were reported for HIV (median 10) and HCV (median 9) cases, but not for HBV or controls. Sexually transmitted diseases were frequently reported by female HIV, and HCV-infected donors (35-36%); HCV-infected female donors also frequently reported sex with an injection drug user (IDU). When both sexes were combined, HCV-infected donors reported the highest frequencies of injecting drugs, steroids or vitamins, or using non-injection drugs, or receiving a blood transfusion in the period of 1958-2011 with 50% of transfusions occurring ≤1990. Reporting having ever spent three or more days in jail, a detention center, shelter or group home was associated with all four viral infections, but was highest among HCV cases. In contrast, HBV-infected donors were more likely to report having lived abroad or immigrated to the US, or having an HBV or HCV infected family member.

Before the DRFS, other studies of risk factor profiles among HIV-infected donors were funded by the CDC for approximately 10 years after implementation of serologic screening in the mid-1980s, and studies of HCV-seropositive donors were conducted in the early 1990s.[3] A study of risk factors for HCV infection in nucleic acid positive (NAT) anti-HCV negative donors from the early 2000s was also reported.[4]

ARC has conducted infection trend analyses.[5,6] The findings show continued HIV risk with the prevalence of HIV in first-time donors hovering around 10 per 100,000 donations in each year of the 10-year period studied and the incidence in repeat donors increasing from 1.49 per 100,000 person-years in 1999-2000 to 2.16 per 100,000 persons-years in 2007-2008.[7] While the prevalence of HCV in first-time donors decreased over this time interval from 345 to 163 per 100,000 donations, the incidence in repeat donors did not decrease and evidence of incident infection in first-time donors increased. Moreover specific

age, gender and minority race/ethnicity groups were over-represented. Significantly increased incidence of both HIV and HCV were observed in 2007-2008 compared to 2005-2006. Similar analyses for HBV have shown an incidence in all donors of 3.4 per 100,000 person-years which is lower than earlier estimates, but remains higher than for HIV and HCV.[8]

Brief reviews of older studies of HIV, HCV, HBV risk factors are provided to establish a historical context for the epidemiology of each of these infections in blood donors.

HIV

Among 38,000 persons in 33 states with confidential name-based HIV infection reporting in 2004, male-male sex was the most frequently reported transmission category, followed by heterosexual contact and IDU.[9] The 1999-2002 National Health and Nutrition Examination Survey (NHANES) results show that non-Hispanic black participants (N=1283) who reported ever using cocaine/street drugs, in addition to those who tested positive for the presence of HSV-2 antibody, had a higher prevalence of HIV infection.[10] In blood donors, risk factors reported by HIV seropositive donors from over 20 years ago were different for males and females. In males, male-male sex was most common followed by IDU, then sex with an IDU, but 27% did not disclose or could not identify a risk, whereas in females, sex with males at risk for HIV was most common (81% of whom were IDU) followed by IDU, but 41% did not disclose or could not identify a risk.[11,12]

HCV

Hepatitis C is the most common blood-borne infection in the United States, and risk factors are associated with percutaneous or mucosal exposures to blood or blood-derived body fluids. A national population-based survey NHANES III, 1988-1994) surveyed approximately 15,000 participants and found that a history of injection drug use was the strongest risk factor for HCV infection.[13] Other significant risk factors included 20 or more lifetime sexual partners, and blood transfusion before 1992. Among blood donors, a matched case-control study of 2,300 participants showed that injection drug use was highly associated with HCV seropositivity and was the most common risk factor reported by US blood donors (about 50%).[14] Data from the Centers for Disease Control and Prevention from 1995-2000 demonstrate that most newly acquired infections are associated with injection drug use, followed by exposure to an infected sex partner or to multiple sex partners, health care work with frequent exposure to blood, and rarely, nosocomial, iatrogenic and perinatal exposures.[15] HCV NAT positive, anti-HCV negative blood donors had the following risk factors, recent injection drug use (IDU), followed by occupational exposure, sexual contact with an HCV-infected partner (who was an IDU), and perinatal exposure.[4]

HBV

The 1988-1994 NHANES data (N=40,000) demonstrate that black race, increasing number of sexual partners, and non-US place of birth were highly associated with HBV infection.[16] Centers for Disease Control and Prevention surveillance data from 1990-2004 show that the proportion of acute HBV cases reporting multiple sexual partners and male-male sex doubled over this time period, indicating that these behaviors are associated with increased risk of HBV transmission.[17]

The greatest improvements in infectious disease blood safety come from preventing the donation of blood from infected donors. To increase the probability of preventing such donations, blood collection organizations need to be able to aggregate data to understand larger patterns across organizations. Standardized data coding, research database processes, and data collection procedures across organizations will benefit transfusion safety. Identifying and reporting risk factors for viral infections in confirmed-positive viremic and seropositive donors is not mandated by the US FDA or required by blood

organizations or standard-setting bodies. Risk factor assessment by blood organizations is currently done as part of individual donor notification and counseling by blood centers, but not in a systematic way within or across organizations. A systematic collection of risk factor data will enhance the information already contained in the centers' databases and allow the FDA and other agencies to monitor the impact of changes in donor eligibility policies.

In the REDS-II Infection Marker Rates and DRFS, donors with donations that tested false positive (controls) were interviewed as a comparison population. These false-positive donors included donors who tested HIV, HCV, HBV, or HTLV serology repeat reactive on one screening test but were not confirmed to have infection. Controls were not matched to cases on any demographics or other factors. The inclusion of controls allowed for an analytical assessment of the statistical association and odds of infection comparing risk behaviors and demographics between those with confirmed infections (cases) to uninfected donors. Table 1 provides risk behavior results showing the odds of HIV infection between cases and controls from the REDS-II study and Table 2 provides risk behavior results associated with HCV infection.

Table 1. Statistical measures of behavioral risk factors associated with HIV infection in blood donors from the REDS-II US Risk Factor Study.[2]

Factors Associated with HIV Infection in Blood Donors	**Adjusted Odds Ratio,* 95% Confidence Interval & p-value**		
Sex with someone who is HIV+	131.7	26.7 – 650.1	<0.001
MSM	62.3	27.6 – 140.4	<0.001
Injection drug use	3.1	0.3 – 28.5	0.30
3+ nights in detention/jail	2.4	1.2 – 4.8	<0.01
Tattoo, body piercing, or 3+ ear piercings	2.8	1.6 – 4.8	<0.001
Multiple sexual partners in last year	2.3	1.4 – 3.8	<0.01

* Adjusted for gender, age, race/ethnicity, income, first time/repeat donor status.

Table 2. Statistical measures of behavioral risk factors associated with HCV infection in blood donors from the REDS-II US Risk Factor Study.[2]

Factors Associated with HCV Infection in Blood Donors	**Adjusted Odds Ratio*, 95% Confidence Interval & p-value**		
IDU	42.1	13.0 – 136.3	<0.001
Household member with Hepatitis	15.4	5.9 – 40.3	<0.001
Sex with IDU	9.7	4.4 – 21.2	<0.001
3+ nights in detention/jail	7.5	4.3 – 12.9	<0.001
Transfusion Ever	5.1	2.7 – 9.6	<0.001
Tattoo or body piercing	3.5	2.0 – 5.9	<0.001

*Adjusted for gender, age, race/ethnicity, education, first-time/repeat status, born in the US

Controls are equally important as part of TTIMS for understanding the behavioral characteristics of the uninfected donor population. The controls that were interviewed for the REDS-II Study would not serve as appropriate comparison controls for blood donors with infections during the TTIMS period (2015 – 2019) for two reasons. First, directly comparing risk behaviors between false-positive donors from the REDS-II Study (2011 – 2012) with cases from TTIMS would involve a time period difference of 4 to 8 years depending on when the TTIMS cases are interviewed. Secular and other changes in the donor base between the two time periods could lead to substantial bias, particularly with respect to the

demographics of donors as the number of blood donations and the approach to donor recruitment in the US have significantly changed over the this time period. Second, because the blood donation eligibility rule for MSM has now changed, it is important to assess if there have been changes in undisclosed risk behaviors in accepted donors with and without infection. Further, by conducting control interviews in TTIMS, we will also be able to assess if the rates of undisclosed risk behaviors such as MSM are different between the REDS-II Study and TTIMS time periods.

This project represents a collaborative study that will include a comprehensive interview study of viral infection positive blood donors at the ARC, BSI, NYBC and OneBlood in order to identify the current predominant risk factors for virus-positive donations and will also establish a donor biovigilance capacity that currently does not exist in the US. Combined data are critical for appropriate national donor infectious disease monitoring efforts. In addition, with implementation of changes in the indefinite donor deferral for men who have sex with men (MSM) to a 1-year deferral since last MSM contact,[18] monitoring the relative prevalence of risk behaviors in donors with confirmed infection is important for the assessing changes in risk following modification of the deferral.[19] Data collected by TTIMS will be useful for both regulatory and educational reasons. For example, this information could be used to target educational interventions to reduce donations from persons with high risk behaviors. This is particularly important in the case of behaviors associated with incident (recently acquired) infections; these donations have the greatest potential transmission risk because they could be missed during routine testing. The combined database will capture infectious disease and risk factor information on nearly 60% of all blood donors and donations in the country.

Objectives

The LRCC project has two primary responsibilities in TTIMS. The first responsibility is to lead the collection, evaluation and analysis of risk factors data in blood donors who have HIV (NAT yield and seropositive), HCV (NAT yield) and/or HBV (NAT yield) positive donations and also donors who test repeat reactive but do not confirm positive based on supplemental/confirmatory testing for the same infections will be interviewed. The unconfirmed (false positive) donors will serve as a comparison group to the confirmed positive donors (items 1 – 4 below). The second responsibility is to establish a biospecimen repository, conduct laboratory analyses of HIV seroprevalent infections to be able to classify them as newly acquired or long standing, and to determine genotypes and, where applicable, drug resistance profiles for HIV (NAT yield and seropositive), HCV (NAT yield) and HBV (NAT yield) infections (these activities are described in a separate Protocol 2 document).

The TTIMS LRCC project purpose is to serve as the coordinating, laboratory, and analytical center for analyses relevant to the evaluation and monitoring of HIV (NAT yield and seropositive), HCV (NAT yield) and HBV (NAT yield) positive blood donor risk factor data, molecular surveillance data and HIV recency testing data. Specifically, the primary objectives are to:

1. Coordinate the collection of risk factor data by the participating blood centers where donors with infections and donors who tested false positive donated.
2. Integrate risk factor data and disease marker surveillance information across different blood collection organizations.
3. Evaluate and monitor risk factor characteristics of donors and donations confirmed-positive for transfusion-transmissible infections.
4. Compare/analyze risk factor data to those obtained in the REDS-II Marker Prevalence and DRFS.
5. Provide logistical support for the TTIMS project and for the Committee/Subcommittee meetings, conferences, and donation(s) transfer/shipment.
6. Serve as the biospecimen repository for the TTIMS project.
7. Perform recency testing on HIV plasma samples from donors with seropositive infection to establish estimates of time of HIV acquisition.
8. Conduct viral genetic sequence analyses on plasma samples for HIV (NAT yield and seropositive), HCV (NAT yield) and HBV (NAT yield) positive blood donors to determine genotypes and drug resistance (where applicable) of donor infections.

Specific Aims of Risk Factor Assessment

1) Determine current behavioral risk factors associated with all HIV-infected donors, and HCV and HBV NAT yield donors, including parenteral and sexual risks, across the participating blood collection organizations.

Hypotheses:
The distribution of risk factors for viral infections in donated blood reported by donors in studies from more than 10 years ago will not be same as those reported today. We expect that factors such as injection drug use will comprise a lower proportion of identified risk in blood donors

with infections, and those sexual exposures, including multiple heterosexual partners (MHP) and male-to-male sex (MSM), will comprise a larger proportion of reported risks for infection.

2) Analyze integrated risk factor, recency and genotype data together because when taken together these may show that blood centers are not achieving the same degree of success in educational efforts to prevent donation by donors with risk behaviors across all demographic groups.

The primary contribution this project can add to a national biovigilance system is to monitor routes and rates of viral infection acquisition that could lead to transfusion transmission. Thus results from this study could also be used to assist in formulating guidelines, informing policy decisions, planning prevention programs, and targeting risk reduction interventions. National reporting systems with coordinated collection and analysis of data have led to specific recommendations that underpin key transfusion safety initiatives in other jurisdictions.[20]

Study Procedures and Tasks

Study Population

The study population for the risk factor interviews will be allogeneic and directed donation blood donors from the four participating blood centers who have specific screening results obtained from routine donation screening from either ARC or Creative Testing Solutions (CTS) laboratories.

Inclusion Criteria

Donors eligible to be interviewed for the risk factor study as part of LRCC activities will be donors who have confirmed HIV, HCV NAT yield, or HBV NAT yield infections and donors who test repeat reactive but do not confirm positive based on confirmatory testing. Table 3 provides the types of each confirmed positive viral infection that will qualify as eligible cases for risk factor interviews.

Defining Infection Status

Consensus Positive Donors

The Donation Database Coordinating Center (DDCC) portion of TTIMS includes development and use of interpretation algorithms to consistently define infections based on routine testing at ARC or CTS. NAT yield donors are considered incident infections versus those of HIV seropositive donors where the time of infection acquisition is unknown using standard laboratory screens. Testing conducted as part of LRCC Protocol 2 will be used to further classify seropositive HIV infections into recent or long-standing status.

Table 3. Summary of consensus positive definitions for HIV, HCV, and HBV cases used to define eligible donors for risk factor interviews as cases.

Donation Test Results	**Study Definition**
HIV	
• Anti-HIV nonreactive (NR) ***and*** • HIV NAT-discriminated reactive (dHIV) ***and*** • HIV NAT-discriminated reactive (dHIV) in an independent sample (e.g. retrieved plasma component) ***or*** confirmed HIV NAT-reactive with or without anti-HIV seroconversion in a donor follow-up sample	NAT-yield (Incident HIV)
• Anti-HIV repeat reactive (RR) ***and*** • HIV NAT-discriminated reactive (dHIV)	Seroreactive + NAT-reactive (Prevalent HIV)
• Anti-HIV repeat reactive (RR) ***and*** • HIV MP-NAT NR ***and*** • Anti-HIV confirmed reactive (IFA, EIA, WB, ChLIA) in an independent sample (e.g. retrieved plasma component) ***Note: 10x replicate testing with at least 1 reactive on dHIV NAT required to define as HIV controller***	Seroreactive + low-level viremia or virologic control (Prevalent HIV)
HCV	
• Anti-HCV nonreactive (NR) ***and*** • HCV NAT-discriminated reactive (dHCV) ***and*** • HCV NAT-discriminated reactive (dHCV) in an independent index donation sample (e.g. retrieved plasma component) ***or*** confirmed HCV NAT-reactive with or without anti-HCV seroconversion in a donor follow-up sample	NAT-yield (Incident HCV)
HBV	
• Anti-HBV nonreactive (NR) ***and*** • HBV NAT-discriminated reactive (dBIV) ***and*** • HBV NAT-discriminated reactive (dHBV) in an independent sample (e.g. retrieved plasma component) ***or*** confirmed HBV NAT-reactive with or without anti-HBV seroconversion in a donor follow-up sample	NAT-yield (Incident HBV)

Exclusion Criteria

Donors with results from any blood donation not meeting the specific testing results defined in Table 3 will not be eligible for risk factor interviews as cases. Autologous donors meeting these infection definitions are not eligible.

False-Positive Donors

Robust confirmation procedures are used to ensure donors who are repeat reactive on one of the screening tests, but negative on all others, are verified by further supplemental testing to be false-positive. These donors are not the same as donors who are classified as having indeterminate testing results.[21] Donors with indeterminate confirmation results will not be eligible as controls for TTIMS. Donations from donors who test repeat reactive but are not confirmed by supplemental testing are believed to be random events and therefore they represent an appropriate sample of the blood donor population. Studies of infected and uninfected blood donors have previously used this strategy to identify controls for case-case control studies[2,22-24] and research has shown that donors with false-positive results on an initial screening test are not infected.[25-27] A recent study has suggested that some false-positive test results for HTLV and HCV may be associated with certain demographics, but for anti-HIV or HBsAg false-positive results no demographic associations were evident.[28]

For TTIMS, we will use anti-HIV screening false-positive donors as controls for all HIV cases. The frequency of false-positive testing results varies according to the sensitivity and specificity and other aspects of the screening tests used. For anti-HIV testing the ratio of false-positive to confirmed positive donors is greater than 15:1. This ratio means that we will have far more false-positive donors than confirmed positive donors as potential participants for the study. Similarly, HBsAg false-positive are straightforward to confirm as uninfected and will serve as an additional source of potential controls. Use of donors with HBsAg, non-neutralized, false-positive donations is of particular relevance to serve as controls for incident [serology negative, nucleic acid test positive (NAT yield)] HBV and HCV cases.

The operational processes that are used for blood screening results notification for false-positive donors represent an opportunity to sample an informative control group that has interacted with each blood center in a largely similar manner to that of cases. These donors are contacted by mail informing them of the results of testing and their false-positive status. Because they have to be contacted and provided the results, which include the false-positive screening tests, these donors may be interested and motivated to complete the questionnaire as part of the counseling process even though they do not have infection. In the REDS-II Risk Factor Study, enrollment of false-positive donors for control interviews was readily achieved.

Control interviews will be conducted using the same study procedures as planned for case interviews with each blood center interviewing its own donors by telephone using the internet-based survey, and the web-based study management system. Controls would be interviewed in years 2 through 5 of the TTIMS program, but would be enrolled in numbers to reflect an overall 1:2 case:control ratio for the entire TTIMS project period, i.e. the total number of cases for the 5 year period will be used to conduct control interviews to achieve a final 1:2 ratio.

Donor Enrollment and Study Management

General Approach

The reports of confirmed infections (HIV NAT yield and seropositive and HCV and HBV NAT yield) and false positive donors provided to each blood center by the DDCC will also be sent to the LRCC and will serve as the denominator data of consensus eligible donors for LRCC activities.

First, we will use a system internal to the LRCC that will not be accessible by other organizations for the purpose of tracking completion of each aspect of LRCC project procedures for each qualifying consensus eligible donor. The DDCC consensus eligible donor reports data will be entered into an activity tracking database at Blood Systems Research Institute (BSRI). We are not planning to maintain TTIMS data in this BSRI-internal activity tracking log, but rather we will use it as the record of LRCC tasks for each participant and specimen set. BSRI will use these data with the donation identification number (DIN) as the key unique, but de-identified, tracking identifier to establish a sample and participant tracking log.

Second, a study management system (SMS) will be developed that will be used by each blood center to monitor recruitment, consent, enrollment, provision of incentives and communication of relevant results back to each participant. Through BSRI's affiliation with UCSF, we will use the study management software Online Collaborative Research Environment (OnCore, Forte Research Systems, Madison, WI). This is a state-of-the-art study management system software package capable of tracking activities related to donors (recruitment, consent, enrollment, completion of study activities, provision of participation incentives), specimens (receipt of specimens, provision to specific testing laboratories, indication of completed testing), and can be used to generate summary reports of each of these activities. For the SMS we will utilize a specific component of the OnCore platform, the Unified Registries Management (URM) system to guide study procedures at each site and to monitor progress. This is a customizable set of study and participant tracking tools that will serve as the SMS for LRCC. The OnCore URM module enables management of clinical research data sets that are configured around an event (e.g., a blood donation) and the ability to create a coordinated cascade of data capture at the person or event level, including deployment of common forms for all participating blood centers and data export tools for analysis in statistical programs.

The OnCore system will be implemented in accord with all required data security and privacy protections, and current standard best practices. Outside of the OnCore URM, each site will have access to donor-specific, personally identifying information (PII) that the LRCC will not have access to. PII will be maintained by each blood center per standard, regulated procedures. These data will be accessed by LRCC project staff within each center for the purpose contacting and recording completion of TTIMS LRCC project activities.

Within the OnCore URM, access levels for all study staff are controlled by LRCC senior staff based on job function. At the donor level, the data captured will include recruitment status (e.g., consented, refusal, pending, lost to follow-up), risk factor interview completed, and participation incentive provided. At the donation or sample level the data captured will include an indicator of successful retrieval of the frozen plasma unit from the index donation, bio-specimens obtained from plasma unit or from alternate sources, specimens accessioned into the repository, recency testing completed, and molecular surveillance testing completed.

The LRCC will create a centralized repository of samples from consensus HIV-positive, HCV NAT yield, and HBV NAT yield blood donations to serve future research uses such as availability for HIV, HCV, and HBV evolutionary geneticists investigating changes in virulence and pathogenicity over time. These mechanisms for obtaining additional specimens shall be ready for implementation to capture other specimens if an emerging agent of concern is identified. The repository is described in Protocol 2.

Control donor interviews will be based on a random sample of anti-HIV, or HBsAg false positive donors in a ratio of 1 case to 2 controls within each blood collection organization.

Description of LRCC Activities

The LRCC will use reports developed by the DDCC subcontractor, Quality Analytics, to initially identify those potential donors who are eligible for participation in the LRCC portion of TTIMS. The diagram titled Transfusion Transmissible Infections Monitoring System (TTIMS), Donation Database Coordinating Center (DDCC) and Laboratory and Risk Factor Coordinating Center (LRCC) maps out the data and specimen flow that will be used to conduct blood center specific activities under the LRCC (Appendix 1). Communication of all study-related data files will occur via secure channels (username and password protected computers, secure file transfer protocols (FTP), and as required per the terms of the contract will use Secure Sockets Layer (SSL) and Transport Layer Security (TLS) or encrypted SSL/TLS connections).

The approach to identifying eligible cases will be driven by data directly obtained from donation testing by ARC and CTS. ARC and CTS testing data will be provided according to donation identification numbers (DINs) and will be electronically transferred to the DDCC data server, as described in the TTIMS DDCC Protocol. These data will define HIV, HBV, and HCV consensus positives. Quality Analytics will use the consensus infectious marker testing algorithms developed for this project and will run interpretation programs to define which combinations of test results meet the required study eligibility definitions. These reports will then be sent back to each participating blood center organization and to CTS by DIN, and will serve as the list uses to retrieve plasma units (if available), residual volumes from testing and for the recruitment of risk factor interview participants. This process removes the need for local blood center IT expertise in running these algorithms and will ensure that eligible donors are defined in the same across all participating sites. BSI, NYBC, and OneBlood testing results will be provided to the DDCC by CTS. Similarly, ARC data will be provided to the DDCC by ARC testing laboratories. The data will flow to the DDCC data server separately, but in parallel from CTS and ARC testing labs.

The LRCC will coordinate and facilitate the activities that individual blood centers will use for recruiting, enrolling and characterizing risk behaviors in seroprevalent and NAT yield HIV blood donors and NAT yield HCV and HBV blood donors. Donors with false-positive results will also be enrolled. Donor counselors at participating blood centers will conduct risk factor interviews. Each blood center will be responsible for recruiting its own blood donors, enrollment of these donors, conducting the web-based risk factor interview, and working with ARC, CTS, and BSRI to provide plasma specimens for the repository and testing at the LRCC.

The four participating blood centers in LRCC estimate they have the following annual number of infections that will qualify for LRCC activities (Table 4).

Table 4. Annual estimates of donors with infections that will qualify for TTIMS participation.

Blood Center	Serology + NAT HIV Positive	HIV NAT yield	HCV NAT yield	HBV NAT yield
ARC	150	20	50	20
BSI	24	1	4	1
NYBC	22	1	4	3
OneBlood	64	1	35	11
Total	**260**	**23**	**93**	**35**

After routine notification of having donated a confirmed HIV-positive donation, HCV NAT yield, or HBV NAT yield, donors will be asked to complete an interviewer-administered telephone questionnaire. The LRCC will build on current operational procedures to facilitate the ease of use of the risk factor interview instrument. As per operational procedures, except in rare circumstances, donors who are HIV positive are notified in person by blood center professional medical staff (physician or qualified donor counselor) and will be asked to complete the questionnaire at the time of notification, or based on professional judgment at a future in-person meeting or by telephone call if agreement for future contact is obtained. Donors with false positive test results will be contacted in the same manner. Trained donor counselors will conduct the interview over the telephone. There are strict operational procedures at all blood centers in place to verify that a person contacted by phone is the donor. If the donor's identity cannot be confirmed via standard operational procedures the interview will not be conducted. Donor counselors will try to contact donors by phone to follow-up to see if the donor received the routine notification letter and counseling materials. Donor counselors will attempt to contact donors up to 3 times by phone, email, or letter. If counselors are unable to reach a donor after 3 attempts the donor will be classified as lost to follow-up. Study information mailer templates in English and Spanish are provided in Appendices 5 and 6. The LRCC will work with each blood center to include the project information mailer as part of the notification letter sent to donors who are eligible for interview.

Although each organization will seek to enroll all persons who meet the study case definitions, it is unrealistic to expect 100% participation. We will strive to achieve no less than 50% and target 75% participation as our enrollment goal for each qualifying consensus definition donor. We believe the provision of a $75 participation incentive to each donor who consents and completes the risk factor interview may be very helpful in reaching the target participation proportion. Total potential enrollment per year is provided in Table 5. Importantly, year 1 enrollment will likely be lower than in subsequent years because risk factor interviews for the first year will mostly be conducted retrospectively following Office of Management and Budget (OMB) clearance to interview donors. An enrollment of less than 50% in the first year is likely the maximum that will be achievable due to the elapsed time before we can contact donors for interviews and the associated likely increased loss to follow-up because of potentially out of date contact information at the time we seek to recruit study participants.

Table 5. Annual estimates of donor risk factor interviews based on different assumed participation proportions.

Assumed participation of donors with confirmed infection	Serology + NAT HIV Positive	HIV NAT yield	HCV NAT yield	HBV NAT yield
100%	260	23	93	35
75%	**195**	**17**	**70**	**26**
50%	130	12	47	18

Assessment and Measurement Procedures

The LRCC will use similar study procedures to those from the REDS-II DRFS study to compile risk factor data for all qualifying HIV infections and HCV/HBV NAT yield infections across different blood collection organizations. Because TTIMS requires both consistency and timeliness in capturing risk factor responses, interviewer administered questionnaires will be performed. This also creates an opportunity for donor counselors to provide additional counseling. Interviews will be electronically transferred to the LRCC as part of a consolidated database of all completed interviews. Data form scanning or key punch entry will not be necessary. The LRCC will conduct quality control and assurance processes that include allowed and out-of-range values; interview quality control reports will be generated and provided back to each blood center on a monthly basis to check and, where necessary, correct and resubmit updated interviews. The DDCC overall database for TTIMS will serve a similar role as in the previous REDS-II Marker Prevalence and DRFS by allowing additional cross-checking of some types of donor-reported information. For example, self-reported first-time or repeat donor status is difficult to verify, therefore we will rely on blood center records to determine first-time or repeat donor status. These blood center data are more reliable than donor self-reported information.

Although not specifically relevant to LRCC Protocol 1, the LRCC will coordinate with the DDCC and participating blood collection organizations regarding collection, tracking, shipping (including freight), storage, and retrieval of all biospecimens for lab characterizations. The primary path by which we will achieve coordination with the DDCC will be through the "Numerator Test Data" reports provided to each blood center and BSRI for the purpose of tracking information (Appendix 1). This information will be integrated into the SMS so that bio-specimen and participant tracking, as well as availability of results from interviews and testing are traceable in monitoring reports. Each participating blood center will have access to only data from its own donors and not to that of other centers.

The unique identifier to be used in this study is ISBT 128 DIN.

The DIN is the ISBT 128 term used to identify the specific unit number assigned to a particular donation. The DIN is composed of three data elements structured in a way that allows each collection to be globally unique. For example, this prevents hospitals from receiving duplicate unit numbers, originating from multiple locations. DIN is not linkable to any other records except by the blood collection organization where the donation was given and the DIN was assigned.

Risk Factor Survey Administration

Each organization, ARC, BSI, NYBC, and OneBlood, will interview its own donors. The LRCC will coordinate and train blood centers in conducting risk factor interviews by donor counselors via telephone. A tailored plan will be developed for each site based on language administration capability (i.e. Spanish-language capability or English-only). The risk factor interview is targeted to be conducted within 30-days of the date the index donation is confirmed to meet TTIMS eligibility definitions (once prospective interviewing is approved by OMB and IRBs, and training is completed).

BSRI is a UCSF affiliate and as such has access to the web-based survey data collection software program, Qualtrics™ (Qualtrics, Provo, UT). Data collected using the web-based interviews are stored on Qualtrics servers in AZ, CO, and UT but can be downloaded at any time (multiple formats, Stata, SAS, Excel, CSV, PDF, etc.). The survey tool will be designed to automatically email or print out individual survey responses at the completion of the interview. Printed copies will be kept by each blood center. In addition, the software can also be programmed to send the output to a designated person upon survey completion or at set intervals. The LRCC will use this feature to collect the survey data in the project database as soon as each interview is finished.

For the purpose of administration of risk factor interviews, all LRCC project staff will access the electronic survey using individually defined usernames and passwords that will be provided by UCSF IT Services. Access will be granted or revoked by BSRI and UCSF. The coordinators and donor counselors will access the interview form via a permanent hyperlink and create a new record by entering data for a new participant using the DIN as the study subject number.

A risk factor questionnaire has been developed that focuses on the risk behaviors associated with human-to-human transmission of viral infections for which blood centers universally screen donated blood (English and Spanish versions included as Appendices 8 and 9). The ability to ask questions about all three viruses on a single instrument is feasible since infected individuals often share risk factors for routes of virus acquisition. Although the risk of transmission varies for each virus, HBV, HCV, and HIV can all be acquired through the following routes: parenteral (examples: blood or blood product transfusion, transplantation, injection drug use, tattooing, body piercing, needle stick injury), sexual, perinatal (examples: during pregnancy, labor, delivery or breastfeeding), and household contact (examples: sharing toothbrushes or razor blades with an infected individual). These routes of acquisition and risk factors have all been previously identified in the literature and are considered to be well-established.[4,14,29-32] Our study is designed to assess the frequency of these routes of self-reported infection acquisition. The study is not designed to assess very rare or newly hypothesized routes of infection acquisition.

We estimate that it will take 5 minutes time to complete verbal informed consent, the questionnaire will require approximately 40 minutes of the donor's time. The instrument has been developed with skip patterns so that the time of administration may vary substantially based on the risk behaviors of different donors. Donors will be interviewed by counselors who are employed by the organization where the donor gave blood. Interviews will be conducted in English or Spanish based on the preference stated by each donor and site capability. Consent will be obtained in the same language as the interview. Data from completed questionnaires from all four participating organizations will be collected in a secure database managed by BSRI. BSRI researchers will not have access to the names or any other personally identifying information, except biometric identifiers.

Analyses and Reporting

The OnCore study management system is designed to keep track of the route of study subject contact, including capturing basic demographic information on donors whom we contact, those who refuse to participate and those we are unable to contact following recruitment efforts (classification categories will include; enrolled, refused, pending, unable to contact, lost to follow-up, interview complete). This information will be analyzed to assess whether demographic differences are evident for donors who participate compared to donors who refuse or are lost-to follow-up.

The LRCC will establish ongoing data analysis capabilities to evaluate and monitor results obtained from risk factor interviews, recency testing, and genotype and drug resistance testing. Prevalence and incidence trends will be primarily monitored by the DDCC. Stratified analyses will be conducted by the LRCC using information captured from the confirmed case listings provided by the DDCC to each center and to the LRCC as well as the additional data collected from risk factor interviews.

Risk factor analyses will include overall analyses, as well as comparison of results to centers that fully participated in the REDS-II study (ARC, BSI and NYBC). This will enable us to compare the risk behavior proportions for HIV infection observed in TTIMS to those determined during the REDS-II DRFS, i.e., to the proportions of donors with HIV that reported IDU, MSM or MHP. We will assess whether the proportion of infection attributable to each risk behavior is approximately the same or different from those observed previously. The comparison of risk factors for new HBV and HCV infections will also be possible, but given small numbers of NAT yield infections, it is unlikely quantitative statistical comparisons can be achieved.

The analysis and reporting of results to the TTIMS Steering Committee (SC) and FDA will be delayed by at least a month following the close of a quarter in order to allow sufficient time for quality control, cleaning and analysis of information. The one month delay following the close of a quarter is important to be confident the data are as complete and accurate as possible. The planned report content and reporting periods are:

A. Quarterly reports (based on achieved enrollment and completed testing at the close of the quarter)
    1. For each type of viral infection:
        a. Number of completed interviews in the quarter by center and overall
        b. Frequency tables of age, gender, race/ethnicity, first-time or repeat status, DHHS public health region, and donation type of interviewed donors
        c. Frequency tables of reported risk factors
    2. Results of HIV recency testing (once LRCC Protocol 2 is implemented)
        a. Frequency tables of HIV recency results by the same categories listed in A.1.b
    3. Frequency tables of combined analyses of recent infections and risk factors

B. Semi-annual reports (based on achieved enrollment and completed testing at the close of the semi-annual period)
    1. Genotype results for HIV, HCV, and HBV and drug resistance results for HIV and HBV
    2. Frequency tables of combined analyses of recent infections, risk factors, and genotypes for each of the three viruses

3. Separate frequency tables of risk factors in HIV NAT yield infections

Triggered Follow-up Investigations

The LRCC will coordinate with the DDCC and participating blood collection organizations to conduct follow-up investigations triggered by significant changes in TTI incidence/prevalence rates and risk factors, as defined by consensus agreement between FDA and the TTIMS SC. One approach might be to rely on 95% Confidence Intervals calculated on quarterly or semi-annual datasets. If the 95% confidence intervals for incidence, prevalence and risk factor frequencies are non-overlapping this may represent evidence of "significant changes". Even so, some random variability is expected in all of these data, and so an alternate approach could be to conduct trend analyses by month or quarter to assess the possibility of sustained change. The shorter the period the data are compared, the higher the likelihood of variability that could appear, but is not in fact significant. Ultimately, the TTIMS SC using the data that have been provided by DDCC and LRCC activities will determine if an investigation is required.

If an investigation is prompted, the investigation will include verifying that the processes of donor and donation qualification for each blood establishment participating in LRCC have been performed in accordance with FDA regulations, cGMP and all standard operating procedures of the blood establishment. This also includes adhering to all manufacturers' instructions, acting on all information provided by the donor at the time of donation and any additional information provided by the donor post-donation (e.g., disclosure of any high-risk behavior). These investigations, should they be triggered, will be conducted within 30 days of their identification.

Statistical Considerations

Power and Sample Size

Power analyses to help guide the understanding of what levels of excess risk can be estimated assuming a case to control ratio of 1:2 with 50% case enrollment was conducted and the expected number of HIV, HCV and HBV cases during the TTIMS period was conducted. The detailed results from the REDS-II Study (Appendix 2) provide information on the prevalence of risk behaviors reported by HIV, HCV and HBV cases and false-positive controls from that study. In addition, a survey study of undisclosed risk factors in accepted male donors conducted as part of REDS-III, found non-compliance with the MSM deferral in uninfected male blood donors of 2.6%.[19] For HIV, we assume a maximum expected prevalence of undisclosed risks in the control group during TTIMS based on these recent data. Power to detect significant associations depending on the excess risk in cases and the baseline prevalence of each behavior in controls with a sample size of 710 confirmed HIV-positive, interviewed donors compared to 1420 interviewed controls is provided in Table 6. The table shows the power at α=0.05 to detect significant associations between risk factors with a prevalence of 2.6, 1.7, 0.5 and 0.25% in controls donors assuming 10, 5, 3, and 2-fold higher odds of specific risk behaviors in confirmed-positive donors.

To place these estimates in context, we will have sufficient power to detect odds ratios just above 2-fold higher for any behavior reported by 2.6% of controls. In addition, although the adjusted odds ratio in the REDS-II study was 3.1 for the association between HIV infection and intravenous drug use (IDU), it was not statistically significant. In that study 0.4% of false-positive controls reported IDU. With the proposed number of controls we will have sufficient power to detect an odds ratio of 5 or higher for IDU if 0.5% of

controls report IDU history. Overall, the proposed ratio of cases to controls for HIV in TTIMS will be able to achieve similar power levels as achieved in the REDS-II study.

Table 6. Power for various risk factor prevalence combinations for HIV cases compared to controls, assuming 50% case enrollment and a 1:2 case:control ratio.

Infectious Marker case/control sample sizes	**Prevalence of risk factor in controls – [Reference]**	**Odds ratio to detect in cases**			
		10	**5**	**3**	**2**
		Power			
HIV 710/1420	2.6%[19]	1.0	1.0	1.0	0.79
	1.7%[2]	1.0	1.0	0.97	0.62
	0.5%	1.0	0.94	0.58	0.23
	0.25%	0.99	0.71	0.33	0.14

The inclusion of control interviews for NAT-only HCV and HBV cases will increase the number of cases and controls over the five year period to a projected 1030 and 2060, respectively. The additional 560 control interviews will be triggered based on being HBsAg false-positive. HBsAg confirmation testing when non-neutralized along with being anti-HBc and NAT negative indicate that any HBsAg false-positive does not have an HBV infection. These controls would be informative for comparing to the up to 280 NAT-only HCV and HBV infections that are planned to be interviewed as part of TTIMS. Power to detect significant associations depending on the excess risk in cases and the baseline prevalence of each behavior in controls with a sample size of 280 incident HCV and HBV confirmed positive, interviewed donors compared to 560 interviewed controls is provided in Table 7. The table shows the power at α=0.05 to detect significant associations between risk factors with a prevalence of 5.2, 2.3, 0.5 and 0.25% in controls donors assuming 10, 5, 3, and 2-fold higher odds of specific risk behaviors in confirmed-positive donors. The estimates are based on risk behaviors that were significantly associated with HCV or HBV infection in controls from the REDS-II Study; 5.2% of controls from that study reported spending 3 or more nights in jail, detention or a group home, and 2.3% of controls reported sex with an IDU.

Table 7. Power for various risk factor prevalence combinations for HCV and HBV cases compared to controls, assuming 50% case enrollment and a 1:2 case:control ratio.

Infectious Marker case/control sample sizes	**Prevalence of risk factor in controls – [Reference]**	**Odds ratio to detect in cases**			
		10	**5**	**3**	**2**
		Power			
HBV & HCV 280/560	5.2% [2]	1.0	1.0	0.98	0.67
	2.3% [2]	1.0	1.0	0.81	0.38
	0.5%	0.96	0.60	0.27	0.12
	0.25%	0.76	0.35	0.16	0.09

For the assessment of the association between IDU and incident HCV, we will be able to estimate a significant odds ratio of less than 9 in cases compared to controls. In the REDS-II Study the association between HCV and IDU was highly significant with an odds ratio of 42.

For other uncommon risk behaviors in the uninfected population, such as those with frequency of 0.25%, if all interviewed false-positive donors are included in the analysis of infection risk factors 2060

controls can be compared to each case group. If this is done, we will have sufficient power ($1-\beta > 0.80$) to detect odds ratios of 10 or higher in cases. Similarly, we will have sufficient power ($1-\beta = 0.80$) to detect odds ratios of 5 or higher if the behavioral prevalence in uninfected donors is around 0.65%.

Statistical Analyses

We will compute descriptive statistics, such as frequencies and measures of central tendency (means and medians) in order to characterize the infected population and catalog donor-reported risk factors likely to be the route of virus acquisition in case groups. We will compare the risk factors reported by donors according to demographics and in different regions of the country to determine if patterns of infection acquisition vary using the Chi-square or t-test depending on the structure of the predictor variable included in the analysis. Independently for each virus, univariable and multivariable logistic regression analysis will be used to compare risk factors when the outcome variable, infection status, can be defined in a dichotomous manner. For example, to assess the association between risk behaviors and demographics when comparing recently acquired HIV to long-standing HIV infection. The multivariable analyses will be important so that we may account for potential confounding with regard to factors such as socio-economic status and education level.

The inclusion of controls will allow for more advanced statistical analyses. In addition to descriptive statistics, such as frequencies, we will be able to use multivariable logistic regression analysis to compare confirmed-positive and false-positive donors to determine the association between risk behaviors, while adjusting for demographics, Public Health Service (PHS) regions, or other factors. The multivariable analysis will be important so that we may account for potential differences between cases and controls with regard to factors such as socio-economic status. Furthermore, advanced exploratory analyses may also be possible, such as multilevel modeling and potentially structural equation modeling. Use of these techniques could generate novel interpretations of patterns of infection in blood donors and also provide for a more direct assessment of how similar or dissimilar infections in blood donors are to the larger sets of data on infections identified through other public health surveillance, and higher risk groups surveillance. These analyses will allow for a deeper level of monitoring of the data from TTIMS and, if other public health datasets can be accessed, a direct comparison to other sources. Examples of published studies using these techniques show there is potential for new insights if these methods are applied to blood donor data.[33-35]

Survey Considerations and OMB Requirements

The LRCC will develop and perform standardized risk interview survey(s), in accordance with administrative processes such as review and approval by Institutional Review Boards (IRBs) and Office of Management and Budget (OMB). We will obtain OMB clearance to allow for the use of the risk factor interview instrument and the planned $75 participation compensation we intend to provide to donors who complete the risk factor interview. Furthermore, all required IRB approvals and other administrative approvals will be obtained. As the lead institution for LRCC activities, BSRI will obtain IRB approval for all activities. Each blood center and CTS will obtain any necessary IRB approvals for their respective activities. We will work with FDA to prepare the required OMB submission documents at each stage of that process.

Risk Factor Questionnaire Content

The risk factor interview covers content on common routes of exposure and also less common routes (Appendices 8 and 9, for English and Spanish versions). In addition the questionnaire will provide each confirmed-positive donor the opportunity to report how he/she believes he/she may have been infected. Four versions of the questionnaire introduction will be developed in consultation with the participating blood centers to reflect the required content for administration of verbal consent as mandated by local IRBs. The risk factor and related survey content is identical for all centers. The risk factor interview is based on the same content that was used in the REDS-II DRFS. That interview was previously approved by OMB (OMB Control Number 0925-0630, expiration date 4/30/2014). Content has been updated to reflect changes in our understanding of risk factors and to address new content relevant in the current time period.

Prospective and Retrospective Interviews

The majority of risk factor interviews during TTIMS will be conducted soon after confirmatory testing is completed from donors who have been newly classified as consensus positive for each infection based on blood donation testing (prospective interviews). We will also obtain human subjects approvals to conduct risk factor interviews of donors from the beginning (September 25, 2015) in order to capture data from the beginning of the contract period (retrospective interviews).

Participant Incentives

Incentives will be provided. Donors meeting consensus interview definitions will receive $75 for completing the interview. As for cases, controls will be compensated $75 for completing the interview. Incentives will be provided through the same operational procedures within each organization that allow for personally identifying each donor. The study investigators and LRCC staff at BSRI will not have access to PII and will not be responsible for providing the incentive payments to participants; each participating blood center will be responsible for ensuring participation incentives are provided to participants.

Human Subjects Considerations

All human subjects and other approval requirements will be met before the donor interviews can begin. Confirmed-positive donors will be asked to complete the questionnaire proximate to the time that they are notified of their infection status. This represents an emotionally difficult and challenging time for donors. Some donors may be completely surprised or even in denial about at the results of testing. The notification process is intended to be as benign as possible. The addition of a questionnaire designed to assess risk behaviors into the notification process may be difficult for some donors to complete. Participation in the risk factor interview is optional and is not a condition for future counseling. Using their professional knowledge and insight, the donor counselors will decide if each donor is in an appropriate state of mind to be interviewed. Donors will be given the option of being contacted at a later time to complete the questionnaire. Donors may refuse participation and future contact.

Each infection has potentially serious consequences for the future health of the blood donor. Part of standard counseling is to encourage that donors seek full medical evaluation by their physician. This is

particularly important for HIV where the seriousness of the infection for long-term health and the potential for stigma is likely to bring distress. As per required operational procedures, no donor identifiers that could reasonably be used to identify specific individuals will be available to the study researchers.

For false positive donors, the interview may also be useful in helping donor counselors with the counseling message and in identifying or ruling-out possible types of behaviors that could lead to false positive testing results. Again, as per required operational procedures no donor identifiers that could reasonably be used to identify specific individuals will be available to the study researchers.

A DHHS Certificate of Confidentiality will be obtained to prevent the project from being compelled to release any information reported by the persons who participate in this study, except under the special circumstances as specified by the Certificate.

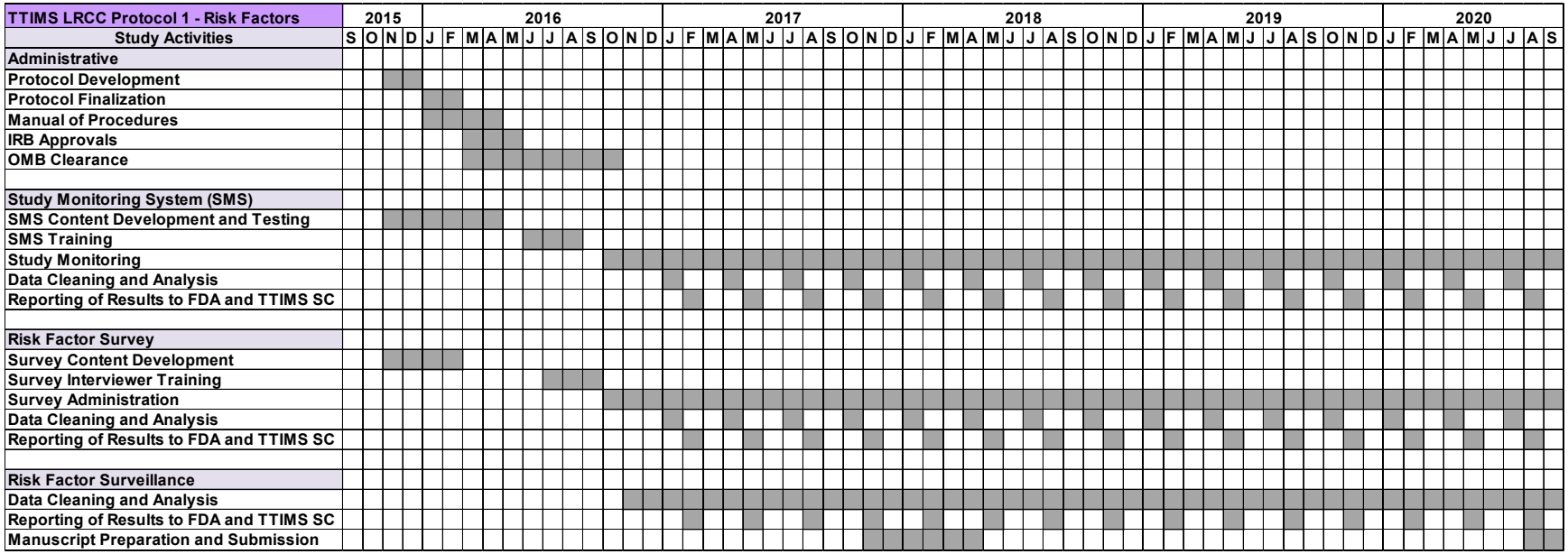
Qualtrics™ HIPAA and HITECH Compliance

HIPAA Statement: With some restrictions, Qualtrics may be designated as a Business Associate when the Qualtrics BA Agreement is signed with a Covered Entity—those organizations that are required to comply with HIPAA privacy rules. All client data are considered confidential, and treated as such, with no specific designation (such as medical (protected health information, PHI), PII, or public). Although, there is a duty of care that Qualtrics maintains with respect to PII data, for the LRCC tasks, PII will not be captured on Qualtrics servers.

Related to HIPAA, HITECH (Health Information Technology for Economic and Clinical Health Act) are updated assessment rules to ensure that data are properly protected and best security practices followed. By using secure and certified data centers, Qualtrics ensures the highest protection and testing as per HITECH requirements.

If the Qualtrics/UCSF partnership dissolves (Qualtrics is a Business Associate), the data remains on the Qualtrics servers for an additional 12 months. All interview data will be held in parallel on servers at the LRCC for the purpose of analysis which will be backed-up on regular schedules. At project completion, the LRCC will request data be purged from Qualtrics servers using existing request procedures. We will request a final transfer of data and deletion from Qualtrics servers at the end of the LRCC contract performance period as part of Transition Out or upon dissolution of the Qualtrics/UCSF partnership.

Timeline


TTIMS LRCC Protocol 1 - Risk Factors
2015
2016
2017
2018
2019
2020
Study Activities
S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S
Administrative
Protocol Development
Protocol Finalization
Manual of Procedures
IRB Approvals
OMB Clearance
Study Monitoring System (SMS)
SMS Content Development and Testing
SMS Training
Study Monitoring
Data Cleaning and Analysis
Reporting of Results to FDA and TTIMS SC
Risk Factor Survey
Survey Content Development
Survey Interviewer Training
Survey Administration
Data Cleaning and Analysis
Reporting of Results to FDA and TTIMS SC
Risk Factor Surveillance
Data Cleaning and Analysis
Reporting of Results to FDA and TTIMS SC
Manuscript Preparation and Submission

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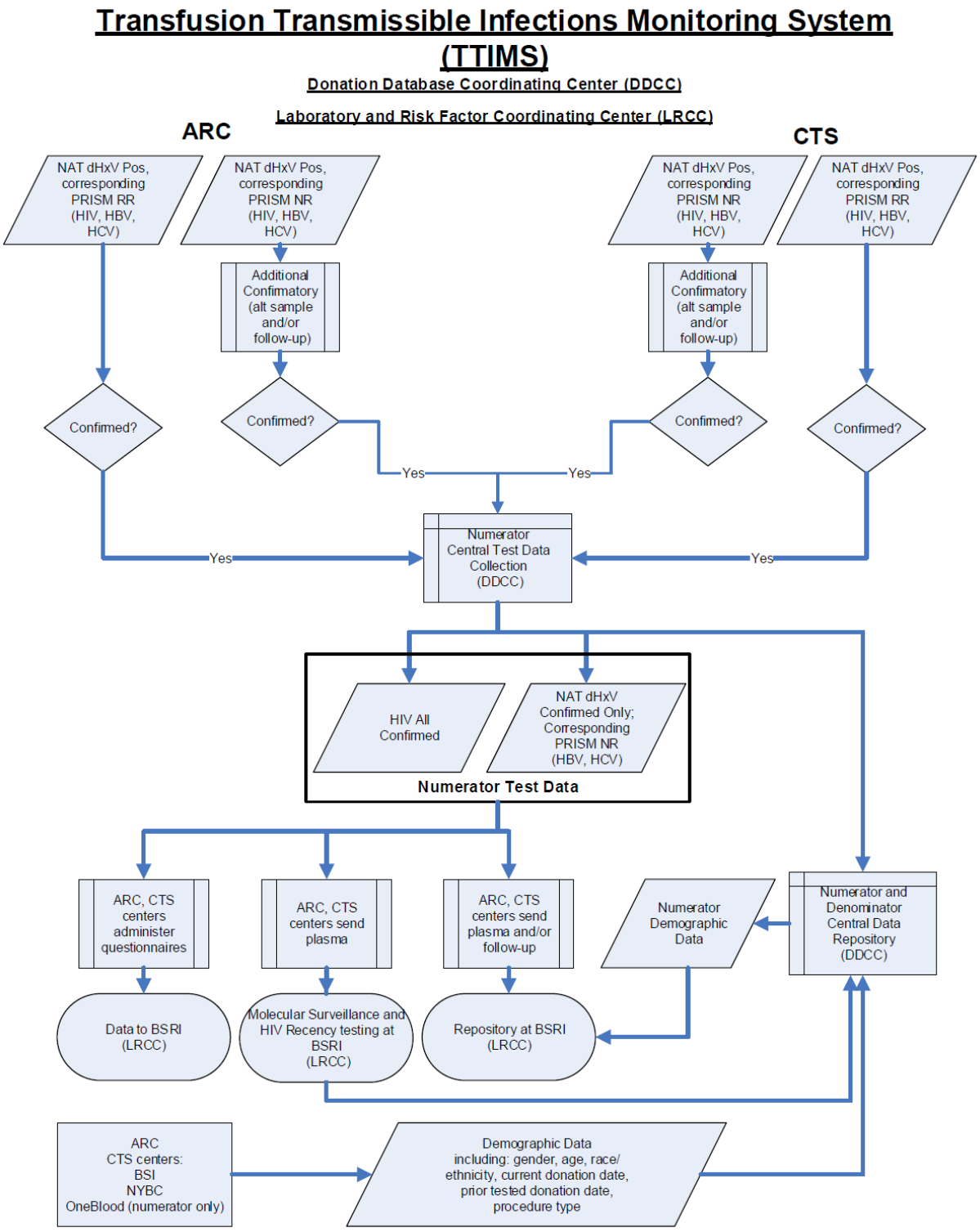
Appendices

Appendix 1 – TTIMS DDCC and LRCC Information Flow Diagram



Appendix 2 – Risk Factor Frequencies Reported by Donors During the REDS-II Study

Table 1. Risk Factor Frequencies Reported by Donors During the REDS-II Study: Sexual, behavioral and other risk factors for participating blood donors by infection status, published in.[2]

Sexual risk behavior	**HIV cases**	**HBV cases**	**HCV cases**	**False-positives controls**
Males	**n= 149 (%)**	**n= 190 (%)**	**n= 186 (%)**	**n= 761 (%)**
Number of female sexual partners, median (IQR)				
Lifetime	4 (1-13)	6 (2-13)	15 (7-30)	5 (2-10)
Last 5 years	1 (0-3)	1 (1-3)	2 (1-3)	1 (1-2)
Number of male sexual partners, median (IQR)				
Lifetime	2 (0-8)	0 (0-0)	0 (0-0)	0 (0-0)
Last 5 years	2 (0-5)	0 (0-0)	0 (0-0)	0 (0-0)
MSM or Sex with MSM, ever				
Yes	92 (61.7)	11 (5.8)	9 (4.8)	13 (1.7)
Monogamous, last 12 months				
Yes	60 (40.3)	119 (62.6)	136 (73.1)	574 (75.4)
Male sexual partner, last 12 months				
Yes	78 (52.4)	7 (3.7)	2 (1.1)	2 (0.3)
Used condom, always*				
Yes	21 (26.9)	2 (28.6)	0 (0.0)	1 (50.0)
Sexually transmitted disease				
Yes	33 (22.3)	28 (14.7)	45 (24.2)	53 (7.0)
Sex for money or drugs				
Yes	5 (3.4)	6 (3.2)	4 (2.2)	9 (1.2)
Sex with injecting drug user				
Yes	7 (4.7)	18 (9.5)	49 (26.3)	15 (2.0)
Not specified, D/N*	20 (13.4)	19 (10.0)	17 (9.1)	26 (3.4)
Sex with hepatitis positive partner				
Yes	4 (2.7)	8 (4.2)	12 (6.5)	5 (0.7)
Not specified, D/N*	17 (11.4)	26 (13.7)	13 (7.0)	18 (2.4)
Sex with HIV-positive partner				
Yes	39 (26.2)	2 (1.1)	1 (0.5)	0 (0.0)
Not specified, D/N*	19 (12.8)	5 (2.6)	2 (1.1)	9 (1.2)
Sex with blood transfusion recipient				
Yes	1 (0.7)	4 (2.1)	10 (5.4)	26 (3.4)
Not specified, D/N*	20 (13.4)	15 (7.9)	18 (9.7)	46 (6.0)

Appendix 2 Table 1: Cont'd	**HIV cases**	**HBV cases**	**HCV cases**	**False-positives controls**
Females	**n= 47 (%)**	**n= 102 (%)**	**n= 130 (%)**	**n= 825 (%)**
Number of male sexual partners, median (IQR)				
Lifetime	10 (4-15)	3 (1-10)	9 (4-20)	4 (1-7)
Last 5 years	3 (1-5)	1 (1-2)	1 (1-2)	1 (1-1)
Number of female sexual partners, median (IQR)				
Lifetime	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)
Last 5 years	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Sex with MSM, ever				
Yes	3 (6.4)	3 (2.9)	4 (3.1)	11 (1.3)
Monogamous, last 12 months				
Yes	28 (59.6)	71 (69.6)	86 (66.2)	653 (79.2)
Male sexual partner, last 12 months				
Yes	43 (91.5)	76 (74.5)	91 (70.0)	676 (81.9)
Used condom, always†				
Yes	6 (14.0)	13 (17.1)	9 (9.9)	92 (13.6)
Sexually transmitted disease				
Yes	17 (36.2)	13 (12.8)	48 (36.9)	106 (12.9)
Sex for money or drugs				
Yes	10 (21.3)	4 (3.9)	12 (9.2)	0 (0.0)
Sex with injecting drug user				
Yes	6 (12.8)	10 (9.8)	60 (46.2)	19 (2.3)
Not specified, D/N*	6 (12.8)	5 (4.9)	9 (6.9)	32 (3.9)
Sex with hepatitis positive partner				
Yes	3 (6.4)	6 (5.9)	19 (14.6)	15 (1.8)
Not specified, D/N*	3 (6.4)	11 (10.8)	8 (6.2)	21 (2.6)
Sex with HIV-positive partner				
Yes	13 (27.7)	1 (1.0)	0 (0.0)	3 (0.4)
Not specified, D/N*	5 (10.6)	1 (1.0)	1 (0.8)	13 (1.6)
Sex with blood transfusion recipient				
Yes	1 (2.1)	6 (5.9)	9 (6.9)	41 (5.0)
Not specified, D/N*	3 (6.4)	8 (7.8)	12 (9.2)	39 (4.7)

Appendix 2 Table 1: Cont'd	**HIV cases**	**HBV cases**	**HCV cases**	**False-positives controls**
Both sexes, lifetime (ever)	**n= 196 (%)**	**n= 292 (%)**	**n= 316 (%)**	**n= 1,587 (%)**
Other exposures				
Injected illegal drugs, steroid or vitamins				
Yes	6 (3.1)	14 (4.8)	116 (36.7)	6 (0.4)
Any illegal drug use (non-injecting)				
Yes	48 (24.5)	59 (20.2)	197 (62.3)	193 (12.2)
Tattoo or body piercing‡				
Yes	128 (65.3)	124 (42.5)	218 (69.0)	671 (42.3)
Jail, prison, detention, shelter or group home (3 nights or more)				
Yes	47 (24.0)	54 (18.5)	181 (57.3)	83 (5.2)
Blood transfusion				
Yes	5 (2.6)	20 (6.9)	57 (18.0)	105 (6.6)
Medical or dental exposure§				
Yes	166 (84.7)	235 (80.5)	308 (97.5)	1,477 (93.1)
HCV/HBV infected member in the household				
Yes	3 (1.5)	44 (15.1)	37 (11.7)	30 (1.9)
Family/self living abroad or immigrated to the US				
Yes	21 (10.7)	149 (51.0)	13 (4.1)	88 (5.6)

* Not specified, D/N is included as a category when ≥10% of cases or controls did not respond or selected "don't know" in response for this topic

†Always used condom with male sexual partners if had one or more male partners in the last 12 months

‡ Tattoo or body piercing or 3+ ear piercings

§ Includes any IM/IV injections, tissue or organ transplant, endoscopy, colonoscopy, dental injection, acupuncture, needle stick injury or body fluid exposure ever

Appendix 3 – TTIMS Study Information Mailer for Cases (English version)

Research Study Invitation

TEMPLATE TO BE MODIFIED FOR LOCAL USE [Text in Brackets Requires Local Information]

We want to invite you to participate in a research study with [*Blood Systems, Inc*]. The study can be done in person or over the telephone and takes about 45 minutes of your time. The following is a description of the research study.

If you choose to participate and complete the interview you will receive $75 for your time. This will be mailed to your home address after you complete the study.

This study is being conducted at four U.S. blood centers: the American Red Cross (ARC), Blood Systems, Inc. (BSI), New York Blood Center (NYBC), and OneBlood in order to obtain a nationwide understanding of risk factors for donating virus positive blood. The goal of the study is to identify self-reported risk factors for donations that test positive for one of three possible viruses, human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV). The study protects your identity because the information submitted to the coordinating center will not include your name or other personally identifying information.

This project is being funded by the US Food and Drug Administration (FDA) and the National Heart Lung and Blood Institute of the National Institutes of Health.

What will happen with the answers I give during the interview?

You will be asked about known risk factors for HIV, HBV, and/or HCV. Each virus is spread in different ways and you may not have had any of the risk factors that we ask about. Your responses will be grouped with other donors who complete the interview. The study will determine how common different risk factors are and will report summary measures on patterns of risk factors in all of the donors that tested positive for the same virus.

If you tell us something during the interview that would have made you ineligible to donate, we will have to add this to your donor record and this may lead to deferral from future blood donation. However, there will be no other repercussions if the answers you give now are different than those you gave when you donated.

How will the privacy of your responses be protected?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the US Department of Health and Human Services.

What is a Certificate of Confidentiality?

With a Certificate of Confidentiality, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under specific circumstances. For example, we will voluntarily disclose information about incidents such as intent to hurt yourself or others.

Who can answer my questions about the study?

Your participation in the study is voluntary and you may decide you do not want your interview responses included. If you have questions about the study or you want to have your interview responses excluded at any time, you may call [*Dr. Brian Custer at Blood Systems Research Institute at (415) 901-0756*].

If you have any questions about the testing results from your blood donation please call [*Donor Counseling and Notification Services at (800) 289-4923 or Dr. Hany Kamel at Blood Systems headquarters at (480) 675-5659*].

If you have any questions about your rights as a research participant in this study, please call the [*University of California San Francisco, Committee on Human Research, which is also known as an Institutional Review Board (a group of people who review the research to protect your rights) at 415-476-1814*].

How do I join the study?

Simply call [*(800) 289-4923*] and one of our specially trained counselors will be happy to enroll you in the study. If we do not hear from you we will likely give you a call to give you a chance to enroll.

Appendix 4 – TTIMS Study Information Mailer for Cases (Spanish version)

To Be Added

Appendix 5 – TTIMS Study Information Mailer for Controls (English version)

Research Study Invitation

TEMPLATE TO BE MODIFIED FOR LOCAL USE [Text in Brackets Requires Local Information]

We want to invite you to participate in a research study with [*Blood Systems Inc.*] The study can be done in person or over the telephone and takes less than 45 minutes of your time. The following is a description of the research study.

If you choose to participate and complete the interview you will receive $75 for your time. This will be mailed to your home address after you complete the study.

This study is being conducted at four U.S. blood centers: the American Red Cross (ARC), Blood Systems, Inc. (BSI), New York Blood Center (NYBC), and OneBlood in order to obtain a nationwide understanding of risk factors for donating virus positive blood. The goal of the study is to identify self-reported risk factors for donations that test positive for one of three possible viruses, human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV). We will also be comparing responses from donors who tested confirmed positive to donors, ***like you***, who tested unconfirmed (false positive) to find out if risk factors are different between these two groups of donors. The study protects your identity because the information submitted to the coordinating center will not include your name or other personally identifying information.

This project is being funded by the US Food and Drug Administration (FDA) and the National Heart Lung and Blood Institute of the National Institutes of Health.

What will happen with the answers I give during the interview?

You will be asked about known risk factors for HIV, HBV, and/or HCV. Each virus is spread in different ways and you may not have had any of the risk factors that we ask about. Your responses will be grouped with other donors who complete the interview. The study will determine how common different risk factors are and will report summary measures on patterns of risk factors in all of the donors that tested positive for the same virus compared to donors who tested false positive.

If you tell us something during the interview that would have made you ineligible to donate, we will have to add this to your donor record and this may lead to deferral from future blood donation. However there will be no other repercussions if the answers you give now are different than those you gave when you donated.

How will the privacy of your responses be protected?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the US Department of Health and Human Services.

What is a Certificate of Confidentiality?

With a Certificate of Confidentiality, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for

information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under specific circumstances. For example, we will voluntarily disclose information about incidents such as an intent to hurt yourself or others.

Who can answer my questions about the study?

Your participation in the study is voluntary and you may decide you do not want your interview responses included. If you have questions about the study or you want to have your interview responses excluded at any time, you may call [*Dr. Brian Custer at Blood Systems Research Institute at (415) 901-0756*].

If you have any questions about the testing results from your blood donation please call [*Donor Counseling and Notification Services at (800) 289-4923 or Dr. Hany Kamel at Blood Systems headquarters at (480) 675-5659*].

If you have any questions about your rights as a research participant in this study, please call the [*University of California San Francisco, Committee on Human Research, which is also known as an Institutional Review Board (a group of people who review the research to protect your rights) at 415-476-1814*].

How do I join the study?

Simply call [*(800) 289-4923*] and one of our specially trained counselors will be happy to enroll you in the study. If we do not hear from you we will likely give you a call to give you a chance to enroll.

Appendix 6 – TTIMS Study Information Mailer for Controls **(Spanish version)**

To Be Added

Appendix 7 – Study Management System Core Content

A. DONATION DATA

Donation Identification Number (DIN): _____

Donor Identification Number (Donor ID): _____

Blood Collection Center: _____

Center Code: _____

Donation Date: Day _____ Month _____ Year _____

Donor Zip code of Residence: _____

B. TESTING RESULTS

Please identify the virus and the confirmed test results from blood donation testing. Please note, all HIV positive donors are eligible for interview. HCV NAT only or HBV NAT only confirmed-positive donors are eligible for interview. Donors eligible for interview as controls include those serology only false positive for HIV and/or HBV.

Confirmed Positive:

Virus: **o HIV**

Markers:

o Anti HIV -1, -2 o HIV NAT If available: o HIV-1 o HIV -2

o HCV

Markers:

o Anti-HCV o HCV NAT

o HBV

Markers:

o HBsAg o Anti-HBc o HBV NAT

Unconfirmed (False) Positive:

- **o** anti-HIV false positive
- **o** HBsAg false positive

C. RECRUITMENT

The date and method of each attempt to contact the donor and the results of that attempt will be recorded using this form.

D. PLASMA UNIT TRACKING

The status of plasma unit, retention tube, and testing lab residual sample retrieval will be documented using this form. Entries include whether retrieval was necessary, successful, and date shipped to CTS or LRCC.

E. SPECIAL SAMPLE COLLECTION AND TRACKING

If there is a need for additional sample collection, the status (successful/date shipped to CTS or LRCC) will be tracked using this form.

Appendix 8 – TTIMS Risk Factor Questionnaire (English version)

OMB Control Number: **XXXX-XXXX**
OMB Clearance Expiration Date: MM-DD-YYYY

SECTION A - DONATION DATA AND VERBAL CONSENT

Notes to interviewer:

1. **Administer this survey as early as possible after the date that disease and marker testing, including confirmation testing, is completed for the donation.**
2. **Review the infection marker testing results before contacting the donor.**
3. **Complete the Donation Data section before contacting the donor.**
4. **Be sure to properly identify the donor according to standard operational procedures**
5. **When reading the possible answers to the donor, do not say " Don't know" or "Refuse to answer"**

DONATION DATA

Donation Identification Number (DIN): _____

Donor Identification Number (Donor ID): _____

Blood Collection Center: _____

Center Code: _____

Donation Date: Day _____ Month _____ Year _____

Donor Type (select one): ○ Case ○ Control

Date of Interview: Day____ Month _____ Year ____

Interviewer Initials: _____

Interview Language (select one): ○ English ○ Spanish

VERBAL CONSENT – PLEASE READ THE FOLLOWING TO THE DONOR:

I am asking you to be part of a research study about risk factors for infectious diseases in blood donors. The study is being done by [Your Organization], other blood centers, the US Food and Drug Administration, and the National Institutes of Health, National Heart Lung and Blood Institute.

FOR CONFIRMED POSITIVES: *I am contacting you because testing on your donation confirmed-positive for a viral infection the last time you donated blood. If you agree to participate, I will ask you questions about possible ways you could have gotten infected.*

FOR FALSE POSITIVES: *I am contacting you because your recent donation tested unconfirmed or false positive. If you agree to participate, I will ask you questions about risk factors for viral infections so we can compare answers from false positive donors, like you, to answers that true positive donors give on the same questions.*

The interview should take no more than 45 minutes. Your participation is voluntary and you may refuse to answer any question. Some of the questions are about private matters such as sexual experiences and drug use. Our purpose in asking these questions is to improve the safety of donated blood. If you tell us something during the interview that would have made you ineligible to donate, I will have to add this to your donor record and this may lead to deferral from future blood donation. However, there will be no consequences if the answers you give now are different than those you gave when you donated blood.

We will keep your responses confidential. To help us protect your privacy, we have obtained a Certificate of Confidentiality from the US Department of Health and Human Services. With this Certificate, the researchers cannot be forced to disclose information that may identify you. The risk of participating in this study is if the information you give is not kept confidential. However no information that identifies you by name will be entered into the database, only the answers to these questions. There is no direct benefit to you of participation other than the knowledge that you are helping efforts to maintain a safe blood supply by allowing us to understand risks and motivations of blood donors.

If you have any questions, feel free to ask me now. You may also call XXX-XXXX. Do you have any questions before we begin?

Do you agree to participate in this study?

- ○ Yes **(If YES, verbal consent obtained)**
- ○ No

[For printed record maintained at blood center]

Signature of Interviewer:

_____ Date: _____

SECTION B – DONOR DEMOGRAPHIC DATA

(Please read the following:) *First, I will ask you some questions about you and about blood donation. I remind you that your answers will be kept confidential.*

1. What sex do you consider yourself to be?

○ Male
○ Female
○ Other (SPECIFY) _____
○ (Don't know)
○ (Refuse to answer)

2. What sex were you assigned at birth?

○ Male
○ Female
○ Other (SPECIFY) _____
○ (Don't know)
○ (Refuse to answer)

3. What is your birth date?
   Day ____ Month ____ Year ____

○ (Don't know)
○ (Refuse to answer)

4. What is your country of birth?

○ USA
○ Other (SPECIFY) _____
○ (Don't know)
○ (Refuse to answer)

5. At the time of your last blood donation, what was the highest level of education you had completed?

○ Never been to school
○ Elementary school
○ Junior high school or middle school
○ High school
○ College or technical school
○ Graduate school or professional degree
○ (Don't know)
○ (Refuse to answer)

6. Are you of Hispanic, Latino, or Spanish origin?

○ Yes

○ No
○ (Don't know)
○ (Refuse to answer)

7. What is your race? **(Please read the following:)** *Federal policy defines "Hispanic" not as a race, but as an ethnicity. Hispanics can be of any race.* **[MARK ALL THAT APPLY]**

○ White
○ Black or African American
○ Asian
○ American Indian or Alaska Native
○ Native Hawaiian or other Pacific Islander
○ Other (SPECIFY) _____
○ (Don't know)
○ (Refuse to answer)

8. At the time of your last blood donation, what was your occupation? **[Interviewer, please ask as an open-ended question, then select the most applicable option below]**

○ Agriculture, Forestry, Fishing, Hunting, Mining, Quarrying, Oil and Gas Extraction
○ Construction and Manufacturing
○ Wholesale and Retail Trade
○ Transportation, Warehousing, and Utilities
○ Information Services (e.g. tv, film, radio, news, library, publishing)
○ Finance, Insurance, Real Estate, Rental, Leasing
○ Professional, Scientific, and Technical Services
○ Management and Administrative Support
○ Educational Service
○ Healthcare and Social Assistance
○ Arts, Entertainment, and Recreation
○ Accommodation and Food Services
○ Public Administration (i.e. Government)
○ Military
○ Retired
○ Disabled
○ Unemployed
○ Other (SPECIFY) _____
○ (Don't know)
○ (Refuse to answer)

9. At the time of your last donation, what was your annual household income from all sources? **[Interview, please read all numerical answer choices]**

○ Less than $10,000
○ $10,000 to less than $30,000

- ○ $30,000 to less than $50,000
- ○ $50,000 to less than $75,000
- ○ $75,000 to less than $100,000
- ○ $100,000 or more
- ○ (Don't know)
- ○ (Refuse to answer)

10. At the time of your last donation, what was your marital status?

- ○ Single, never married **SKIP TO QUESTION 12**
- ○ Living together, but not legally married
- ○ Married
- ○ Separated or divorced
- ○ Widowed **SKIP TO QUESTION 12**
- ○ (Don't Know) **SKIP TO QUESTION 12**
- ○ (Refuse to answer) **SKIP TO QUESTION 12**

11. At the time of your last donation if you were married or living with a partner, what was the gender of this person?

- ○ Male
- ○ Female
- ○ Other (SPECIFY) _____
- ○ (Don't know)
- ○ (Refuse to answer)

12. Which of the following best represents how you think of yourself?

- ○ Straight/heterosexual
- ○ Bisexual
- ○ Gay/lesbian/homosexual
- ○ Something else
- ○ (Don't know)
- ○ (Refuse to answer)

13. Have you ever been vaccinated against hepatitis B virus?

- ○ Yes
  - 13.1 Were you vaccinated as an….?
    - ○ Infant
    - ○ Child
    - ○ Adult
    - ○ (Don't know)
    - ○ (Refuse to answer)
- ○ No
- ○ (Don't know)
- ○ (Refuse to answer)

14. Before your last donation did you ever take **PRE**-exposure prophylaxis, or PrEP?
[Interviewer, please read the following:] *PrEP is antiviral medication taken daily for months or years to reduce a person's chance of getting HIV*.

○ Yes
○ No **SKIP TO QUESTION 16**
○ (Don't know)
○ (Refuse to answer)

15. In the month before your last blood donation, were you taking **PRE**-exposure prophylaxis, or PrEP?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

16. Before your last donation did you ever take **POST**-exposure prophylaxis, or PEP?
[Interviewer, please read the following:] *PEP is antiviral medication taken daily for 28 days after a person' has had a single high-risk exposure to HIV.*

○ Yes
○ No **SKIP TO QUESTION 18 for HIV positive donors, otherwise skip to Question 19**
○ (Don't know)
○ (Refuse to answer)

17. In the month before your last blood donation, were you taking **POST**-exposure prophylaxis, or PEP?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

18. [***For HIV confirmed-positive donors only***] Did you know you were infected with HIV before you donated blood?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

19. Before your last donation, did you ever take anti-retroviral therapy for HIV infection?

○ Yes
○ No **SKIP TO QUESTION 21**
○ (Don't know)
○ (Refuse to answer)

20. In the month before your blood donation, were you taking anti-retroviral therapy for HIV infection?

○ Yes

○ No
○ (Don't know)
○ (Refuse to answer)

21. Before your last blood donation, did you do any activities that you think may have put you at risk for an HIV infection or hepatitis infection?

○ Yes

21.1 What was the activity or activities? **[Interviewer, please ask as an open-ended question, then select the most applicable option(s) below:]**

- ○ Heterosexual contact
- ○ Homosexual contact
- ○ Unsafe sexual contact (did not use condoms or other protective barriers)
- ○ Sexual contact, not specified
- ○ IDU
- ○ Medical/Dental procedure
- ○ Accidental needle stick
- ○ Tattoo/Piercing
- ○ Blood transfusion
- ○ From mother at birth
- ○ Non-sexual contact (work/family exposure)
- ○ Travel or living in a foreign country
- ○ Other (SPECIFY)_____
- ○ (Don't know)
- ○ (Refuse to answer)

○ No
○ (Don't know)
○ (Refuse to answer)

22. Can you specify the date when you think you might have got infected?

○ Yes

22.1 Month_____ Year _____

○ No
○ (Don't know)
○ (Refuse to answer)

23. At the time of your last donation were you aware that the activity you thought might be the reason for your infection could place you at a higher risk for infection?

○ Yes

23.1 How did you find out the activity could place you at higher risk for infection? **[Interviewer, please ask as an open-ended question, then select the most applicable option below:]**

- ○ Healthcare provider
- ○ Blood center
- ○ Internet
- ○ Friends
- ○ Other (SPECIFY)_____

○ (Don't know)
○ (Refuse to answer)

○ No
○ (Don't know)
○ (Refuse to answer)

24. Before your most recent donation had you previously donated at this or any other blood or plasma center or blood drive? **[IF YES, MARK ALL THAT APPLY]**

○ Yes

24.1 Where did you donate?
○ This blood center
○ Another blood center
○ At a plasma center where I was paid for donating
○ (Don't know)
○ (Refuse to answer)

○ No
○ (Don't know)
○ (Refuse to answer)

25. Please tell me whether any of the following reasons or factors contributed to your decision to donate blood. For each statement, please answer yes or no.
[READ SLOWLY AND MARK AN ANSWER FOR EACH]

a. I wanted to donate blood to help someone in need
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

b. In response to a TV or radio campaign, a phone call, or letter from blood bank
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

c. I was encouraged or pressured by family, friends, coworkers, or by someone at a blood drive
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

d. I wanted to get my test results for my blood
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

e. I wanted to get the incentives for donating that the blood bank was offering
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

f. I donated to help others after a natural or man-made disaster or tragedy occurred
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

26. Is there any other reason why you came to the blood center?
○ Yes (SPECIFY) _____
○ No
○ (Don't know)

○ (Refuse to answer)

27. Did any of the following factors influence your decision to come to the blood center? For each statement, please answer yes or no.
[READ SLOWLY AND MARK AN ANSWER FOR EACH]

a. Blood center testing is confidential
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

b. Blood center testing is more accurate than at other test sites
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

c. Blood center testing is free
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

d. I think that the tests would identify any problem with my blood
○ Yes ○ No ○ (Don't know) ○ (Refuse to answer)

28. Outside of blood donation, have you previously been tested for HIV?

○ Yes

28.1 When was the last time you were tested for HIV?
Month_____ Year _____
○ (Don't know)
○ (Refuse to answer)

28.2 What was the result of the test?
○ Positive
○ Negative
○ (Don't know)
○ (Refuse to answer)

○ No
○ (Don't know)
○ (Refuse to answer)

29. Outside of blood donation, have you previously been tested for HBV?

○ Yes

29.1 When was the last time you were tested for HBV?
Month_____ Year _____
○ (Don't know)
○ (Refuse to answer)

29.2 What was the result of the test?
○ Positive
○ Negative
○ (Don't know)
○ (Refuse to answer)

- ○ No
- ○ (Don't know)
- ○ (Refuse to answer)

30. Outside of blood donation, have you previously been tested for HCV?

- ○ Yes

    30.1 When was the last time you were tested for HCV?
    Month_____ Year _____
    - ○ (Don't know)
    - ○ (Refuse to answer)

    30.2 What was the result of the test?
    - ○ Positive
    - ○ Negative
    - ○ (Don't know)
    - ○ (Refuse to answer)

- ○ No
- ○ (Don't know)
- ○ (Refuse to answer)

SECTION C – RISK FACTORS ASSESSMENT – PART I

(Please read the following:) *In this next section, I will ask you some questions about behaviors you may or may not have engaged in that can increase the risk of infection. Some people may have had many different experiences while others have not. I am asking you for this information because the data could help improve the safety of the blood supply. I remind you that your answers will be kept confidential.*

For the next few questions unless stated otherwise the term "sex" refer to any of the following activities, whether or not a condom or other protection was used:

1. *Vaginal Sex (contact between penis and vagina)*
2. *Oral Sex (mouth or tongue on someone's vagina, penis, or anus)*
3. *Anal Sex (contact between penis and anus)*

31. Using these definitions of sex, in the 12 months before your last donation did you have sex?

○ Yes
○ No **SKIP TO QUESTION 34**
○ (Don't know)
○ (Refuse to answer)

32. In the 12 months before your last donation did you have sex with only one partner?

○ Yes
○ No **SKIP TO QUESTION 34**
○ (Don't know)
○ (Refuse to answer)

33. To the best of your knowledge, in the 12 months before your last donation did your partner have sex with only you?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

Now I am going to ask you about sexual partners and sexual contacts you have had over different time periods in your life.

34. How many **male** sexual partners have you had in your lifetime? Please include both ongoing partners and one-time encounters with men.

_____ IF NONE, SKIP TO QUESTION 39
○ (Don't know)
○ (Refuse to answer)

35. In the 5 years before your last blood donation, how many **male** sexual partners did you have? Please include both ongoing partners and one-time encounters with men.

_____

○ (Don't know)
○ (Refuse to answer)

36. In the 12 months before your last blood donation, how many **male** sexual partners did you have? Please include both ongoing partners and one-time encounters with men.

_____
○ (Don't know)
○ (Refuse to answer)

37. For this question do not include oral sex. Regarding your **male** sexual partners and one-time encounters with men in the 12 months before your last blood donation if you had vaginal or anal sex how often did you use condoms or protective barriers?
○ Never
○ Sometimes
○ Always
○ (Don't know)
○ (Refuse to answer)

38. Before your most recent blood donation, when was your last sexual contact with a **male**?

Month _____ Year _____
○ (Don't know)
○ (Refuse to answer)

39. How many **female** sexual partners have you had in your lifetime? Please include both ongoing partners and one-time encounters with women.

_____ IF NONE, SKIP TO QUESTION 44
○ (Don't know)
○ (Refuse to answer)

40. In the 5 years before your last blood donation, how many **female** sexual partners did you have? Please include both ongoing partners and one-time encounters with women.

_____
○ (Don't know)
○ (Refuse to answer)

41. In the 12 months before your last blood donation, how many **female** sexual partners did you have? Please include both ongoing partners and one-time encounters with women.

_____
○ (Don't know)
○ (Refuse to answer)

42. For this question do not include oral sex. Regarding your **female** sexual partners and one-time encounters with women in the 12 months before your last blood donation if you had vaginal or anal sex how often did you use condoms or protective barriers?

○ Never
○ Sometimes
○ Always
○ (Don't know)
○ (Refuse to answer)

43. Before your most recent blood donation, when was your last sexual contact with a **female**?

Month _____ Year _____

○ (Don't know)
○ (Refuse to answer)

44. Before your last donation, did you ever have a sexually transmitted disease, also known as a STD? Examples of STDs include gonorrhea, chlamydia, syphilis, genital herpes, genital warts, and HPV.

○ Yes

44.1 Can you tell me which STD?

○ Gonorrhea
○ Chlamydia
○ Syphilis
○ HPV
○ Genital herpes
○ Genital warts
○ (Don't know)
○ (Refuse to answer)

○ No **SKIP TO QUESTION 46**
○ (Don't know)
○ (Refuse to answer)

45. In the 12 months before your last blood donation, did you have a STD? Examples of STDs include gonorrhea, chlamydia, syphilis, genital herpes, genital warts, and HPV.

○ Yes

45.1 Can you tell me which STD?

○ Gonorrhea
○ Chlamydia
○ Syphilis
○ HPV
○ Genital herpes
○ Genital warts

- ○ (Don't know)
- ○ (Refuse to answer)

○ No
○ (Don't know)
○ (Refuse to answer)

46. Before your last donation, did you ever inject drugs, steroids, or vitamins not prescribed by a health care provider?

○ Yes
○ No **SKIP TO QUESTION 50**
○ (Don't know)
○ (Refuse to answer)

47. In the 12 months before your last blood donation, did you inject drugs, steroids, or vitamins not prescribed by a health care provider?

○ Yes

47.1 Can you tell me what substance was or substances were injected? **[MARK ALL THAT APPLY]**

- ○ Heroine
- ○ Cocaine
- ○ Methamphetamine
- ○ Other (SPECIFY)_____
- ○ (Don't know)
- ○ (Refuse to answer)

○ No
○ (Don't know)
○ (Refuse to answer)

48. Before your last donation, did you ever share needles or syringes with another person?

○ Yes
○ No **SKIP TO QUESTION 50**
○ (Don't know)
○ (Refuse to answer)

49. In the 12 months before your last blood donation, did you share needles or syringes with another person?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

50. Before your last donation, did you ever use any drugs that you did not inject, that is, drugs that are smoked, snorted, inhaled, or taken orally? Please do **not** include the use of marijuana when answering this question.

○ Yes
○ No **SKIP TO QUESTION 52**

○ (Don't know)
○ (Refuse to answer)

51. In the 12 months before your last blood donation, did you use any drugs that you did not inject, that is, drugs that are smoked, snorted, inhaled, or taken orally? Please do **not** include the use of marijuana when answering this question.

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

52. Before your last donation did you ever intentionally engage in sex while "high" or "drunk"?

○ Yes
○ No **SKIP TO QUESTION 54**
○ (Don't know)
○ (Refuse to answer)

53. In the 12 months before your last blood donation, did you intentionally engage in sex while "high" or "drunk"?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

54. Have you ever given or received money or drugs for sex?

○ Yes
○ No **SKIP TO QUESTION 56**
○ (Don't know)
○ (Refuse to answer)

55. In the 12 months before your last blood donation, did you give or receive money or drugs for sex?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

SECTION C – RISK FACTORS ASSESSMENT PART II

(Please read the following:) *Now I am going to ask you about other risk factors or behaviors that can increase the chances of infection. Please answer each question to the best of your knowledge. I am asking you for this information because it could help to improve the safety of the blood supply. I remind you that your answers will be confidential.*

56. How many tattoos do you have on your body? (When answering this question please include permanent cosmetics (lip, brow or eyeliner), which are applied in a similar way as tattoos).

○ 0 (No tattoos) **SKIP TO QUESTION 59**
○ 1
○ 2
○ 3 or more
○ (Don't know)
○ (Refuse to answer)

57. In the 12 months before your last blood donation, did you get a new tattoo or had one re-applied? (Again, when answering this question please include permanent cosmetics (lip, brow or eyeliner), which are applied in a similar way as tattoos)

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

58. Where did you go to have your most recent tattoo(s) applied?

○ Tattoo parlor
○ Beauty salon
○ At home or a friend's house
○ At a party or rave
○ In jail, prison or a detention center
○ (Don't know)
○ (Refuse to answer)

59. In total, how many ear piercings do you have?

○ 0 (No piercings) **SKIP TO QUESTION 61**
○ 1
○ 2
○ 3 or more
○ (Don't know)
○ (Refuse to answer)

60. In the 12 months before your last blood donation, did you get any new ear piercings?

○ Yes

○ No
○ (Don't know)
○ (Refuse to answer)

61. In total, how many body piercings do you have?

○ 0 (No piercings) **SKIP TO QUESTION 63**
○ 1
○ 2
○ 3 or more
○ (Don't know)
○ (Refuse to answer)

62. In the 12 months before your last blood donation, did you get any new body piercings?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

63. Have you ever spent three or more nights in a row in any of the following? **(MARK ALL THAT APPLY)**

○ Jail or Prison
○ Detention Center (For example, juvenile detention or inpatient treatment)
○ A Shelter or Group Home
○ None of the above **SKIP TO QUESTION 66**
○ (Don't know)
○ (Refuse to answer)

64. In the 12 months before your last blood donation, did you spend three or more nights in a row in jail, prison, a detention center, a shelter, or a group home?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

65. In total, how long did you spend in jail, prison, a detention center, a shelter, or a group home?

○ Less than 1 month
○ 1 month to less than 6 months
○ 6 months or more
○ (Don't know)
○ (Refuse to answer)

SECTION C RISK FACTOR ASSESSMENT PART III – Sexual Partner Exposures

[Please read the following:] *These next questions ask about the health and risk factors of your current and previous sexual partners. While you may not know their exact medical histories, please answer these questions to the best of your ability.*

I will now remind you of the definition of sex for the purposes of this questionnaire. The terms "sexual contact" and "sex" refer to any of the following activities, whether or not a condom or other protection was used:

1. *Vaginal Sex (contact between penis and vagina)*
2. *Oral Sex (mouth or tongue on someone's vagina, penis, or anus)*
3. *Anal Sex (contact between penis and anus)*

66. Have you ever had sex with anyone who has injected drugs, steroids or vitamins not prescribed by a health care provider?

○ Yes
○ No **SKIP TO QUESTION 68**
○ (Don't know)
○ (Refuse to answer)

67. In the 12 months before your last blood donation, did you have sex with anyone who has injected drugs, steroids or vitamins not prescribed by a health care provider?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

68. Have you ever had sex with a male who has had sex with another male?

○ Yes
○ No **SKIP TO QUESTION 70**
○ (Don't know)
○ (Refuse to answer)

69. In the 12 months before your last blood donation, did you have sex with a male who has had sex with another male?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

70. Have you ever had sex with anyone who has tested positive for hepatitis?

○ Yes
○ No **SKIP TO QUESTION 72**
○ (Don't know)
○ (Refuse to answer)

71. In the 12 months before your last blood donation, did you have sex with anyone who has tested positive for hepatitis?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

72. Before your last donation, did you ever have sex with anyone who has tested positive for HIV?

○ Yes
○ No **SKIP TO QUESTION 74**
○ (Don't know)
○ (Refuse to answer)

73. In the 12 months before your last blood donation, did you have sex with anyone who has tested positive for HIV?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

74. Have you ever had sex with anyone who has received a blood transfusion?

○ Yes
○ No **SKIP TO QUESTION 76**
○ (Don't know)
○ (Refuse to answer)

75. In the 12 months before your last blood donation, did you have sex with anyone who has received a blood transfusion?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

SECTION C RISK FACTOR ASSESSMENT PART IV – Medical and Other Exposures

[Please read the following:] *This next set of questions asks about medical procedures you may have undergone or accidents you may have experienced. I once again remind you that your answers are confidential.*

76. Have you ever received a blood transfusion?

○ Yes

76.1 When was the last time you had a blood transfusion?
Month_____ Year _____

○ (Don't know)

○ (Refuse to answer)

○ No

○ (Don't know)

○ (Refuse to answer)

77. Have you ever received an organ or tissue transplant? Examples of tissues that are commonly transplanted include bone, skin, corneas, heart valves, stem cells.

○ Yes

77.1 What type of organ or tissue?
(SPECIFY) _____

○ (Don't know)

○ (Refuse to answer)

77.2 When was the last time you received a tissue or organ transplant?
Month _____ Year _____

○ (Don't know)

○ (Refuse to answer)

○ No

○ (Don't know)

○ (Refuse to answer)

78. Have you ever received acupuncture?

○ Yes

○ No **SKIP TO QUESTION 80**

○ (Don't know)

○ (Refuse to answer)

79. In the 12 months before your last blood donation, did you receive acupuncture?

○ Yes

○ No

○ (Don't know)

○ (Refuse to answer)

80. Have you ever had a needle stick injury (accidentally been stuck by a needle or other sharp instrument after it was used for providing medical care to someone else) or some other unintentional needle stick?

○ Yes
○ No **SKIP TO QUESTION 82**
○ (Don't know)
○ (Refuse to answer)

81. In the 12 months before your last blood donation, did you have a needle stick injury?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

82. Did you ever get someone else's blood, body fluids, vomit, or feces splashed into your eyes, mouth, or in an open skin wound?

○ Yes
○ No **SKIP TO QUESTION 84**
○ (Don't know)
○ (Refuse to answer)

83. In the 12 months before your last blood donation, did you get someone else's blood, body fluids, vomit, or feces splashed into your eyes, mouth, or in an open skin wound?

○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

84. To the best of your knowledge, before your last donation was anyone **living in your household** (including family, friends or roommates) infected with HIV, hepatitis B or hepatitis C?

○ Yes

84.1 Can you tell me which person(s) is/are/were infected?

[MARK ALL THAT APPLY]

- ○ Mother
- ○ Father
- ○ Sister or brother
- ○ Spouse or partner
- ○ Child
- ○ Another relative
- ○ Roommate
- ○ Friend
- ○ (Don't know)
- ○ (Refuse to answer)

○ No
○ (Don't know)
○ (Refuse to answer)

85. Are you currently taking antiviral therapy?
○ Yes
○ No
○ (Don't know)
○ (Refuse to answer)

END OF QUESTIONNAIRE

[Please Read] *Thank you for taking the time to complete this questionnaire. If you have any questions or concerns, you may ask me now. You can also contact Donor Counseling and Notification Services for more information at (XXX) XXX-XXXX.*

[Interviewer Comments: Please provide any additional comments or impressions about the risk factors disclosed or not disclosed by the donor]

_____
_____
_____

Appendix 9 – TTIMS Risk Factor Questionnaire (Spanish version)

To Be Added