REDS-II DONOR IRON STATUS EVALUATION (RISE) STUDY

Sponsored by:

The National Heart, Lung, and Blood Institute

Transfusion Medicine Branch

National Institute of Health

SUPPORTING STATEMENT A

Request for Revision and Renewal

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SUPPORTING STATEMENT A

Introduction and Summary

Iron loss is a known consequence of blood donation. Although the overall health significance of iron depletion in blood donors is uncertain, iron depletion leading to iron deficient erythropoiesis and lowered hemoglobin levels results in donor deferral and, occasionally, in mild iron deficiency anemia. Hemoglobin deferrals represent more than half of all donor deferral, deferring 16% of donation attempts by women. This Iron Cohort study has been developed under the National Heart, Lung, and Blood Institute's (NHLBI) Retrovirus Epidemiology Donor Study-II (REDS-II) contract. The contract for REDS-II was awarded in August 2004 to six blood centers and a coordinating center (CC). The blood centers include the American Red Cross New England Region (NEARC), Dedham, Massachusetts; the American Red Cross Southern Region (SARC), Atlanta, Georgia; Blood Center of Wisconsin (BCW), Milwaukee, Wisconsin; Hoxworth Blood Center (HBC), Cincinnati, Ohio; the Institute of Transfusion Medicine (ITxM), Pittsburgh, Pennsylvania; and Blood Centers of the Pacific (BCP), San Francisco, California. Westat, located in Rockville, Maryland, serves as the CC. The CC is responsible for protocol implementation, monitoring, data management and analysis. A REDS-II central laboratory contract was also awarded to Blood Systems Research Institute in San Francisco, California.

Among the six REDS-II blood centers, a longitudinal study of iron status in two cohorts of blood donors will be conducted. The first cohort will be comprised of 840 first time and returning (reactivated) donors for whom baseline iron and hemoglobin status can be assessed without the influence of previous donations, and a second cohort of 1500 frequent donors, where the cumulative effect of additional frequent blood donations can be assessed. For each cohort, donors will routinely donate blood during the study period. As part of the research study, a sample of their blood will be collected for laboratory testing.

At the baseline and final study visits, hemoglobin levels and a panel of iron protein and red cell and reticulocyte indices will be measured. The final study visit is defined as the latest visit occurring 15-24 months after the initial enrollment visit. At these visits donors will complete a self-administered survey (Attachments 1, 2) assessing past blood donation, smoking history, use of vitamin, mineral and iron supplements, use of aspirin, intake frequency of heme-rich foods, and for females, menstrual status and pregnancy history, and questions on Restless Leg Syndrome (RLS) questions and Pica . A DNA sample will be obtained once at the baseline visit to assess three key iron protein polymorphisms. Further, throughout the study when a

subject returns, fingerstick hemoglobin or hematocrit values will be obtained and plasma will be collected for selected measurements of ferritin, and sTfR levels to the extent possible. Test results and survey data will be combined with demographic, anthropomorphic, racial/ethnic, and zip code (to estimate altitude) data routinely compiled at all REDS-II centers.

The primary goal of the study is to evaluate the effects of blood donation intensity on iron and hemoglobin status and assess how these are modified by demographic, reproductive and behavioral factors. This study aims to identify laboratory measures for predicting the development of iron depletion, and hemoglobin deferral in whole blood and double red cell donors as that could be potentially useful for donor management. The data collected will help evaluate hemoglobin distributions in the blood donor population (eligible and deferred donors) and compare them with NHANES data. It will also help formulate a predictive model for the development of iron depletion, hemoglobin deferral and/or iron deficient hemoglobin deferral in whole blood donors, which could be beneficial to developing optimal whole blood donation frequency guidelines.

Secondary objectives include elucidating key genetic influences on hemoglobin levels and iron status in a donor population as a function of donation history; and establishing a plasma and DNA archive to evaluate the potential utility of future iron tests and genetic polymorphisms.

Restless leg syndrome (RLS) is a neurologic movement disorder in which patients complain of crawling, aching or indescribable feelings in their legs or just have the need to move. Pica is an eating disorder defined as compulsive ingestion of non-food substances. Both disorders are strongly associated with iron deficiency. Blood donation results in the removal of 200-250 mg of iron from the donor. It is well established that repeated blood donation can produce iron deficiency, yet the prevalence of RLS and Pica among blood donors is unknown. The REDS-II Steering Committee discussed and approved the addition of eleven questions to the study final questionnaire designed to assess the prevalence and severity of RLS and pica in blood donors enrolled in the RISE Study in December 2008. These particular study subjects are an ideal study population for the investigation of RLS and pica in blood donors. Over 2,400 subjects with variable donation intensity (e.g. frequency with which a person donates blood) are currently enrolled in the RISE Study. About 1500 subjects (and a minimum of 1200 subjects) are expected to complete the final questionnaire. The iron status of all of these subjects is well characterized, including measurement of plasma ferritin and soluble transferrin receptor along with hemoglobin/hematocrit. These laboratory values allow each subject to be defined as 1) iron replete, 2) iron deficient without anemia or 3) iron deficiency anemia. The responses to the questions concerning RLS and Pica on the final questionnaire will be compared with the

laboratory test values to determine associations between blood donation and the development of RLS and Pica.

A. Justification

A.1 Circumstances Making the Collection of Information Necessary

Introduction

Deferral for low hemoglobin levels is the most common cause of presenting donor loss, particularly in females. Within the New England Region they represent more than half of all deferrals,[1] nearly all being women. Approximately, 15% of women presenting at blood drives are deferred for their hemoglobin level, in contrast to approximately 5% of male donors. The deferral of large numbers of presenting female donors, many of whom do not return or are again deferred on repeat presentation, leads to significant problems maintaining, let alone increasing the blood supply –a principal goal of REDS-II.

Several cross sectional studies of blood donors, using older measures of iron status have indicated that being female, frequent donation and not taking iron supplements are predictors of iron depletion. However, none of these studies have included racial/ethnic, anthropomorphic, or behavioral factors and none have evaluated the impact of newly discovered iron protein polymorphisms.

Collecting the proposed information is a vital part of the overall responsibility of the Federal Government and U.S. blood collection centers to ensure the safety and availability of the national blood supply. NHLBI has a Congressional mandate, Sec 421 [285b-3] and 422 [285b-4] to ensure the overall safety of the blood supply. An important aspect to this assurance is ongoing epidemiology and laboratory research regarding blood donation practices and procedures to ensure the safety of donors while ensuring a blood supply adequate to fulfill the nation's needs. The NHLBI strategic plan for FY 2002-2006 includes work to continue improving the safety and supply of blood for transfusion and this study supports this NHLBI mission.

This study will develop better predictive models for the development of iron depletion and hemoglobin deferral (with or without iron deficiency) in blood donors. It will allow for improved donor screening strategies and open the possibility for customized donation frequency guidelines for individuals or classes of donors thus helping protect the well being of blood donors. It will provide important baseline information for the design of targeted iron

supplementation strategies to replace iron loss in blood donors, and improved counseling messages to blood donors regarding diet or supplements. Finally, the elucidation of the effect of genetic iron protein polymorphisms on the development of iron depletion will enhance the understanding of the role of these proteins in states of iron stress, using frequent blood donation as a model.

A.2 Purpose and use of the information

Data collected in this study will be of practical use to the blood banking community and to the Federal Government (See Section A.1.). In addition to the traditional route of peer reviewed scientific publication, previous REDS-I study data were the subject of numerous requested presentations by Federal and non-Federal agencies, including the FDA Blood Products Advisory Committee, the HHS Advisory committee on Blood Safety and Availability, the AABB Transfusion-Transmitted Diseases Committee, and the Americas Blood Centers Association. We anticipate similar requests for data generated from this study. The questionnaires for data collection have been designed to meet the analysis objectives detailed in Section A.16. There are two versions of the questionnaire for the purpose of collecting data at the baseline and final visits (Attachments 1, 2). Attachment 3 lists the questions by study objectives along with their specific goals and source. The broad categories of information to be collected are:

Baseline Questionnaire:

- Donation history
- Smoking history
- Diet
- Use of vitamins, supplements and aspirin containing pain killers
- Reproductive history (for female donors only)

Final Questionnaire:

- Smoking history
- Use of vitamins, supplements and aspirin containing pain killers
- Reproductive history (for female donors only)

- Restless Leg Syndrome questions
- Pica questions

A. 2.1 Scientific Justification for RISE Repository

A small portion of the blood collected will be frozen and stored in the repository for possible later use. These samples will be used as other tests for iron status or iron genetic markers are developed. Routine whole blood donation results in removal of about 250 mg of iron from the donor. Since males typically have about 500 to 1000 mg of stored iron, while females have much less, blood donation places a significant stress on iron metabolism. Over the past 6 years there have been major advances in our understanding of iron metabolism. These advances were catalyzed by the discovery in 2001 of hepcidin, an iron regulatory hormone made by the liver.[1,2] Hepcidin prevents iron absorption from the gastrointestinal tract and iron release from the reticuloendothelial system. Patients with hemochromatosis have inappropriately low hepcidin levels and continue to absorb iron despite elevated iron stores. In contrast, patients with the anemia of chronic inflammation have inappropriately high hepcidin levels (hepcidin is an acute phase protein) and do not recycle iron from the reticuloendothelial system to produce new red blood cells.

Establishment of a plasma and DNA archive containing samples from blood donors with well defined donation histories will be a valuable resource for study of how hepcidin and other recently discovered iron regulatory proteins respond to the stress of iron loss via blood donation. These studies of iron metabolism in healthy blood donors will provide new information that will help us to develop new strategies to prevent iron deficiency in blood donors and to understand the pathophysiology of diseases with altered iron metabolism. A repository is needed because many of these proteins and/or their related genes have been discovered so recently that reliable assays for their measurement are still in development. In addition, a repository will be needed to rapidly assess the utility in patients and in blood donors of new proteins or genes discovered to regulate iron metabolism.

Examples of iron regulatory proteins that have recently been discovered include hemojuvelin, ferroportin, and transferrin receptor 2. These three proteins, as well as the *Hfe* protein originally linked to patients with hemochromatosis, all regulate hepcidin production.[3] In August 2007 three additional important papers were published describing important advances in our understanding of iron metabolism. The publication of these papers in the same month emphasizes how rapidly this field is advancing. First, a new plasma/serum assay for hepcidin using liquid chromatography mass spectrometry was published in Blood.[4] This new assay is

important because previous assays for hepcidin could only reliably detect it in urine. Second, a common variant allele associated with restless leg syndrome and low serum ferritin levels was described in the New England Journal of Medicine.[5] Third, a paper in Nature Medicine described the function of a protein called GDF15 produced by erythroblasts in the bone marrow.[6] It was shown that GDF15 released from the bone marrow prevents hepcidin production by the liver resulting in increased iron absorption from the gastrointestinal tract. Identification of this pathway is important because it describes the molecular mechanism for the inappropriate absorption of iron by patients with thalassemia. This results in iron overload in these patients which is often exacerbated by the iron received through frequent blood transfusions to treat their anemia.

A plasma and DNA linked repository with well characterized donation histories and classical iron markers already measured will allow assessment in these donors of genetic, chemical or cellular markers of iron status. This would encompass currently known iron regulatory proteins as reliable assays become available as well as proteins or genes that have not yet been discovered. A potential strategy, consonant with the efforts of this protocol, would be to search for genetic biomarkers which predict an individual donor's capacity/intensity for donation. The repository would also enable the follow-up of any unexpected findings in the RISE study, and the resolution of testing discrepancies, if necessary. Finally, the repository will be a valuable resource for more general inquiry into the regulation of iron, such as may be important in patients with a variety of disease states.

A 2.2 Summary of Activities since Previous OMB Submission

Subject enrollment for the RISE study started in December 2007. The baseline phase of the study ended on June 1, 2008 and 2454 donors were enrolled in the study. So far 23 donors have been de-enrolled leaving a total of 2431 study subjects. See Tables A2.2.1 and A2.2.2 below for start dates and number of donors enrolled in the study.

Table A2.2.1: RISE Study start dates

RISE Study Start Dates	Blood Center
December 11, 2007	NEARC
December 17, 2007	BCW
January 02, 2008	HBC, BCP
January 07, 2008	ITxM, SARC

Table A2.2.2: Number of donors enrolled in RISE study

Donor Status	Number of donors
First Time/Reactivated	914
Repeat	1517
Total	2431

Follow-up visits for the study started in late February 2008. As of February 15, 2009, 1932 subjects have made 5292 follow-up visits.

Table A2.2.3: Number of Follow-up Visits

Donor Status	Number of Visits
First Time/Reactivated	1132
Repeat	4160
Total	5292

Laboratory Testing and Compilation of Test Results

Baseline ADVIA samples collected at the blood centers were tested and results were transmitted electronically bi-weekly to the Coordinating Center. The Coordinating Center had developed procedures to QC ADVIA results to remove duplicates and discrepancies. All of the baseline ADVIA data has been cleaned. In July 2008, the protocol was amended to perform ADVIA testing on follow-up samples collected from repeat female donors. Three blood centers, ITxM, BCW and HBC, are performing this testing and transferring data to the CC in the same fashion as for the baseline samples. Westat will continue to follow QC procedures similar to those for baseline samples and will generate QC reports monthly. Additionally, hard copies of ADVIA data are reviewed for QC purposes as data is received from the BC.

Iron assay testing has been performed on all of the baseline study samples and Westat has received test results on all samples. Strategies for selecting the interim samples for iron testing are yet to be determined. All final samples will be sent for iron assay testing. All baseline samples have been

shipped to the Central Laboratory from the blood centers for polymorphism testing. Testing is nearly completed.

Procedures were developed for QC of data. Monthly QC reports are generated and distributed to the blood centers. Each blood center is responsible for reviewing these reports and providing information on edits. All of the baseline data and follow-up data through November 2008 has been QCed and edited.

Data Analysis

Analysis of baseline data is currently being performed. Longitudinal analysis to evaluate all study hypotheses including the effects of blood donation intensity on iron and hemoglobin status and assess how these are modified as a function of baseline iron/hemoglobin measures, demographic factors, and reproductive and behavioral factors will be performed after the end of the study.

Data collection and QC is an ongoing activity that will continue through March of 2010. Data analysis will be concluded in May 2010.

A.3 Use of Information Technology and Burden Reduction

Due to the simplicity of the questions, we believe a self-administered, paper questionnaire that donors can quickly complete in private at the time of donation is the least burdensome form of data collection. The responses to the questionnaire will be entered into a secure, web based, data capture system by specially trained REDS-II research coordinators.

Donors will be assured of the confidentiality of their responses. A label will be placed on the paper questionnaire with a unique Subject ID number assigned to each enrolled donor. Use of the Subject ID on the questionnaire will allow for tracking of survey responses without entering identifying information into the study database. The link between the Subject ID number and the identity of the donor is only maintained by the blood centers. This link is maintained should there be a need to re-contact the donor in the future or should the donor wish to withdraw from the study. The CC will not have access to any donor identifying information.

Efforts to minimize respondent burden are described below:

- The questions are presented along with easy-to-read instructions and skip patterns to avoid having respondents answer unnecessary questions.
- The questionnaire contains tried and tested questions from previous REDS survey, the California Smoking Survey,[2] the NIH Diet History Questionnaire;[3] the National Health and Nutrition Examination Survey (NHANES)[4] and the Mansfield-Voda-Jorgensen Menstrual Bleeding Scale [5].

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

None of the iron status studies conducted in the past have included racial/ethnic, anthropomorphic, or behavioral factors and none have evaluated the impact of newly discovered iron protein polymorphisms. This information is not routinely collected by U.S. blood collection centers in the course of their regular donor screening operations.

A.5 Impact on Small Businesses or Other Small Entities

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

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

Questionnaires will be administered at the baseline and final follow-up visit for the two donor cohorts (first time/reactivated and repeat donors). This will help to study the impact of diet, behavior, use of supplements, reproductive history for females, and frequency of donation on the iron status of the donor. In addition, RLS and Pica questions will be asked at the final visit. Blood samples will be collected at these two visits and also during the interim visits.

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

The proposed data collection is consistent with 5 CFR 1320.5.

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

The 60-day Federal Register Notice requesting comments was published on March 9, 2009. No comments were received in response to this notice. There has been consultation outside of NHLBI to conceptualize and design the proposed study. The final study design was developed, reviewed, and approved by the REDS-II subcommittee, the REDS-II Steering Committee, and the Observational Study Monitoring Board (OSMB) (See Attachment 4 for a complete list of members). The OSMB reviewed the final protocol and provided input and comments (See Attachment 5). Revisions were made to the sample size and consent document incorporating the suggestions of the OSMB.

A.9 Explanation of Any Payment or Gifts to Respondents

Study participants will not receive any payments or gifts.

A.10 Assurance of Confidentiality Provided to Respondents

The Privacy Act does not apply to the proposed data collection since identifiable information will not be collected on this questionnaire.

A.11 Justification for Sensitive Questions

The deferral of large numbers of presenting female donors, many of whom do not return or are again deferred on repeat presentation, leads to significant problems maintaining, let alone increasing the blood supply – a principal goal of REDS-II. The relationship of blood donation to iron stores was first elucidated by Simon, et al. in a cross-sectional observational study of blood donors.[6] The overall frequency of iron depletion was 8% in male blood donors and 23% in female blood donors. The loss of approximately 230 mg iron with each whole blood donation along with a limited absorption capacity leads to a high incidence of iron deficiency in frequent donors, especially women. More than two thirds of body iron is contained in red cells, and red cell loss is the major route for iron loss from the body.

To satisfy study objectives, it is essential to collect information on factors that influence iron balance in women. This includes menstrual history, as well as the number,

outcome (live birth, still birth, or whether they were miscarriages/terminated pregnancy) and date of pregnancy.

The average menstrual period results in a loss of 15-25 mg of iron contained in shed red cells. This causes pre-menopausal women to have a dietary requirement that is 50% higher than men. There is considerable variability in the frequency and amount of menstrual bleeding. The age of onset of menopause is quite variable as well. Because there is this significant variation among women in their iron loss from non-blood donation sources, it is necessary for the protocol objectives to accurately assess these variables. In fact, it is expected that menstrual variables may be important in determining the ability of a woman donor to donate at her desired frequency.

Pregnancy places an even more extreme, although short-term, iron stress on women. The average pregnancy causes a woman to lose 700-1000 mg of iron, equivalent to the donation of 3-4 units of blood. Miscarriage or other earlier termination of pregnancy will have a lesser, but meaningful impact on body iron stores. Thus a woman's pregnancy history is highly important as a variable to explain her ability to donate blood subsequently.

For additional information see Attachment 3. There is no attempt to recruit female donors based on specific reproductive histories. Special attention has been devoted to carefully design possible sensitive questions related to pregnancy history in a straightforward and non-judgmental way. Demographic variables (e.g., age, gender, race/ethnicity), genetic factors (e.g., transferrin G277S polymorphism, HFE markers), behavioral factors (e.g., mineral supplements, smoking) are all known to impact iron or hemoglobin status. The study proposed here will investigate how these factors interact with one another to influence the development of iron depletion and deficiency in blood donors. These questions have been developed, tested, and are used by the National Health and Nutrition Examination Survey (NHANES) conducted by Health and Human Services (HHS). In addition, being aware of the possibly sensitive nature of the pregnancy related questions, the following steps will be taken to assure the confidentiality of respondents:

- Identities of donors who enroll in the study are known only to the blood center. All information is transmitted to the CC via a secure web portal and will contain only Study ID numbers. These numbers can be linked to the donor's identity only by the blood center. Once entered and data verified, the blood center will not retain the hard copy questionnaires.

- To help ensure privacy, the questionnaire will be self-administered.

- All data will be stored in a secure location, accessible only to authorized study personnel.

- Donors are advised of the voluntary nature of their participation in the study and of the steps taken to ensure the confidentiality of the information collected. See Informed Consent Document, Attachment 6.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

Burden hours and annualized costs to respondents have been revised based on the time required to complete the revised final visit questionnaire. We estimate the new time to be 15 minutes because of the additional eleven questions.

The annualized cost to respondents is estimated at $15,588 for the baseline visit and $6,894 for final visits based on $18 per hour. It is estimated that each respondent will spend about 22 minutes (0.37 burden hours) reading and understanding the study information material and completing the baseline questionnaire and about 15 minutes (0.25 burden hours) completing the final follow up questionnaire. The respondent population of U.S. blood donors represents a wide range of wage rates. Therefore, the $18 per hour wage rate was selected based on reported overall labor force mean hourly earnings in 2004[7].

Table A.12. Estimates of hour burden and annualized cost to respondents

Type of Respondents	Estimated Number of Respondents	Estimated Number of Responses per Respondent	Average Burden Hours per Response	Hourly Wage Rate ($)	Estimated Total Annual Burden Hours Requested
Blood donors at Baseline Visit	2,340	1	0.37	18	866
Blood donors at Final Visit	1,530	1	0.25	18	383
					1,249(Total)

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

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

A.14 Annualized Cost to the Federal Government

The total cost to the Federal Government for the proposed study is estimated to be approximately $3.2 million for a 24 month period, or an annualized cost of approximately $ 1.6 million. The annualized cost for the baseline questionnaire is $15,588 and the final questionnaire is $6,894.

A.15 Explanation for Program Changes or Adjustments

The estimates of burden hours in Section A.12 have been recalculated for the revised final visit questionnaire Eleven new questions on RLS and pica were added per the direction and approval of the REDS-II Steering Committee, the rationale for which is previously described in the Introduction and Summary section.

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

The schedule for study activities is shown in Table A.16.

Table A.16. Study Activities

Step	Date of completion	Comment
Donor enrollment and baseline assessment Visit	December 2007–May 2008	Five months allotted to recruitment in the study. However some centers plan to start recruitment in December 2007, while others will start in January 2008.
Baseline Laboratory Testing	June–July 2008	Up to two months allotted for receiving results of tests conducted on all samples taken at baseline
Baseline data compilation and cleaning	August 2008	This step includes development of baseline data frequency dictionaries
Baseline data analyses/interpretation	November 2008–February 2009	Statistical analyses of baseline data
Interim Period	June 2008–July 2009	Research staff not at blood collection sites.
Follow-up period	December 2007–May 2008 to February 2009–July 2009	19-20 months follow-up period (minimum of 15 to maximum of 24 months)

Final donor visit	July 2009–December 2009	Six months allotted to obtain final data on each donor
Laboratory Testing	January–February 2010	Testing of purple top tubes obtained during follow-up (ferritin/ sTfR) and testing of specimens obtained during the follow-up visit.
Data compilation and cleaning	March 2010	QC and formation of dataset
Data analyses	April–July 2010	Four months for longitudinal data statistical analysis

Subject to NHLBI approval, data will be disseminated to the scientific and blood banking community and others through peer-review journal publications, and presentations at government (FDA Blood Products Advisory Committee) and professional meetings (American Association of Blood Banks).

A.16.1 Baseline Tabulations

We will use descriptive statistics to evaluate the distributions of all baseline variables. We will use log-likelihood χ^2 statistics (or exact tests if cell sizes are too small) to evaluate if the distribution of a categorical characteristic (e.g., high vs. low baseline hemoglobin in first-time/reactivated donors; high vs. low HYPOm) is significantly different among groups (e.g. gender, race/ethnicity, iron supplementation vs. not). For comparison of continuous characteristics among groups, we will compare means among several groups by conducting t-test (two groups) or analysis of variance (> 2 groups); or if a non-parametric method is more appropriate by conducting a Wilcoxon rank-sum test (two groups) or a Kruskal-Wallis test (> 2 groups). Correlations and coefficients of determination may also be used to evaluate the association between two continuous variables. To evaluate whether two continuous variables are equivalent (such as evaluating if the hemoglobin level obtained by fingerstick HemoCue® is similar to that obtained from a pre-donation venous draw), a paired t-test could be used.

The baseline venous hemoglobin measures from FT/reactivated donors will be weighted (to reflect differential sampling probabilities of deferred and non-deferred donors) to determine estimates of the mean hemoglobin levels for the blood donor population by age, gender and race. These means will be compared to the NHANES-III data results.

A.16.2 End-of-Study Evaluations

Study hypotheses will be tested using cross-sectional analyses of end-of-study variables (primarily final visit iron status variables and donation intensity). These analyses will be based on the log-likelihood χ^2 statistics associated with the corresponding 2x2 tables. Males and females will initially be analyzed separately.

The sample sizes were determined to test hypotheses concerning the final visit iron status variables. In addition, longitudinal models will be developed to evaluate changes in iron status variables over time. For example, fingerstick hematocrit may decline over time with a slope that depends on donation intensity (such an analysis will be restricted to the centers that will use HemoCue® as their test-of-record).

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

The OMB expiration date will be displayed in the upper-right hand corner of the questionnaire.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

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

REFERENCES

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[2] California Smoking Survey: At http://webtecc.etr.org/cstats/base/publications/docs/Survey_CTS2002_Eng_Screener.pdf

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[7] U.S. Department of Labor, Bureau of Labor Statistics. Employment Statistics Survey: Occupational Employment Statistics, National Data 2004.[1]

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