FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

July 27, 2010

The Hilton Washington DC North/Gaithersburg
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TABLE OF CONTENTS

P R O C E E D I N G S

Agenda Item: Opening Remarks

DR. HOLLINGER: Since this is the second-day session for the Blood Products Advisory Committee today, as you know, we are going to deal with blood donor hemoglobin/hematocrit acceptance standards and frequency of donation.

We have a couple of questions that the committee will be asked to vote on today. These questions deal with the hemoglobin standards, whether they should be changed for men and/or for women. So that is the question that we will have to pay attention to. Then we have several comments -- they have asked us for several comments on other areas that we will deal with.

So with that in mind, I think we will go around again, with the committee that is here, we will go around the table and introduce everybody. We have three new people here today. So I will start out, and then we will go this way around. I am Blaine Hollinger. I am a professor of molecular virology medicine and epidemiology at Baylor College of Medicine in Houston.

DR. GLYNN: Simone Glynn. I am the Branch Chief for the Transfusion Medicine and Therapeutics Branch at NHLBI, NIH.

MS. BAKER: I am Judith Baker, the Administrative

Director for the Federal Hemophilia Treatment Centers in Region IX. I am based at UCLA.

DR. BOWER: William Bower. I am a medical officer in the Office of Blood, Organ and other Tissue Safety, CDC, Atlanta.

DR. TROXEL: I am Andrea Troxel. I am Associate Professor of Biostatistics at the University of Pennsylvania School of Medicine.

DR. MC COMAS: I am Katherine McComas. I am an Assistant Professor of Communication at Cornell University.

DR. BIANCO: I am Celso Bianco. I am the Executive Vice President of America's Blood Centers. I am a non-voting industry representative.

DR. MC CULLOUGH: I am Jeff McCullough, Professor of Laboratory Medicine and Pathology at the University of Minnesota.

DR. BRITTENHAM: I am Gary Brittenham. I am a Professor of Pediatrics and Medicine and Pediatric Hematology at Columbia University in New York.

DR. RAGNI: I am Margaret Ragni. I am a Professor of Medicine in the Division of Hematology Oncology at the University of Pittsburgh.

DR. MANNO: I am Catherine Manno. I am the professor and Chair of the Department of Pediatrics, and a pediatric hematologist at New York University.

DR. EMERY: My name is Brian Emery. I am the Designated Federal Officer with the PHS and on the committee.

Agenda Item: Statement of Conflicts of Interest, Announcements, Recognition of Retiring Committee Members

DR. HOLLINGER: Thank you. I think we will have the statement of conflict of interest if we could, please.

DR. EMERY: This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on July 26, and will be part of the public record for the Blood Products Advisory Committee meeting on July 27, 2010.

This announcement addresses conflicts of interest for Topic II, the discussion of blood donor hemoglobin/hematocrit qualification standards, donor iron status, and interdonation interval. This is a particular matter of general applicability based on the agenda and all financial interests reported by members and consultants related to Topic II. No conflict of interest waivers were issued under 18 USC 208(b)3 or 712 of the Food Drug and Cosmetic Act.

Dr. Celso Bianco is serving as the industry representative, acting on behalf of all related industry and is employed by America's Blood Centers in Washington, D.C. Industry representatives are not special government employees and do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remind members and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant as a personal or an imputed financial interest, the participants need to excuse themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with any firms, its products, and if known its direct competitors.

Thank you.

DR. HOLLINGER: Thank you, Brian. Just a couple of announcements. First of all, if anybody lost a pair of glasses from yesterday, it was found right back here in about the second or third row to my left. So if these are your glasses, you may come up and get them. They don't quite work for me, otherwise I would have just kept them.

Just a couple of other announcements. If you need to make transportation arrangements, the committee, that is, need to make transportation arrangements, see Pearl outside. They already have an idea when everyone is leaving, and so they have already a little bit taken care of that, so we can share cabs to the various airports.

The second thing is, the next meeting of this

committee is December 14-15, so keep that in mind. I think you have all been notified of that. It will be here in the same hotel. I hope all of you have gotten your power back on, at least those of you who live in this area. We are glad we have power here, finally.

I think Dr. Epstein has an announcement that he would like to make at this time.

DR. EPSTEIN: The members at today's meeting are completing their terms, and so I have the privilege to provide some acknowledgements of public thanks to those who have worked so hard on behalf of the FDA and the public health.

First, I would like to call Dr. Katherine McComas, if you could come up and receive a plaque, a certificate and a handshake. I would also like to call up Dr. Simone Glynn.

Back to you, Blaine.

Agenda Item: Topic II: Blood Donor Hemoglobin/Hematocrit Standards and Frequency of Donation

DR. HOLLINGER: We have our task set out for us. It is a half-day meeting. I am asking the presenters to try to reduce their talks by maybe two to three or four minutes so we have time after each talk for questions, so just keep that in mind. If you can't do it then we will work around it.

We will start by an introduction by Dr. Illoh from

OBRR, the FDA, who will give us an introduction.

Agenda Item: Introduction

DR. ILLOH:: Good morning. My name is Orieji Illoh, and I am a medical officer with the Division of Blood Applications in the Office of Blood Research. Today I will be introducing the topic titled hemoglobin/hematocrit acceptance standards and interdonation interval in blood donors.

The outline of the talks today will include an introduction, a very brief introduction. Then I will talk about the hemoglobin standards that we have currently. I will give a little regulatory history. I will talk about the hemoglobin standards in relationship to population norms, the relationship to the status of the donor, a comparison with the international standards, and then the estimated change or effects of any changes of the hemoglobin standards on the blood supply.

Then I will switch to the interdonation intervals. For that, I will talk about the current U.S. and international requirements. I will talk about the relationship of the interdonation interval in terms of the iron status of the blood donor, and any effects with any changes to the interdonation interval on the blood supply.

Then I will finally put out the questions that the committee will be looking at today.

So today's discussion involves the balance between donor safety and blood supply. We are going to be looking at donor safety issues, which includes the hemoglobin standards and also the interdonation intervals, but also we have to consider the blood supply issues. What we will be looking at is the impact of any changes in hemoglobin standards or interdonation interval on blood supply.

Why are we here today? Why are we talking about adjusting hemoglobin standards? Adjustment of the hemoglobin standards may establish ranges within physiologic norms. Doing so may avoid donations from male donors who are considered to be in the anemic range. Also, this may allow donations from females who are considered to be in normal range, in quotation marks. In fact, about 95 percent hemoglobin donor deferrals occur in women currently. We all know that hemoglobin deferrals have a negative impact on future blood donations.

In terms of the interdonation interval, adjusting the interdonation interval may improve donor safety by allowing adequate time for iron recovery and decreasing the incidence of iron deficiency among blood donors.

The hemoglobin measurement. The current requirement is codified in CFR 640.3(b)(3). This requires a blood hemoglobin level of no less than 12.5 grams per deciliter or a hematocrit of 38 percent in both male and

female allogeneic donors. The purpose of this requirement is to insure the collection of potent products, but also to insure donor safety.

Hemoglobin measurement as performed in the blood centers. The test characteristics are typically done by a simple point of care test. The testing methods like many lab tests differ and are affected by physiologic and operator variables. The quantitative methods reliably measure hemoglobin within .2 grams per deciliter to .5 grams per deciliter.

In terms of its relationship to donor health, this test is used as an indirect measurement of the iron status of the donor. However, we know there are studies that show that hemoglobin is not a good indicator of iron stores.

What about the chronology of the FDA requirements for hemoglobin standards? I think to many here, this is not a new topic. There have been discussions about changing hemoglobin standards and interdonation interval in the past. In fact, the threshold of 12.5 grams per deciliter was established in 1958 and has not changed. The interdonation interval of eight weeks was established in 1999, i.e., was finalized in the rule, and has not changed since then.

There have been previous public discussions about hemoglobin standards and iron status of blood donors. In 2001, June, there was a workshop sponsored by the NHLBI and

industry, and they discussed maintaining iron balance in women blood donors of childbearing age. In this workshop they discussed iron deficiency in female pre-menopausal blood donors. They discussed medical issues related to iron replacement, and iron replacement and possible protocols. At the end of this workshop, the participants recommended implementation of a research program on iron replacement.

In November 2007 the FDA published a proposed rule, and asked for comments and supporting data on changing the hemoglobin or hematocrit levels to 12.0 grams per deciliter or 36 percent as acceptable minimum values for female allogeneic donors. They also asked for the possibility of adverse effects if a minimum of 12.0 grams per deciliter or a hematocrit of 36 percent is used for females. They also asked for comments or supporting data on the possibility of adverse effects if a minimum of 12.5 grams per deciliter, which is our current standard, or a hematocrit of 38 percent is maintained for males. Finally, they asked for comments or supporting data on interdonation interval.

The FDA did receive comments to this proposed rule. I have here representative comments to the proposed rule. Some said, wait for the results of the retrovirus epidemiology donor study on iron status in blood donors, some of which results will be discussed today by one of our speakers. Some agreed with the proposal to lower the

hemoglobin acceptance standard in women to 12.0 grams per deciliter. You saw the comment that hemoglobin down to 12.0 grams per deciliter is normal for females, and had a potential to improve the blood supply.

Others disagreed with the proposal to lower the hemoglobin standard in women to 12.0 grams per deciliter. They argued that this did not have a positive benefit to the donor, and that this may make women susceptible to iron deficiency anemia.

In 2008 some members here will remember that we discussed iron status in blood donors at the BPAC meeting. At this meeting committee members agreed that iron depletion in blood donors is a concern. They discussed testing for iron status in the donor setting and discussed alternative strategies to mitigate iron depletion. Among the topics discussed here were iron supplementation, dietary recommendations, changing the hemoglobin/hematocrit acceptance standards, or modification of the interdonation intervals.

Finally, the Advisory Committee on Blood Supply and Availability in December 2008 in their meeting made the following recommendations. They said FDA should reconsider the hemoglobin acceptance values and probably adopt different gender appropriate acceptance values. They argued that the current single value of 12.5 grams per deciliter permits

acceptance of a significant number of anemic males while excluding many normal females.

I will talk about the considerations for changing hemoglobin acceptance standards. Before we do this, first of all we have to try to understand what we will accept as a normal limit of hemoglobin to define anemia. We all know there are different definitions out there.

In this publication from *Blood* in 2006, the authors looked at the NHANES and Scripts-Kaiser databases. What they did here was to exclude individuals who were iron deficient based on their ferritin levels and transferrin levels. They then proposed that the hemoglobin levels below which five percent of the normal subjects in the population will be found will be considered anemic.

Here, you see they defined a hemoglobin of 13.7 grams per deciliter in white males to be below the five percent of normal. For black males it was 12.9 grams per deciliter, for white women, 12.2 grams per deciliter and for black women, 11.5 grams per deciliter.

This graph shows the hemoglobin distribution in men based on the NHANES II data. What this shows, the black lines represent Caucasian males while the gray lines represent black males. The red arrows, I put these here to show levels at which five percent of the population would fall below. We have here about 13.5 or 13.7 for white males

and about 12.9 for black males.

You can see that this black bar here represents our current hemoglobin standard. The black bar shows that the males that are currently being accepted as blood donors fall below that five percent population who are considered below normal.

This is the same graph for women, black representing Caucasian females and gray representing the African-American females. Once again, these are the arrows that represent where the levels below five percent will fall for both races. The black bar represents our current hemoglobin acceptance standards, so we are accepting females way above the five percent which is considered anemic.

Before considering any changes to the hemoglobin standard, I guess we have to ask ourselves several questions. One could be, are there any adverse effects of maintaining a minimum hemoglobin of 12.5 grams per deciliter as we do now for males. In addition to the fact that these levels fall below what is considered a physiologic norm for males, there is concern that underlying medical conditions may not be addressed when you select such males for blood donation. There is also concern that selecting such people could promote iron deficiency.

Another question could be for females, if you want to adjust the hemoglobin standard for females, are there

adverse effects of lowering the hemoglobin to 12.5 grams per deciliter or a hematocrit of 36 percent for females. There is a lot of concern that this might potentiate or promote iron deficiency.

I want to show you here the experience of the Australian Red Cross. Here they published the iron story status of donors with different pre-donation thresholds. In 2004 the threshold for males was 12.6 grams per deciliter and 11.8 grams per deciliter for females. They show here the overall incidence of iron deficiency among their blood donors, 6.2 percent in males and 22 percent in females. In 2005 they adjusted their threshold to 13.6 grams per deciliter for males and 12.0 grams per deciliter for females. Note that this change was not really a significant change. However, they did not see any significant change in the incidence of iron deficiency among the blood donors, so it remained at 6.0 percent for males and 20.6 percent for females.

Dr. Barbara Bryant, who is one of our speakers today, presented this information in the last BPAC meeting in 2008. What she did here was to look at blood donors and show an association between hemoglobin levels and their iron status.

What you can see here is that when the male blood donors have hemoglobin at 13.5 or greater, about 19 percent

of them are iron deficient. Keep in mind that these are blood donors, so we expect to find iron deficiency among blood donors, especially if they are frequent blood donors. When you go down to hemoglobin levels of about 12.5, note the N of nine, about half of them are iron deficient, and this continues to increase after hemoglobin levels drop.

For female blood donors, she shows similar information. If you had female blood donors with hemoglobin levels of 12.5 or more, about ten percent of them were iron deficient. When you drop down to 12.0, to 12.4, about 14 percent of them were iron deficient. This increased as their hemoglobin levels decreased further.

Once again, these are blood donors, probably a combination of first time and repeat blood donors. I'll let Dr. Bryant discuss that during her talk.

In comparison to what the other countries do, I just have a short chart here showing the current hemoglobin standards for different countries. The U.S. is at the bottom. We require 12.5 grams per deciliter for both sexes. So does Canada. However, the Council of Europe requires gender specific hemoglobin standard, 13.5 for males, 12.5 grams per deciliter for females. Australia's current standards is 13 for males and 12.0 zero for females, and the United Kingdom is 13.5 for males and 12.5 for females.

Any changes in the hemoglobin standard will affect

blood availability. If it is changed for males, there is probably going to be a loss of blood donors if the level is raised for males. Also, there is concern that you will lose male African-American donors. These donors typically, though they are the minority in terms of blood donors, they do provide special phenotypes of RBCs required for sickle cell patients, for example.

Changing the standards may also affect the availability of male plasma, which we collect a lot of now to prevent the incidence of transfusion related acute lung injury.

Published literature has suggested that if the standard is changed to 13.5 grams per deciliter, for example, there will be a loss of about three percent Caucasian donors, but as many as 21 percent African-American donors. So this is a crude estimate here. This is not an exact estimate, but assuming you lose about four percent male blood donors and you have about four million male donors yearly and their donation is about 1.5, this could lead to a 240,000 units per year.

Dr. Eder will be giving us more factual figures when she presents their projected estimate of gains or losses based on the American Red Cross data.

For females, if the standard is dropped to 12.0 grams per deciliter, for example, there will be a gain of

about nine percent Caucasian female donors, as published in *Transfusion* some years ago. So using that nine percent, a crude estimate will be that if you are looking at four million female blood donors, with an average donation rate of 1.5 times per year, there will be an approximately gain of 540,000 units per year. Once again, this is just a crude estimate. We will actually hear actual figures from Dr. Eder.

Now I will switch to the interdonation interval. An appropriate interdonation interval should insure donor safety by allowing time for adequate red cell recovery. Our current requirement for the interdonation interval is codified in CFR 640.3(b), which states that a person may not serve as a source of whole blood more than once every eight weeks. This comes to about six donations per year.

I think we all know that following blood donation there is some degree of iron loss. It comes to about 200 milligrams. We all know that premenopausal women have lower iron stores than men, and that frequent blood donations deplete iron stores. Also, replacement of lost iron is dependent on exogenous sources.

Iron deficiency does have some adverse effects which can include anemia, fatigue, there have been reports of restless leg syndrome, possible cognitive impairment, depression and anxiety. However, there are reports of the

beneficial effects of low iron stores in males undergoing repeated phlebotomy. This includes a favorable lipoprotein profile compared to non-blood donors. There have been reports of a lower risk of cardiovascular disease among such individuals, and a possible reduction of iron induced oxidative stress.

There are studies that have looked at the prevalence of iron deficiency among blood donors. I have a summary of a few up here. I think the conclusions in most of these studies are about the same. The REDS-II iron study will be discussed by Dr. Cable today, but preliminary information shows that there is a high prevalence of iron deficiency in frequent blood donors.

In a study published in *Transfusion Apheresis Science* last year, the authors showed that repeat donations lead to a decreased ferritin in male and female donors. Another study looking at platelet apheresis donors -- and with platelet apheresis you will have some degree of red cell loss also -- they also showed a clear correlation of iron deficiency with the frequency of donation. Finally, a study published in *JAMA* in 1981 showed that depletion of iron stores occurs gradually with increased frequency of blood donation.

This is a graphical representation of one of the studies showing the change in hemoglobin over time. Actually

hemoglobin levels do not change as significantly as the ferritin levels. So you can have a blood donor with a relatively normal hemoglobin, but decreased ferritin stores.

The international standards for hemoglobin are shown in previous slides, but also this slide contains the standards for interdonation intervals. You can see that they vary by country. I have the United States at the top of this table followed by Canada; we have similar standards. But for the United Kingdom it is 112 days, for Australia it is 84 days. Then when you go to other countries, in addition to gender specific hemoglobin standards, they have gender specific interdonation interval requirements. So typically shorter for females or rather interdonation interval for females and a little bit shorter for males.

Increasing the interdonation interval may decrease the risk of iron deficiency. By so doing, this will allow more time for iron recovery and allowing more time for iron recovery will decrease future donor referrals for low hemoglobin. However, any changes to the interdonation interval will obviously affect the blood supply.

Increasing the interdonation interval will affect the ability of red blood cells, especially O negative red blood cells, and red cells with other rare phenotypes. This will also affect collections that are collected by apheresis, in addition to red cells, probably other blood components,

platelets or plasma. This may also affect the availability of donors for reagent manufacturers.

Once again, in terms of numbers, Dr. Eder will give us some projections on how much gains or losses that will have in terms of adjusting any standards.

The key points for today's presentation include one, donor safety issues. We are looking at blood collection from anemic males with the current hemoglobin standard. We are also going to be looking at iron deficiency due to frequent donations, but also we have to consider blood availability issues. There is a potential gain of female blood donors if the hemoglobin standard is adjusted. However, there is also a potential loss of male blood donors if the standard is raised, and probably an even further loss of donors if the interdonation interval is changed.

We have five questions for the committee today. Two will be voting questions.

Question one reads, does available scientific evidence support changing the donor hemoglobin acceptance standards for males. If yes, what hemoglobin acceptance standard does the committee recommend.

The second question, same as number one, just for females.

The third questions will involve a comment from the committee. Please comment on the risks and benefits of

extending interdonation intervals as a strategy to prevent iron deficiency in male donors. The same question applying to females for number four.

Then number five will be, if any changes to the hemoglobin standard or interdonation interval were to be made, what medications can be considered to lessen possible adverse effects on the blood supply.

Our speakers today will be Dr. Richard Cable from the American Red Cross. He will be discussing the REDS-II donor iron study. Dr. Barbara Bryant from the University of Texas Medical Branch in Galveston will be discussing the NIH study on iron stores in blood donors. Finally, Dr. Anne Eder from the American Red Cross will be discussing the impact of any changes to the hemoglobin standards or interdonation intervals on the blood supply.

I think that is it. Questions?

DR. HOLLINGER: Thank you, Dr. Illoh. Any questions right at this time?

DR. BRITTENHAM: First I would like to compliment her on a clear presentation of the questions that are to be considered today.

I just wanted to make one point. The study that is referenced in *Transfusion* suggesting if you decrease the hemoglobin level in women donors from 12.5 to 12, it was proposed only in the context with iron replacement.

DR. ILLOH: Right.

DR. BRITTENHAM: But it wasn't proposed as a move without taking care of the problem of iron deficiency, but only with iron replacement.

DR. ILLOH: Yes, certainly.

DR. RAGNI: I wonder if you could share with us, because I was not here, and I think it was in November of 2008 when this issue was brought before this group, what the decision was and perhaps why the lack of decision at that time was to change the standards.

DR. RUDA: Not quite fair, because she wasn't with the FDA at that time, but I was, so I'll do my best.

One of the questions was, does the committee think that iron deficiency was something that we needed to be concerned about. The overwhelming vote was yes. The others were essay questions. Some of the issues that were considered were, what tests were available, are there other tests that could be used. There was discussion about possible other tests, including ferritin tests, but the concern was, there wasn't any rapid ferritin test that could be used and it couldn't be done prior to donation.

Then there was discussion and presentations about iron supplementation and possible use of iron supplementation. At that point we canvassed the country to see who was doing iron supplementation and the only folks who

were doing was Dr. Bryant, who was at NIH at the time, and Dr. Waxman, who was at the Blood Bank of Indiana. So even though that was an issue that had been discussed at NIH consensus conferences, there wasn't much take-up by the blood bank community. I should mention also, Dr. Brittenham has published on iron supplementation. But at that point it was just NIH and the Blood Bank of Indiana doing iron supplementation.

So we had one yes or no vote, and the committee agreed this was an issue to be concerned about. Then the others were essay questions about what could be done. There was wide-ranging discussion, including donor education.

DR. MC CULLOUGH: Two questions. Thanks for the very nice presentation.

DR. ILLOH: Thank you.

DR. MC CULLOUGH: In the two graphs that you showed with the 95 percent cutoff hemoglobin values, did you say that that was data from non-iron deficient subjects?

DR. ILLOH: The table I showed you --

DR. MC CULLOUGH: It is the two graphs. And if those were all known to be non-iron deficient, is there any kind of data in the general population?

DR. ILLOH: The graphs were from the NHANES data. Those probably included iron deficient individuals. The table I showed you, this table here, the authors excluded

people who were iron deficient.

DR. MC CULLOUGH: The other question, and maybe Anne will speak to this, later on toward the end, you showed hemoglobin and iron status in multiple donations. The hemoglobin didn't change. So that would suggest that changing the interdonation interval won't necessarily reduce deferrals for hemoglobin. It looks like it would be the same. Maybe Anne will speak to that.

DR. ILLOH: I think probably Dr. Cable will speak to that.

DR. BRITTENHAM: That was a study that was conducted only over a period of one year, so it shows that the iron stores are decreasing, but not to a point that they influenced the mean hemoglobins.

DR. ILLOH: Right, that is the Red Cross study. I think you are talking about the two graphs that I showed, the hemoglobin levels and this one?

DR. MC CULLOUGH: Yes.

DR. ILLOH: I think what it shows you is that you cannot use the hemoglobin as a measurement or as an indicator of the iron status of the donor, because hemoglobin level could remain within normal limits or acceptable limits. Meanwhile, the iron stores will be decreased.

DR. BRITTENHAM: Right, until the iron stores are exhausted. Then if you keep taking blood, the hemoglobin

will fall.

DR. ILLOH: Right. I think Dr. Cable will share more information about that.

DR. HOLLINGER: Thank you, Dr. Illoh. Let's move on then to the next speaker, which is Dr. Barbara Bryant from the University of Texas Medical Branch in Galveston. She will talk on iron status in blood donors.

Agenda Item: Iron Status in Blood Donors

DR. BRYANT: Good morning. I would like to thank the committee for inviting me to come present my findings.

As has already been presented this morning, iron deficiency in first-time and repeat blood donors is a real challenge in transfusion medicine. Iron is an essential element that is lost with each blood donation. Approximately 242 milligrams for men and 217 milligrams for women is lost with each unit of whole blood that is donated.

The normal iron stores in men are 1,000 milligrams, but women only have 350 milligrams. So in order for a donor to continue to donate blood and to compensate, iron is mobilized from the body's iron stores and there is an increased absorption of iron from the diet. But this balance can still be difficult to maintain in premenopausal females and regular routine blood donors.

At the NIH in 2006, we decided to establish a protocol where we looked at the role of oral iron replacement

in the routine management of blood donors. The background was that approximately eight to 12 percent of all whole blood donor visits to the Department of Transfusion Medicine ended in deferral for low hemoglobin levels. So we established a three to four year study. We wanted to enroll up to 2,000 low hemoglobin donors. These were donors picked by hemoglobin screening. They would come in to donate and be deferred. The screening was done by fingerstick method, using the HemoCue. We wanted to enroll up to 500 control donors. Control donors are people who are passing the hemoglobin screening and are not taking oral iron supplementation.

The goals of the study were to analyze the cause of low fingerstick hemoglobins, quantitate the prevalence of iron deficiency and study the long term effects of blood donation on the donor's hemoglobin level and iron stores, and to also evaluate the safety, practicality and efficacy of distributing oral iron replacement to blood donors.

When a donor would come in to donate at the NIH and they had low fingerstick hemoglobin, they had the opportunity to meet me. I would go out and talk with the donors and see if they were interested in participating in this protocol. So I would get informed consent and we had a questionnaire that we went through with the donors, which I will talk about in just a second. Then we drew laboratory tests. We chose a

CBC, just your basic iron studies, ferritin, percent transferrin saturation, serum iron and transferrin. In some circumstances we would do other labs as indicated, such as the hemoglobin electrophoresis.

The donor health screening questionnaire was a focused medical history screening, in which we tried to identify the causes of low hemoglobin values and depleted or deficient iron stores. In this questionnaire we asked the donor, have you ever been told that you have low hemoglobin or have you ever been told that you are iron deficient. Have you ever taken iron before? If so, for how long? What was the response to iron? We asked them if they or family members had a history of anemia or iron deficiency, any issues dealing with cancer, especially colon cancer, or issues dealing with a hemoglobinopathy, if someone in the family knew they had a hemoglobinopathy.

We also asked specific questions of the donors, if they had bright red blood from rectum, if they had ever noticed melena, also questions about, did they ever cough up blood vomit or have blood in their urine.

So any time we picked up a response to these questions that were concerning, we referred them immediately to their primary care physician. Based on the answers to these questions, sometimes I could determine right up front whether I needed additional laboratory testing. The classic

example was if someone said, oh yes, we have members of the family with beta thal trait or beta thalassemia, or I have always tried to donate blood, I have always been deferred, and so has everybody in my family. In situations like that we would do a hemoglobin electrophoresis.

Let me explain how we defined the iron stores. First off, we used ferritin to reflect the total body iron stores. There are a lot of different tests out there that are good, that do a real good job of estimating the body iron stores, but we chose ferritin for several reasons. First off, it was available. It was cheap. I got the results within 24 hours, and we felt like it was a good reflection of the total body iron stores.

In our study, at the NIH the normal range for a woman for ferritin is nine to 120. In our study a woman was caused iron deficient if her ferritin was less than nine. Then I established what was called the iron depleted category. This was in the low normal range, and I chose the numbers nine to 19. A lot of people argued I could have made that range even larger and probably still been accurate, but I wanted to keep it narrow, and not gather too many people in this iron depleted category that maybe didn't below there. Then a woman was considered iron replete if her ferritin was greater than or equal to 20.

For men, the normal range is much larger, 18 to

370, so men were considered iron deficient if their ferritin was less than 18. They were considered iron depleted with a ferritin between 18 and 29, and ferritin was replete if it was greater than or equal to 30.

We did a 39-month study in which we enrolled 1,355 low fingerstick hemoglobin donors. Of this, 87 percent were female and had a mean fingerstick hemoglobin of 11.8. There were 13 percent males, and they had a fingerstick hemoglobin of 11.9, so pretty close to each other. We also enrolled 410 control donors; 36 percent were female and they had a fingerstick hemoglobin of 13.7, and men, 94 percent with a mean fingerstick hemoglobin of 14.9.

Here is the donor demographics. Here is the low hemoglobin group, those that presented at study enrollment with a low fingerstick hemoglobin, and then the control group, those that had normal hemoglobin. As you can see, in the low hemoglobin group, it was more likely to be females than the control group. The males were more likely in the control group.

As far as the breakdown by race, there were more African-Americans in the low hemoglobin group than in the control group, and more Caucasians in the control group.

Here we have a category of first-time donors. This is a little bit misleading. This includes truly first-time donors, never donated blood before, but it also includes

donors who were first-time blood donors at the NIH. Many of those had donated previously at other institutions. But we saw more of these first-time donors, quote-unquote, in the low hemoglobin group.

Also, number of prior donations. I wanted to track that. I thought naively that there would be a magic number that you would get to with women, that after they donated X number of units of whole blood, they had low hemoglobin. But it was about 10.2 units for them, but the range was one to 103, and then the same range for the control group, and men at 26.7. So there is a difference between males and females, but no magic numbers.

Here are our results. In the low hemoglobin group 30 percent of the females were iron depleted and 23 percent were outright iron deficient. So 53 percent of the females in the low hemoglobin group were either iron depleted or deficient. The males, eight percent were iron depleted, but 53 percent were iron deficient. That makes sense. Because of where the cutoff is at 12.5 grams per deciliter, by the time the man gets down to that level, he is blow the normal range of hemoglobin for a man and is more likely to be iron deficient. So 61 percent of the men were either iron depleted or deficient in the low hemoglobin group.

Interestingly enough, in my control group, remember, these are donors who are passing hemoglobin

screening and donating blood, we found that -- and they are not on iron replacement -- the females, 29 percent were iron depleted and ten percent iron deficient, and the males, 18 percent iron depleted and 21 percent iron deficient. So even in the control group, our donors had a passing hemoglobin screening and we were collecting units of blood from, 39 percent were iron depleted or deficient.

Again, we broke down the association of fingerstick hemoglobins with iron status and venous hemoglobin in women. I have this broken down by greater than or equal to 12.5. This is of course my control arm. Then I have hemoglobin levels of 12.0 to 12.4, 11.5 to 11.9 and less than 11.5. This shows the iron status of women.

In the greater than or equal to 12.5, ten percent of the women are iron deficient. Then when you go to the 12.0 to 12.4, that goes up to 14, so really not much difference. But then there is a jump, when you go to 11.5 to 11.9, 24 percent are iron deficient. Then as you go lower, 40 percent are iron deficient.

I also wanted to take a look at venous hemoglobin, venous hemoglobin being the gold standard for what your hemoglobin level is. However, in the United States most of us use fingerstick hemoglobin and we don't do venous hemoglobins. I wanted to see how that correlated. We know that a drop of blood from your finger is different than

different than what is in your vein. Many people argue that each drop of blood is just a little bit different.

So we compared the fingerstick hemoglobin levels and asked the question, was venous hemoglobin really greater than or equal to 12.5. In the fingerstick group that was greater than or equal to 12.5, we had pretty good concordance here, 80 percent. But in the 12 to 12.4 fingerstick hemoglobin range, 55 percent had a venous hemoglobin greater than 12.5. So that is just something to keep in mind, that we use fingerstick hemoglobin, but it is not really the gold standard for someone's hemoglobin.

The same type of chart for men. I broke this out a little bit in more detail. This is showing fingerstick levels of greater than or equal to 13.5, 13 to 13.4, 12.5 to 12.9, 12 to 12.4 and then less than 12. So these three columns over here are my control group.

In men that had fingerstick hemoglobins greater than or equal to 13.5, 19 percent were iron deficient, in the range of 13 to 13.4 26 percent. Then in the range of 12.5 to 12.6, still it is 56 percent. My N is still nine. You would have thought I would have gotten more donors in this category, but I didn't. In the 12 to 12.4, 46 percent, and then it increases to 62 percent as the hemoglobin level decreases.

Again, the venous hemoglobin correlates very nicely

on the higher ends, but as you get to this 12 to 12.4, 69 percent really did have CBC hemoglobins greater than 12.5. We used to laugh sometimes that as you got a fingerstick hemoglobin between 12 and 12.4, it was really a flip of a coin as to whether that would match up to the 12.5 requirement if you had venous hemoglobin screening.

So the donors in our study that were in the low hemoglobin arm of the study and control donors with documented iron deficiency were given oral iron therapy. We used ferrous sulfate or ferrous gluconate, 325 milligrams. We gave them a 60-pack of iron. It was in a child-resistant blister pack. The biggest complaint in my whole study was that the iron was hard to get out of the blister pack. It was not only child resistant, but pretty much adult resistant. People had to take a knife or scissors after it.

We asked the donors to take one tablet half an hour before bedtime with half a glass of water. In our study we had 68 percent compliance. Of the donors placed on iron, 79 percent were given ferrous sulfate. We used that as the first line of therapy, as to most physicians. Initially, 21 percent of our donors said, I have been on iron before, I don't tolerate it well enough. I don't want to take that iron, so we had 21 percent we moved straight to ferrous gluconate.

Out of the 79 percent that were started on ferrous

sulfate, 22 percent developed an intolerance and had to be switched to ferrous gluconate. Of those that were switched, four percent were intolerant both to sulfate and gluconate.

Of that original 21 percent that reported intolerance to iron, we put them on the gluconate, and eight percent were intolerant to gluconate. So although both of the tablets took 325 milligrams, the elemental iron in ferrous sulfate is 65 milligrams, as opposed to the elemental iron in gluconate, which is 38 milligrams. So there is a difference in dosage here.

Overall in the study, about five percent of our enrollees were intolerant to both sulfate and gluconate. And the most common complaint was G.I. upset, either constipation, diarrhea or abdominal pains.

Here is what happened in the effect of iron therapy on the low fingerstick hemoglobin donors. On this graph I have fingerstick hemoglobin in purple, venous hemoglobin in blue and ferritin is the gold. Remember, we started at about 11.8, 11.9 for the donors. These are visit numbers. One each of these visits, when a donor came back in, we did a questionnaire where we looked at had anything changed. We checked for risk factors, how much iron they had taken. Then we drew labs and they were allowed to donate if their hemoglobin was greater than or equal to 12.5. They were given additional iron.

I want to say that donors at the NIH who do not pass fingerstick hemoglobin screening are deferred for 60 days. That has always been our policy. At a lot of hospitals and blood centers, if you are deferred for low fingerstick hemoglobin you can come back tomorrow, next week, later this afternoon, that type of thing. But at the NIH you were automatically deferred 60 days.

So they would come in and take their iron and come back to donate. We saw the fingerstick hemoglobin increase quite significantly, about a gram and a half. Then as they continued to donate whole blood, the fingerstick hemoglobin remained pretty much constant, and the venous hemoglobin mirrored this as well. The ferritin levels, starting in the low range, we gave them iron, and the iron stores replenished. It took a little bit loner. We saw the hemoglobin increase first and then the ferritin would lag behind. As they continued to donate blood and take the ferritin, they would replace their iron stores.

We also looked at the red cell distribution width. It would increase and then go back down into the normal range. The MCV, mean corpuscular volume, we would see that on the low side, but then increase into normal range. So in this study we saw normalization of the laboratory parameters once we put the donors on iron, even as they continued to donate blood.

Now, inherent in this study with my low hemoglobin group were these donors that I gave iron to that did not have iron depletion or deficiency. Remember, I saw the donor in the donor room. Based on the low fingerstick value they were put in the low hemoglobin category. I drew the labs and I gave them some iron and sent them home. The next day I got the lab results, and there were donors who did not have iron depletion or deficiency. We decided to let them continue taking the iron to see what would happen.

On this graph, I have this broken out by apheresis males, apheresis females, whole blood male and whole blood female. The hemoglobin again being about 11.8 or 9, when I put them on iron, even though according to our definitions they were not iron depleted or deficient, we saw an increase of approximately one gram per deciliter in the hemoglobin of these donors when we put them on iron. So the women went up and maintained a normal hemoglobin, as did the men, and even probably more striking is the apheresis donors, because they are not losing as much red cells as these whole blood donors are.

What happened to their ferritin. I am giving them iron and they really don't meet the criteria of iron depleted and deficiency. I wanted to make sure I wasn't sending someone's ferritin way high. I didn't. Here are the whole blood females. Their ferritin level was in the normal range.

I gave them iron, they continued donating blood, and their ferritin levels stayed about even. The men wobbled a little bit, but very much even, and the apheresis male and female went up and down, but nothing above normal range. They always seemed to hover right in the same area.

What about the control arm? These are the guys that came in to donate blood, had normal fingerstick hemoglobins and were not taking iron. If you watch these donors with each donation, here is ferritin level by donation visit, their ferritin level keeps dropping as they come in to donate blood.

These were control donors that had low ferritins on their initial visit. I put them on iron so their ferritin level went up. These were picked up on the second visit, these on the third and these on the fourth visit. So we could correct their ferritin, their iron stores, by giving them iron, but if left alone, this is the path that they would take.

There were no donors in our study found to have ferritin or transferrin saturation level suggestive of hemochromatosis. Also, the careful screening with the questionnaire and also by watching these lab results, there were no malignancies reported or detected, and any time there was a question or concern about someone not responding to iron, they were sent to their primary care physician. All

donors with iron deficiency anemia were given a letter and a copy of their labs to go to their primary care physician. As a matter of fact, we gave copies of the labs to the donors and the participants whenever they wanted copies of these to share with their physicians.

I was asked just briefly to talk about the correlation of low MCV in the iron levels and iron store status in some of our donors. We also had another study that went on during this time period where we looked at low MCV donors. I am just going to show a few slides on that.

These were donors in the apheresis area that had low MCVs, recurrent low MCVs, and they had normal hemoglobins, 12.5 grams per deciliter or higher. We wanted to take a look at these donors and see if we were missing anything. The low MCVs could be related to iron deficiency or it could be a hemoglobinopathy like an alpha or a beta chain variant.

In a 15-month period we identified 30 out of 33 apheresis donors that had repeatedly low MCV values. These donors were 43 percent African-American and seven percent Asian, whereas our apheresis donor population was about 16 percent African-American and 1.5 percent Asian, so that makes sense.

But iron deficiency was present in about 60 percent of these donors. Forty percent had just isolated iron

deficiency, that is all they had, and 20 percent had an iron deficiency plus the hemoglobinopathy. Then there was another 40 percent that just had hemoglobinopathy.

What we had to do in these cases was frequently treat the iron deficiency to determine if there was an underlying hemoglobinopathy such as an alpha thal trait.

Let me explain. We called somebody presumed alpha thal trait if they had normal iron stores, a low MCV and an elevated red cell count. So in donors that presented with low MCV and did have acquired deficiency we would have to fix the iron deficiency first, watch them for several months, and then re-run the hemoglobin electrophoresis, and then determine if they had alpha thal trait. The only true way to prove alpha thal trait is of course gene analysis, chain analysis.

In the iron deficiency group, 40 percent, hemoglobinopathy 40 percent. I had numerous alpha thal trait patients, hemoglobin S trait with an alpha thal trait, hemoglobin G-Philly with an alpha thal trait and a hemoglobin Lepore. In the iron deficiency and hemoglobinopathy group, I had six donors. After fixing the iron deficiency we found that five of them had alpha thal trait and one had hemoglobin C trait. So MCV was also a useful tool to detect iron deficiency and hemoglobinopathy in a healthy blood donor population, and could be used to determine if there was

something you could fix, if they needed iron replacement.

In conclusion, overall based on the information of our iron study, the recommendations that we would like to make to the FDA is to examine the hemoglobin thresholds for both female and male donors, as we talked about already today. Based on our studies and the iron status of female donors, we feel that we could lower the fingerstick hemoglobin threshold to 12.0, because there wasn't really a large increase in the number of donors that were iron deficient in this category, between 12 and 12.4.

Also, for male donors, raise the fingerstick hemoglobin threshold to 13.0 based on the iron studies and the fact that 12.5 percent is at the lower normal range if not below the normal range of hemoglobin for men.

Also, administer a two-month supply of oral iron tablets to all donors with hemoglobin less than 12.5. With men who have had previous blood donation, if they don't respond after taking 60 days of iron, they probably need to go see their primary care physician. Males who have never donated blood before that come in with hemoglobins of less than 12.5 need to see a primary care physician. And males with hemoglobins less than 12 or females with hemoglobins less than ten all need to be referred to their primary care physician.

Evidence based recommendations based on this study.

We felt it was safe to routinely administer a two-month supply of oral iron tablets sufficient to replace the iron lost in one unit of whole blood to all whole blood donors. You could run a single ferritin level, and that would pick up your donors with hemochromatosis, but after that, giving iron was safe.

When a donor gives you a unit of blood, there are 240 milligrams of iron in that unit of blood. If you give them oral iron replacement, just one tablet a day for 60 days, the donor has an increased absorption of iron post donation, and they will absorb in that 60 days the equivalent of 236 milligrams of iron. So they give us iron and then we give them iron back, and sometimes a T-shirt, so they come out ahead of the game.

I would like to acknowledge my team at the NIH that has worked on this study, but especially our NIH blood donors.

Thank you.

DR. HOLLINGER: Thank you, Barbara. Questions?

DR. GLYNN: I wanted to know if you could comment on what now is routinely done at the NIH clinic. Do you give the iron supplementation?

DR. BRYANT: The donors that have continued to have the low fingerstick hemoglobins are given iron. It is just good routine medical care. Those that were enrolled in the

study, once you were noted to have low hemoglobin and iron depletion or deficiency, you just remained on iron. They are offered iron every time they come in and donate whole blood.

DR. GLYNN: What I was wondering is, has there been any follow-up on -- there is a difference when you are in a study and you have close follow-up. I am assuming that you were calling them on a regular basis, and you had a very good relationship with the donors?

DR. BRYANT: Yes.

DR. GLYNN: So do you have any idea now about, do they really take the iron supplement? Does it make a change in their ferritin? Have you had any follow-up, now that you are doing this operationally?

DR. BRYANT: We have just recently moved away from enrolling people in the protocol. We have closed the protocol.

I do want to address the point about calling donors. When I first started this protocol, I had no idea that we would have this many donors enrolled, so I thought, I'll just call everybody.

So I was calling everybody. When you came in and joined the protocol, you got a call from me about your lab results. Then when you came back in, you got another call. So as you can imagine, as this went on, I was making 25 to 30 phone calls a day, giving people their lab results. With the

normalization of the lab results, they just didn't want to know about it; it was the same thing it was last time.

So we started calling them -- after we had been in the study for about a year and a few months, I said I will always call the donors on their first sample, to let them know what it was. Then I would only call them if there was a change. So yes, this was labor intensive, doing all the calling.

My understanding, what they are doing now, is, when a donor comes in, they do offer them iron and get the lab studies and call them with the lab results. Then periodically they will check. I don't know if they have actually established it will just be once a year, or if they don't pass fingerstick hemoglobin a second time in their donation history, of course they get all new labs again.

DR. MC COMAS: Do you have data that examines how many of the donors have a primary care physician, or how often they are visiting them? Perhaps you have some from your data, and if you have any data to talk about the larger donor pool in general?

DR. BRYANT: If I understand, you want to know what percentage of these donors had primary care physicians. A lot of them did. Because we would offer them the lab results to share with their primary care physician, and also if their lab results were low, we would tell them to go see a primary

care physician. Sometimes if it was alarmingly low, I would get on the phone with the primary care physician and say, your patient came to try to donate blood today, and their hemoglobin is 8.5, can you fit them in today or tomorrow to be worked up.

So we did have a good relationship with some of the physicians in the community. There was from time to time someone who said, I don't have a primary care physician, and we would help them try to find one. Also, what I picked up in this study, there were a couple of donors that in the questionnaire, have you ever had black tarry stools, and they will say, yes, what is with that? I have been having that for two or three months. So we would help find them somebody if they didn't have a primary care physician, someone that could see them in the next few days. But we would refer them to a primary care physician with their lab results in hand.

DR. MC COMAS: I guess my comment is that people may say also that they have a primary care physician, but then they don't regularly, for whatever reason. So just something I comment on.

DR. RAGNI: That was a wonderful study, very, very exciting.

DR. BRYANT: Thank you.

DR. RAGNI: I noticed that previous cutoffs and also your suggestions address the issue of race. I'm sure

there is a reason, but I am new to this, so I would be very interested in why that might be, since there are apparently some differences.

DR. BRYANT: We saw some of the same results that were presented this morning, but African-Americans seemed to have 0.8 grams per deciliter, up to one gram per deciliter, lower hemoglobin values. We just saw that. Of course, they have a higher incidence of the alpha thal trait. But even with that taken out of the equation, they are just a little bit lower, which is even a bigger challenge, especially for African-American women. The normal range of hemoglobin for a woman is 11.1 to 15. So every day we are turning away absolutely healthy women in this range of 11.1 to 12.4 that can't donate. As we saw in the study, the majority were -- we saw more African-Americans in the low hemoglobin arm than we did in the control arm.

DR. RAGNI: I'm just curious. That would then lead to the next question, which is, should there be norms based on race, because they are different. I'm just asking, because I don't know very much about this.

DR. BRYANT: That would make sense to do that. However, this is America, and race is one of those questions. Are you African-American? I am biracial. So how would this fit in? The U.S. is a melting pot, so it is very interesting.

I did ask a lot of questions about ancestry, because I wanted to -- if I was going to do hemoglobin electrophoresis, did I really have a reason to do it. I would ask questions like, where are your ancestors from, and I would get some real interesting answers, everything from New Jersey to whatever. But we were trying to figure out the racial makeup. A lot of times it was, how do you identify yourself, which of these eight categories do you pick, and we would have the donors pick. We also had the Other and Unknown categories, so that was interesting; some donors didn't want to tell us.

So yes, it would in some situations make sense. But from an operational standpoint it is very difficult.

DR. EPSTEIN: I just wanted to comment on that point. Certainly FDA is also aware that stratifying by race makes physiologic sense. The problem is that it introduces a lot of operational complexity in the donor room.

The way we have sorted that out is that since the normal values are higher among Caucasians, you aren't doing harm rejecting donors whose normal level is lower, because you just don't collect from them at whatever cutoff. So it is not a donor safety issue, it is a missed opportunity if you will to have a more robust supply of bloods for antigenic variants, but it is not a donor health issue if you have a higher than otherwise needed cutoff.

DR. BRYANT: That's right.

DR. BRITTENHAM: You had a wonderful program of iron replacement. In the absence of such a program, would you still recommend changing the hemoglobin standard for women from 12.5 to 12?

DR. BRYANT: Yes, I would. The normal range of hemoglobin for a woman is 11.1 to 15. If we could rationally say that 12.5 for a male was okay, that is the lower level of normal. Actually, 12.5 on up, or 12.7 at a lot of hospitals on up, is the normal range for hemoglobin.

We have kind of estimated that a .5 gram hemoglobin drop is seen after someone donates blood. So if your thought is, you want to set a standard so if their hemoglobin drops you don't make them anemic when they walk out, you could go with the 12.0 for women, because even if they dropped a half a gram by giving a unit of blood, they are still in the normal range of hemoglobin.

Also, based on the iron studies, it did not show that there was an increased incidence of iron deficiency in that 12 to 12.4, as opposed to the 12.5 and higher.

DR. BOWER: Since you have operationalized this, could you comment on, if you have had any issues with the 21 percent of people who are intolerant, or any adverse reactions, and how you handle that.

I am getting to what Jay was talking about, about

operationalizing in the donor room, how you would expect other blood banks to handle this.

DR. BRYANT: Well, first off I want to say that I carried a Blackberry forever, and was available 24 hours a day to take all complaints on iron issues. They were given my pager number, given a card, told to call me if you have a problem, even if it is constipation I want to hear about it. So I was available. We switched donors from sulfate to gluconate if they had symptoms.

Now we don't even bother with the sulfate. We just go straight to gluconate. The gluconate seemed to do well in the study. Less people had reactions to gluconate right up front. When you talk to hematologists, it is the kinder, gentler iron, and most people just use gluconate right off the top, and it worked very well. So that is how that is handled.

So donors do call in with any kind of problem that they are having, and they are told to discontinue iron if there are any issues.

DR. BOWER: So it sounds like you have to have a dedicated person to administer this program.

DR. BRYANT: Right. Of course, this was a study, so we had a lot of personnel on board for this. Initially it was just me, and then we had some nurses that were involved that could take the phone calls and work in the donor room.

Someone has to follow up with these donors that had concerns. It was interesting; as I did this study, donors that were on the protocol would call and say, hi, it is Sue, and I want to talk about my lab results. They were so funny, they thought they ere the only one on the protocol. It took a lot of time and energy to do this.

However, what it showed was that you didn't have to necessarily call these donors with lab results every time you did labs. Not many of them called in with the complaints. Once we got them on the correct formulation of iron, they were just fine, and we rolled very, very smoothly. Once we eliminated the ferrous sulfate, now that we have gone to just doing it operationally, 22 percent aren't calling in and saying they are having trouble. So we are just looking at the 80 percent.

DR. HOLLINGER: Barbara, just for my own information, on terminology, it seems to me that iron depleted is worse than iron deficient, but that is not the way you used that. Can you help me to understand why iron depleted -- if you are iron depleted, I would think that iron deficient would come before depleted.

DR. BRYANT: What happens in a donor when they don't get enough iron, they deplete their iron stores first, and then their iron stores become deficient. They can't support the red cell production. So what we would see in

these donors is what we say in the control group. The ferritin would drop. It would be in the normal range, replete, and then drop to this depleted level, and then become deficient.

If you follow these donors, if they don't get iron replacement, then their hemoglobin starts to drop. In blood banking we don't really step into the hemoglobin drops, so you have probably gone through a depleted phase and then the hemoglobin starts getting affected. By the time you are deficient, they just don't have enough iron stores to support the red cell production that they have, so they are making smaller red cells, more anemic red cells. So deficient is worse than depleted.

DR. HOLLINGER: We talk about normal range here with quotes around it, I would think, for women. The normal range is set up by looking at women who are menstruating in general. Also, their ferritin levels are lower, you give them a lower ferritin level than men do. It is almost arbitrary. You say women have a normal range of say 12 and a half, men is 13, 13 and a half. But I think we have set that up a little bit because of the grouping of women who are menstruating, and I'm not so sure that these normals are -- whether you would really call them normal or not.

DR. BRYANT: If anything, I was on the conservative side. We were probably on the lower side, calling them iron

deficient. Some people indicate that by the time you have a ferritin less than about 25, you are iron deficient.

If you talk to neurologists who are treating restless leg syndrome, which is something else that we did study in this group, restless leg syndrome and pica, neurologists consider you iron deficient if your ferritin is less than 50.

We know that low ferritin levels can exacerbate or cause restless leg syndrome. So if you go to a neurologist with symptoms of restless leg and your ferritin is less than 50, you are on iron. You are on iron several times a day until you get your ferritin up before they will evaluate you for these issues.

So what is really iron deficient? I just took the normal range, what is reported out in our laboratory, and if you were below normal you were iron deficient, and then I set up this iron depleted category, which was like below normal range. But that is true.

MS. BAKER: Great study, thank you.

DR. BRYANT: Thank you.

MS. BAKER: In your slides, perhaps I missed it, but do you have the age ranges or percent menopause within your controls for the females?

DR. BRYANT: Yes. On the slides that show -- that was a question that we did ask the women. We asked about

menstrual history. We also asked about duration and intensity of menstrual cycles. I referred quite a few women to the ob-gyn. This is the percent menopausal in the group. So even in the control group, three percent menopausal, but even down here in the lower hemoglobin group we had four percent menopausal here.

Something we found out pretty quickly in the menopause question. A lot of people go through menopause, that that perimenopausal time area they could have had very heavy menstrual cycles. So by the time they hit menopause they are no longer having monthly blood loss, but they have probably sustained quite a bit of blood loss prior to that. It could take years until they actually replenished their iron stores after being iron deficient if you are just doing it by diet.

DR. HOLLINGER: Thank you. We will move on to our third speaker this morning, Dr. Richard Cable, American Red Cross, who will give us a talk on new results from a multi-center prospective study of donor iron status.

Agenda Item: New Results from a Multi-Center Prospective Study of Donor Iron Status

DR. CABLE: Good morning, Dr. Hollinger. I still wish I were Dr. McCullough.

I am here to present the results to date, preliminary results for much of the study, of the REDS-II

iron status evaluation.

A couple of disclaimers. One is, I will disclose for Simone that she is an author of this, so you will have to take her comments with that in mind.

Also, I just wanted to mention, when we presented this in September 2008, the study had just finished enrolling subjects -- I will explain that -- and we presented very preliminary enrollment data which I am going to complete today, and then start to talk about some of the longitudinal data, which is really the core of the study.

REDS-II is a multi-center research program funded by NHLBI. Its purpose is to conduct studies on the safety and adequacy of the blood supply. It consists of six participating U.S. blood centers listed here, a coordinating center at Westat and a central laboratory, Blood Systems Research Institute lab.

RISE or the REDS Donor Iron Status Evaluation Study, is a longitudinal study involving all six centers. It is designed to evaluate the effects of blood donation intensity or basically frequency in interval on iron and hemoglobin status, so it is very much on target in its objectives to what you are talking about today.

We recruited two cohorts of blood donors that when added together don't necessarily reflect the U.S. blood donor population, as you can see. The first group, we would have

liked it to have been a first-time donor cohort, but because this was a study that required significant follow-up and known likelihood of first-time donors not to always return, we wanted to supplement the N that was available with donors who had not given blood for more than two years.

We called them reactivated donors. They weren't specifically recruited into the study, but rather when they showed up after not having been at a blood drive for two years, they were recruited into the study, with the logic on our part that their iron status would have returned to normal or near normal status. As I will show you later, they don't appear to be any different than first-time donors in their blood status. After three years rest they appear to be recovered from the insult of iron the blood donation represents.

The second cohort was a frequent donor cohort, the ones many of the studies have talked about, who had donated at least twice for females or at least three times for men, in the previous year.

Both kinds of donors agreed in the informed consent and informational material to donate frequently at the same rate, twice or more a year for the women in the study and three times or more for the men in the study. The theoretical time of follow-up was anywhere from 15 to 24 months, because we had a six-month enrollment period and we

had a six-month final visit period, and depending on how it was lined up and so on, we ended up with 15 to 24 months on the study.

We studied iron and related variables at the baseline visit and at the end of the study. In addition we tried very hard to track as much as we could for the interim visits that occurred between. We were able to measure all donation outcomes because we record outcomes for all donors in REDS. As I will show you, we were able to get lab samples from many of these donors, and for budget reasons we had to target a subset of those samples for additional iron studies in the interim between the first and the final visit. Those were all the first-time reactivated donors who have special interest, donors who were hemoglobin deferred, and an additional selection of female repeat donors, primarily focused on a separate study I am not going to talk about, which was to evaluate the Advia hematology analyzer. Some of those particular sites sell indices as laboratory measures, but I am not going to mention that further today.

We gathered just a raft of data on these donors because our logic was that rather than just study donors as a group, we wanted to look at things about donors that made them different from each other. That is, we wanted to look very much at donor polymorphisms, donor differences in lifestyle and so on. We measured a whole variety of things

which we are now being challenged to try to analyze, because there is a whole lot of data there to analyze.

On every visit we recorded the fingerstick hemoglobin/hematocrit that was done by the six operating center staff, regular staff. The only change in routine was that copper sulfate was not allowed for entry in the study. You had to have a quantitative measure. But they used the usual quantitative measure. If they were doing copper sulfate at the time, this was the method that they used to re-test copper sulfate donors. So it was a routine quantitative measure.

There were four different devices used among the six centers, so there was quite a diversity of qualification schemes.

We drew a venous sample, and on that sample we used a HemoCue analyzer for the purpose of uniformity that was applied to venous samples, not to fingerstick samples. Two of the centers used another HemoCue device for fingerstick values. We used the HemoCue rather than an auto analyzer because we thought that provided more uniformity across all six centers. The research staff were trained to do the HemoCue analysis in the lab, usually the next day after the collection.

We also froze plasma aliquots. Those were sent to Arup Laboratories, and they performed plasma ferritin and

soluble transferrin receptors on these samples of interest. We also formed a plasma repository which has continued to be available and will be used for additional studies.

We wanted to look at genetic influences. We identified two groups of polymorphisms of interest. One was hemochromatosis. We chose to study the two most common polymorphisms, C282Y and H63D. We also studied a transferrin polymorphism that Boydler's lab had identified that was associated with a higher incidence of iron deficient anemia in women. We thought that might have some influence on the ability of people with these polymorphisms to donate blood and maintain their iron.

We gave a donor a rather extensive questionnaire in which we asked about their donation history, both lifetime and in the last one and two years. We asked about lifetime and recent smoking history. We didn't do a formal dietary history because we felt that was too overwhelming, but we did ask about consumption and frequency about a whole bunch of dietary items that are thought to be high in iron.

We asked about self-prescribed multivitamins, minerals and iron supplements. We asked about use of aspirin and why they were taking aspirin, and for women only we asked about menstrual status, the nature of their periods and frequency, and a detailed pregnancy history.

This was the RISE enrollment results. This has

been cleaned up a little since we presented it to you in September. It is only off by about 15 or so donors.

In the four different cohorts, we achieved the recruitment targets. Overall we enrolled 2425 donors. As I said, these are not together representative of normal blood donors coming in. We were completely missing the routine blood donor, the casual blood donor, but it is what we are studying and what we are going to show you.

When we looked at all the enrollment measures on the 2425 samples, we showed them as medians with two and a half to 97 percent ranges, because several of these parameters didn't normally distribute, and we thought it was more generally useful to show it as a median and range.

You can see that in black the two sexes showed what you would expect for the differences in hemoglobin, ferritin and what we are measuring as a measure of iron deficient erythropoiesis. I will talk about this more, the logarithm of a soluble transfusion receptor over the ferritin.

There is the normal sex difference here. In both sexes, the frequent donors had changes in the directions, all of them statistically significant, of iron depletion and/or lower hemoglobin, albeit not very much for the hemoglobin, as Dr. McCullough had mentioned.

I wanted to avoid scrupulously the argument about iron depleted, iron deficient, because the literature is just

a rat's nest, at least we thought it was. So we coined our own terms, and we are going to ask you to try to stick with us on this.

We defined a person who was really iron deficient as having a plasma ferritin less than 12. We didn't use gender specific values, because we felt that if women are more iron deficient than men to start out with, we are still looking at iron deficiency, and they are still iron deficient, so we should compare them against a standard. Most of the literature would suggest that under 12 you don't have bone marrow iron stores and you pretty much don't have any iron in your stores. It is a fairly specific finding, and it is pretty easy to measure.

We did use plasma rather than serum. Plasma reads a little lower, so that might make some differences with other papers.

We defined iron deficient erythropoiesis as the logarithm of sTfR over ferritin of above the 97 and a half percentile. We didn't use a one-tailed five percent test, we used a one-tailed two and a half percentile test. We used as the reference group first-time men. We didn't use first-time women because so many of them were already iron depleted. Again, we were looking for a population that almost certainly did not have iron depletion at all or loss of iron at all, so we used our first-time male donor cohort to get the normal

range. This turned into a value of 2.07.

A number of other papers have used numbers in the 2.3 and 2.4 range, but many of them used normal range derived from a mixed gender population. We thought we should stick with men, and it is an interesting argument.

In any event, this ratio has been shown to best correlate with other measures of iron deficient erythropoiesis in the bone marrow and other measures of erythropoiesis.

I showed you data somewhat similar to this, a little bit differently conveyed, in September of 2008 as my last slide, to show you that the incidence of low iron stores was extremely high in blood donors.

Here are the two cohorts with the percentage of donors in the cohorts at baseline and enrollment that had values below these numbers. For first-time males, none of them had ferritin less than 12 and two and a half percent of them had iron deficient erythropoiesis, but that was how it was defined, so you would expect two and a half percent of normal to be outside of normal, and so they were.

You can see that first-time women as we know are more likely to be iron depleted, so six and a half percent had ferritin under 12 and 24 percent had an abnormal log. We call it a log RF ratio, and I will too for the purpose of getting it to roll off my tongue quickly during the talk.

When you look at the frequent cohorts, it is really quite astounding what happens even to men and especially to men. The prevalence of AIS or IDE as defined here starts to approach that of women, and is in fact higher than non-blood donor women. So being a frequent blood donor makes a man more like a woman, I like to say.

I think one of the take-home messages here is, if we are going to talk about iron depletion, we have to be gender neutral here, because men have a right to be iron replete as well as women. I say that with all respect to the distaff side.

This kind of chart figure has been shown in a number of papers since the very excellent study in 1981, which I recommend people read, the Toby Simon *JAMA* article. This is the grandson of a granddaughter of. I showed in September 2008 Australian data which showed up in your briefing paper, and you can't really tell the difference between these graphs. They are virtually identical graphs. One graph is a graph of the geometric mean ferritin against the number of donations in the past 12 months, with zero being our first-time reactivated cohort. Then donors who on official records donated one, two, three, four or more greater than or equal to five donations in the prior 12 months before entry.

Men start out much higher, as we showed, but rather

quickly in their giving blood in the last 12 months, start to look an awful lot like women, as I showed before. It is interesting, how quickly the groups come together after two donations or three donations in a year.

I think that is very relevant to the interval question and the duration question you are asking yourself. Just that little bit of donation, which would easily meet all of the standards that we have been discussing, men still look a lot like women when they donate at that level. I think that therefore the effect on women of iron at that interval is probably something similar; a little bit of blood donation adds a whole lot to your iron. That is one of the themes we developed.

As Dr. McCullough mentioned in the earlier questions, there is not too much effect on hemoglobin, although you can see it occurring more clearly in men. There is a drop of a half a gram in men and only a tenth of a gram in women in the hemoglobin between frequent and first-time cohorts. You can see here the same early drop followed by maybe a little bit more continuous drop in men.

Since the last presentation, we have done considerable modeling with univariate analysis, and then taking more statistically significant results and putting them into a multivariate model. We have modeled every statistically significant result from the questionnaire from

our testing, from donor demographics, from donation records, that we can think of, and we put them all into a multivariate model. I am going to show you the results of significant odds ratios in the multivariate model that we found. This is all from the enrollment data, before we started the study.

If you look at the most significant result, it was clearly the donation frequency in the last two years prior to enrollment. We used two years for technical reasons, but you would have seen the same result with one year.

First of all, I mentioned that these two cohorts, the first-time, with no donations and the reactivated donor with no donations using the first-time as the reference group, there is no statistically significant difference or measurable distance between these two. Therefore we felt comfortable combining them into the same cohort for most of the rest of the analysis; you will see it combined.

When you look at the repeat cohort, with increasing number of donations in the last two years, you get some pretty impressive odds ratios, particularly for iron deficient erythropoiesis, but even with ferritin less than 12. So a male who gives ten or more times in two years has nearly 20 times the odds of a non-donor or first-time donor of having a ferritin under 12, and 50 times the odds of having iron deficient erythropoiesis as we defined it in this study, and a rather steady change in the odds ratio with

increasing donations.

Looking at some other variables that were relevant, one was age, but only in women. We had to nest age within gender. There is essentially no influence of age on iron stores in men, but a substantial relationship in younger women of both kinds of iron depletion in women. So that obviously is related to menstruation and is a manifestation of something we well know.

If you take out age in women and also take out menstrual status, and we will be talking about that in a moment, the remaining gender component, the effect of gender absent those two factors, is rather modest. In other words, if women don't menstruate, they are an awful lot like men from the point of view of iron status.

Weight was somewhat important, but only in the very large donor was the reduction in the risk, as you would expect, since a unit of blood represents less of their total body iron stores. But there is a tendency that it is probably a continuous function across weight.

Other significant enrollment variables, and I will pause for a moment on the second one here. We studied smoking. We expected that perhaps because smoking raises the hemoglobin it might allow people who are more iron depleted to donate, to fall above the donation threshold, even though they were iron depleted. We would have expected therefore

smokers to be more iron depleted. In fact, we found the opposite. Smokers had lower odds for iron deficient erythropoiesis, but not for AIS.

Upon further reflection, it seems like the sTfR measurement but not ferritin is affected in smokers, and there have been articles to that effect. So I think this is an artifact of the test of soluble transferrin receptor. It is an unknown reason, but smoking had an effect on it. So I don't think that is necessarily a reflection of iron stores in blood donors, since it didn't show up in the more specific AIS measurement.

We asked donors if they took multivitamins with or without iron and/or separate iron supplements or separate mineral supplements. We added together all answers that suggested they were taking some iron in a pill form as self administered. Fully 40 percent of these donors already were taking iron. That might tell you something about the effectiveness of supplementing with iron when 40 percent of them already are without your having said anything. I think that is a very interesting observation.

Donors who did take iron are only slightly less likely to have the more severe iron depletion, AIS, with an odds ratio of .7. There was a similar non-significant tendency for IDE as well. So there is a minor benefit from taking on your own iron supplements as a blood donor. We

found what you would expect. In having two abnormal HFE genes, whether it was mixed or homozygous for either variant, but it was a rather modest effect and we saw no impact of heterozygosity for either gene. There have been some thoughts that heterozygotes might be better able to donate blood; we saw no evidence of that.

Pregnancy or pregnant status as you would expect correlated quite nicely with the tendency to AIS in a statistically significant difference in IDE. At one center, the odds of having both AIS and IDE were about twice the other centers. We haven't quite worked out why that might be, but there seems to be a center effect as well.

So these were the significant variables in this model for iron depletion from the enrollment data.

I now want to turn our attention to very early analysis of longitudinal data. These donors started after the enrollment visit, to remind you to donate two to three times a year, males and females, if they were following the study protocol. I will show you how many of them did and didn't. We ended the study with a six-month period ending in January 2010, in which people gave a final visit. At the final visit, we made sure everybody had lab samples and they completed another questionnaire to ask them about changes in some of the more volatile measures like, have you started or stopped smoking, have you started or stopped taking iron

supplements, and so on. We are working hard on that data.

The slides I showed you to date on the enrollment data were done with the analysis. The article has been submitted, and it was just recently accepted in *Transfusion*. So we expect to see this in press in four to six months, I was told. As soon as the galleys are proofed and all that, we would be happy to share it with the FDA staff. It has got a lot of detail, it is quite data rich.

But we are early on in the longitudinal data. This is a very preliminary analysis for this meeting, and I hope it doesn't disappoint anyone with its current status.

Here is what happened to these four cohorts over the follow-up period. As you would expect, we dropped out 20 to 30 percent of the first-time cohorts. They just didn't come back at all. So we had an enrollment data point and no other data on these donors. Very few of the frequent donors however fell out, so that 96 and 97 percent of the frequent donors kept coming back. I guess that is no surprise to those of us in blood centers. Whereas we had 70 to 80 percent donors with one or more visits.

For all the donors who came back at least once, the average return visits were 3.3, 3.1, somewhat higher, 5.4, 5.5. The average time in study, and that would include someone who came back once after 12 weeks and then never came back again, these weren't the people who completed to the

final visit, these were anybody who came back at all, the average time here was about 2.7 donations per year of time and about 3.8 donations per year here. We hesitate to put that in your list of intervals that you are thinking about because A, it is a completely different population and B, this really does represent the ongoing blood donor. It represents people who dropped out of the donor pool mixed in with them.

These donors came to visit 12,695 times. It gave 11,381 donations of either whole blood or double red cells. The remainder of the visits were deferrals; I'll get back to that. Of the 11,381 donations, ten percent were double red cells, 90 percent were whole blood.

These visits, the 12,695 visits, consisted of the enrollment visits I mentioned. I want to emphasize that we only enrolled accepted donors initially. So we have no data on deferred donors de novo. No deferred donors were included in all that data I had just been showing you. So you really can't use the enrollment data to say much about the enrollment cutoff, because we had no data below the hemoglobin cutoff here.

There were 1334 final visits, so a little over half of the donors managed to come back and schedule a final visit, complete a questionnaire, and we have a full data set. So that group will be subject to a different analysis than I

am about to show you now. We had nearly 9,000 interim visits, where often they didn't identify themselves in the study, so sometimes we didn't have lab samples and so on. But we knew whether they were accepted or deferred when they donated through our regular REDS-II database that recorded all visits to the six centers over the period of time.

The deferrals, 1200, consisted of 945 hemoglobin deferrals, 84 percent female, 16 percent male, maybe a little bit more men than you had seen earlier. I'm not sure why. 268 other deferrals.

To simplify the protocol, we told people who were deferred for other than hemoglobin, thanks, but you have to fall out of the study now. So some of those people that only came back once or twice would have liked to continue, but it was too complicated, tracking people who were deferred for three months and when they came back and so on, so we chose not to include them. But all the hemoglobin deferrals were asked to come back, and many of them did.

Finally, in order to supplement the final visit, 101 of the final visits were sampled only, but because we weren't following up the impact of blood donation going forward, it didn't really matter if they only gave us a sample on that final visit.

Then looking at the samples we have, just so you know the richness of the data source, we have venous

hemoglobin and iron measure in all 2425 of the enrollment visits. Of these 8900 interim visits, we have about 6700 samples, so we have venous hemoglobins done on all of them, but for budget reasons we only did 2700 iron measures, and I mentioned those three groups that were targeted for iron measures early on in the talk. Of the 1334 final visits, we have samples and data on almost all.

Interestingly enough, we did ask that people who were hemoglobin deferred to allow us to take a sample that day or within four weeks of the deferral, and we were successful about half the time in getting them to agree to give a sample. So we could tell those hemoglobin deferrals what the iron status was of half of them.

What we have to present today is a model to predict hemoglobin deferral. This is an attempt to use the kinds of information that you would routinely know at a blood center. It would be an attempt to use the data you have today to predict the deferral today. The data you have today includes how long it has been since your previous blood donation.

The model included gender, age, race, weight and how many days since your last red cell donation, and how many donations total of red cell in the last 24 months. Finally, we recorded whether the last donation was a single or a double red cell as another variable.

We used a repeated measures logistic regression

model. For the statisticians, I have got a lot more fun words that I don't understand at all, but I could spit it out if I was tortured to death. But the objective of the model is to account for the fact that multiple donations and therefore multiple measurements came from the same donor. So there was a within-donor correction for the multiple measurements when one donor gave more than one visit.

This model used those variables I mentioned, the ones that are available at a blood drive, to try to predict whether that donor would be accepted or deferred for hemoglobin that day. As you can see, for race you would see what we already know, which is that blacks have a greater odds of being deferred than Caucasians. There is a little tendency for Hispanics, but it wasn't significant.

Women, and we had to go with weight and gender segments for this comparison, because this was nested within gender, but women this size and age had seven and a half times the odds ratio of males of that size and age. You have seen similar results with all the other strata.

Looking at age again, very similar data to what we saw in the cross-sectional study. No effect of age in men, a little bit different result in women. Young women are more likely to be deferred. Interestingly, older women were somewhat less likely to be deferred than the reference group which was 40 to 49-year-old women.

Of most interest to this group I know is the days since last donation. We divided it finely for you into four-week segments. What we observe is a definite relationship, but the odds ratios are somewhat modest. You will notice, there is a suggestion that the odds ratio fall off rapidly as these intervals get longer, go from 2.3 to 2 to 1.5 and finally non-significant at 20 to 24 weeks versus more than 32 weeks.

So we decided to look at the raw data on the next graph. This is unadjusted data, because this kind of model isn't easy to accommodate non-categorical linear use variables like days or weeks are hard to put into a model correcting for the repeated measures for donors. I won't get into it any farther, except to say we haven't got that data yet.

But we do have the raw data to show you. I think it is kind of interesting that this is now the raw hemoglobin deferral rate. As we know, women are deferred at a higher rate than men and the first-time donors at a higher rate than women and frequent women.

There is a relationship in frequent women, in fact, in most of the groups, towards lower deferral rate, the longer you wait between donations. But the effect is far from cliff-life; it looks almost continuous, with ups and downs that are probably statistical in nature. We aren't

quite sure what to make of this upswing at the end. But we don't see in here any magic number to choose, but if you wanted to prevent deferrals, you would choose this interval. Somebody did mention that we would expect fewer deferrals if donors wait longer. This says that, but it doesn't say at what point you should draw a line.

So to summarize this second model, of 9900 return donations during RISE, nine and a half percent with hemoglobin deferrals, and this model predicted the odds that any visit following the enrollment, we weren't able to assess the odds of deferral during the enrollment visits, because we only accepted donors who enrolled.

The following donors were significant: Days since last donation, race, gender, age in women and blood center. I didn't show you that data, but there were some variations between blood centers in hemoglobin deferral rate, which you would expect.

But the following variables were not significant: Weight, interestingly enough, the number of donations given in the last 24 months, a longer term measure of blood donation intensity, didn't seem to have an effect on whether you would get deferred as a donor. And also interestingly enough, it didn't seem to matter whether your previous donation was whole blood or double red cell; your deferral chances were the same. Although keep in mind that you had to

wait 16 weeks if you were double read by regulation. I will talk a little bit about that. That was a little bit of a surprise.

To wind it up, conclusions from our original enrollment data that I showed earlier. Frequent whole blood and red cell donors have a high prevalence of iron deficiency. Ferritin levels decrease with increasing donation frequency but more markedly so in men. Donation intensity, gender, weight and age are the most important independent predictors of iron depletion, measured in our terms AIS and IDE, and reducing the allowable frequency of blood donation would be likely to reduce the prevalence of iron deficiency among donors. The data suggests it might help to supplement donors with routine iron supplementation, but certainly doesn't prove that.

Then the preliminary conclusions to the longitudinal data, which is very limited at this point. The most significant predictors of hemoglobin deferral at a visit appear to be fewer days since the last red cell donation, but not the number of red cell donations in the last two years, being female, being black, and if you are a woman, being younger.

I wanted to just spend the last couple of slides talking about --

DR. HOLLINGER: Dr. Cable, could you come to a

conclusion quickly on this?

DR. CABLE: Yes. These are the analyses we are planning to do in the future. Maybe we can talk about that if there are questions about it. We also are planning some analysis related to use of laboratory measures.

Finally, what we hope is that when we are done, this data will be able to be utilized to project the impact of various guidelines on iron status of donors, potential hemoglobin deferral and the adequacy blood supply, which is what this committee is interested in.

Thank you.

DR. HOLLINGER: A very interesting study. Any questions from the committee for Dr. Cable?

DR. BIANCO: It is going to be a fundamental study for all of us, but in essence the question that we are trying to answer is not just the potential for hemoglobin deferral, because the hemoglobin deferral here is protecting the donor, and at what level. So if the potential donor doesn't donate, we are doing the right thing. So what would be that cutoff point? And you will be able to derive that from your data.

DR. CABLE: One of the first models we hope to do is a model very similar to what you saw, but that would predict the iron status, not the hemoglobin deferral status, at a visit. So it is also the question of iron depletion.

DR. HOLLINGER: Any other questions from the

committee? Thank you, Dr. Cable.

The fourth talk then is by Dr. Anne Eder from the American Red Cross, who will discuss proposed changes to the hemoglobin and donation interval criteria for whole blood donation and projected impact on current American Red Cross collections.

Agenda Item: Proposed Changes to the Hemoglobin and Donation Interval Criteria for Whole Blood Collections and Projected Changes on Current American Red Cross Collections

DR. EDER: I think I can make up some lost time. I am going to present what we project the impact to be of the proposed changes on the current donor base.

We were asked these four questions. One was split into two parts. What would be the impact of changing the minimum pre-donation hemoglobin from 12.5 which it currently is for both men and women to 13 for me or 13.5 for men, or lowering it to 12.0 for women. What would be the impact of changing the interdonation interval from eight weeks, which depending on when you start donating in a calendar year, turns out to be about six to seven times a year, to 12 weeks or about four to five times per year for men or to 16 weeks or about three to four times per year for women.

This is the balance sheet that I am going to fill in during this talk. But I will say at the outset that we

are imposing new rules on a static data set, so it is important for us to keep in mind that we didn't try to account for compensatory changes that would occur in a complex system or identify whether there were dynamic interactions between the changes. Regardless, I will present what we feel are the best estimates of what these changes would have on the blood supply, using the available data sources.

For the sake of time, I will just say that the data that you are going to see for the interval projections were -- we did it both ways, but I will present only the frequency, that is, modeling men to have a fractional frequency of about four to five times or 4.3 times and women three to four times per year.

What are the available data sources? The American Red Cross collects about 43 percent of the nation's blood supply in these geographic areas, distributing more than six million red cells, so encountering more than seven and a half million presenting donors.

All the hemoglobin values that you see are fingerstick HemoCue values in the presentation.

To address the first two questions of the minimum hemoglobin, this slide shows the largest available data set which was more than 700,000 presenting donors in our New England region, data collected by NHLBI, the REDS-II data

group. This data set represents more than 95 percent of not only accepted donors, resulting in a successful donation, but also deferred donors. So we were able to look at the distribution of more than 300,000 presenting males and presenting females.

We used these distributions -- this is the 12.5 line, so increasing it for men to 13, this would represent -- I will show you on the next slide that this represents about four percent of presenting donors, increasing it to 13.5, this represents about ten percent of presenting donors. For women, lowering it from 12.5 to 12.0, this represents about five percent of presenting donors. That is shown on the next slide.

So we took those projected for men, the projected additional deferral that raising the minimum hemoglobin would have on our calendar year donations in 2008 for men. Here is that four percent. So we project that it would reduce the number of donations in the system by more than 140,000. Increasing it to 13.5 reduces it by more than 380,000.

For women, lowering the minimum hemoglobin to 12.0, the projected gain in presentations is about five percent. You would reduce hemoglobin deferrals by an estimated 40 percent, by at least 40 percent, possibly more. This does project out to a gain in more than 190,000 or almost 200,000 donations.

Here is the balance sheet. We will come back to it.

Looking at interval, which we modeled both as changing the interval which effectively changes the frequency with which you let donors donate. This is data from the American Red Cross, a cohort of whole blood donors in calendar year 2008, where a donor was identified as first donation and followed for 365 days.

The breakdown of the number of annual donations, donors who give once, twice, three, four, so forth shows the percentage of donors that fall into these categories and the result in donations that they give.

By changing the frequency for women, it would result in about 11 percent of donors and would result in a decrease of more than 260,000 or about seven percent of donations. For men, about eight percent of donors or more than 150,000 or about five percent of donations.

I told you I would get us caught up. Here is the final balance sheet with the numbers I just presented and the projections presented as a percent of the gain or loss, so it can be applied to other blood centers if desired.

Increasing the cutoff for men from 12.5 to 13 would result in a decrease of four percent. If that occurred with a decrease for women it would result in a gain for five percent, so it would be just about a wash. However, changing

the donation frequency would have a profound effect on donations.

In the American Red Cross system, this is what I just said, changing the minimum hemoglobin requirement to 13.0 for men and 12.0 for women is predicted to have little effect on balance of total collections. Changing the donation interval would be predicted to have a significant detrimental effect on collections.

I think I got us caught back up. I am happy to take questions.

DR. HOLLINGER: Questions for Dr. Eder?

DR. BRITTENHAM: You emphasized that you were considering just the static consequences, as you are taking the results under the present system and then trying to estimate from those to what the future system would be. But that doesn't take account of what the effect of changes were to have on subsequent donations.

So what I would like to focus on is the effect in women. Iron deficiency is primarily a difficulty in women who give blood frequently. So if you decrease from 12.5 to 12, then initially it is true you will get a return from that, because women who would have previously deferred you now accept.

But many of those are already iron deficient, so they won't be able to replete their hemoglobin by the time of

the next donation. So then they will be deferred. So do you have any sense, since you have been working on these figures, do you have any sense of how much of an impact that would have?

DR. EDER: I think the previous two speakers presented some data that tries to get at that. To answer your question, we thought about and talked about that there may be an interaction. I think that we have seen some evidence that there isn't one, either because most donors don't come back four, five and six times. Our model is what it is. We imposed new rules on a static data set, so it is entirely possible.

DR. GLYNN: I would say that the RISE data may help in the future, trying to figure out that question for a particular hemoglobin, like those who were deferred. We could look at that subset and then see what happens to them.

DR. BRITTENHAM: That would be very helpful.

DR. GLYNN: We just do not have those data yet. I agree, personally I think there is an interaction between hemoglobin cutoffs and interdonation interval. I don't think you can look at one without looking at the other, and take both of them into account.

DR. MC CULLOUGH: Anne, your change in hemoglobin for males and females pretty much balances off, which presumes there are roughly equal numbers of those donors.

I'm sure you know male versus female total donors. Is it about the same?

DR. EDER: It is about 50-50, yes.

DR. MC CULLOUGH: The other question may be related to the conversation. I didn't want to take the time to ask Rich about the slide that showed that multiple donations of ferritin levels fall fairly quickly, and by three or four donations the male and female values are almost the same. So would that affect the thinking about the last question?

Also, Rich, did you make everybody iron deficient? It looked like those values were more like around ten after three or five donations. So would that affect your thinking about how the status might change? I'm not sure what the question is exactly.

DR. EDER: I agree. You raise a good point that needs to be further considered.

DR. HOLLINGER: Richard, do you want to respond any further to that?

DR. CABLE: Well, I think we would expect a reduction in the hemoglobin deferral rate if we stretched it out, but you wouldn't expect a reduction more than twofold, I don't think, observation of two. I'm not a statistician. Somebody help me out here. If the odds ratio is two, that means the odds of being deferred are twice if you give in eight weeks than in 32 weeks. That suggests to me that no

matter how much you stretch out donations, you are not going to recover more than -- simpleminded, I know -- half the deferrals. Am I right about that?

So the deferral rate wouldn't go to zero. You wouldn't cover all these donors. But exactly how much I think you would have to model in a more robust mathematical way somehow.

DR. GLYNN: The potential loss of donations appear to be large, at least for the interdonation interval. Can you discuss a little bit what could be done if that really happens? What kind of things can you do?

DR. EDER: Recruitment, understanding donor motivation, increasing recruitment are currently our ongoing challenges. So I think we would need to identify -- we are collecting from more high schools, which did not really make a huge contribution. So I don't think you can lower the donation age any more to identify new donor groups.

I think recruitment is a challenge. I think we need to be vigilant to reduce unnecessary deferrals that don't contribute to donor safety or recipient safety. I think any unnecessary deferral not only is an immediate loss, but a future loss as donors become discouraged. Understanding lapsed donors, the work that you have done to understand the motivations of lapsed donors, to understand and explore what are acceptable incentives, to consider

possibly eliminating the current requirements for variances for donors with hemochromatosis who otherwise meet all eligibility standards. Those are a few things that come to mind.

DR. GLYNN: Can you comment on iron supplementation? Would that be something you would consider?

DR. EDER: I do think that iron supplementation -- I think the studies that have looked at it haven't shown -- either haven't looked, or the studies that have looked haven't shown a significant yield of additional donations. So perhaps if it was studied more carefully, in more detail. But the studies that have looked at it don't see a huge return from donor supplementation.

I have to say as a blood thinner perspective, it also seems of concern that you are trying to supplement them and get more blood out of them and keep them one step ahead of getting depleted. But it is possible. It hasn't been studied. The studies that have looked at it haven't seen a huge return with respect to donations.

DR. BIANCO: I just want to remind ourselves of the presentation by Dr. Illoh initially. This is looking at the entire population, but a population of frequent donors is biased towards the O negatives, towards the U donors and those donors that become very important in the collection

system.

I wonder if we did an analysis of these data, looking at blood groups, how much different things could look with the higher frequency donations.

DR. BRITTENHAM: I do want to make a comment about the efficacy of iron supplementation in increasing donations. In at least the program that we used, where the intent was not to identify donors who had become iron deficient and then treat them, but to prevent iron deficiency by replacing the iron that women gave. This was restricted only to women, that women gave at donation to replace that iron. We were successful in increasing donations per donor by one per year. I think that is among frequent donors.

Now, this was restricted to frequent donors, to those who provide an important component of the total blood supply. It was able to prevent iron deficiency and increase donations by one unit per donor per year.

DR. EDER: Thank you for pointing out what I failed to. I do think a focused targeted approach has demonstrated benefit.

DR. HOLLINGER: Any other questions from the committee? Just to clarify for myself, from the American Red Cross standpoint, and I will ask also Celso from the ABC standpoint, do you see a need for change from the current standards? And if so, why do you see that there is a need

for a change? For what purpose?

DR. EDER: I can share with you my personal opinion. Maybe I should ask Dr. Richard Benjamin, the Chief Medical Officer of the American Red Cross, if he wants to step up to the microphone.

DR. BENJAMIN: Richard Benjamin, Red Cross. Thank you for handing it on, Anne. I'm not sure I am very thankful.

I think we are all trying to do the right things for donors here. I think we look at the medical issues and say, first of all changing hemoglobins to appropriate levels makes sense, then trying to maintain iron repleteness also makes sense.

I think we should also remember, how much evidence do we have of actual adverse outcomes for donors for this iron insufficiency? We don't have a lot of data showing that the donors are adversely affected. We are adversely affected because we defer them.

So I think we need to be circumspect about making major changes that will impact the blood supply, based on laboratory criteria rather than actual measured clinical outcomes. I think we should do the right thing. We should find ways of balancing the effect on the blood supply while serving our donors in the correct way.

My personal view on interdonation interval, if I

was faced with a ruling by the FDA that we should extend donation intervals or reduce the number of donations per year, I would much prefer to see that framed in, the blood centers should put in policies and procedures that protect donors' iron levels. So give us an option to give iron, give us an option to do ferritin levels, give us an option to restrict interdonation intervals. Don't mandate one solution to the iron depletion problem. That may have a massive effect on the blood supply.

So we would like to see those options, and work out the ones that make the most economic sense to us, be it recruiting new donors, be it giving iron supplementation. We would like to work out what is good for the Red Cross. On the other hand, the 78 blood centers, they may have different solutions to the problem that may be just as effective at protecting blood donors.

So I would like the options to be handed on to us, not to be mandated by the FDA.

DR. EDER: If I could just add, I do think Dr. Benjamin has identified that there are a number of options. I would only add, please keep in mind that I wish we could function like the NIH, but I don't want seven million donors calling me. So the approach is one with a public health perspective.

DR. HOLLINGER: Celso, do you want to comment?

DR. BIANCO: No, I don't want to comment, but I will. I essentially agree with what has been said by Anne and by Richard, that some flexibility is needed there.

We want to protect the donors. We were very involved with Dr. Brittenham a few years ago in 2001 on the iron replacement effort and the consensus approach that was taken there. We haven't found a practical way. The confounding thing there a little bit was the attention that was given to these donors. We haven't found a system, although a few have tried, to provide that same attention so that they would comply with the replacement recommendations.

But I think that it is very important to see how fast Dr. Cable and the whole group from REDS can provide us with the additional data. We are not seeing clinical outcomes. Ultimately the iron deficient donor will have lower hemoglobin and will be deferred. So we are getting close to the danger zone, but in essence ultimately I think we are deferring the majority of the donors that should not donate, where it would represent a risk for them.

DR. HOLLINGER: Thank you, Celso. I think we will go on. Thank you, Dr. Eder. We will finish up with the FDA perspective. Dr. Illoh is going to come back up and give us that perspective then.

Agenda Item: FDA Perspective

DR. ILLOH: First of all, I just want to thank our

speakers, Dr. Eder, Dr. Cable and Dr. Bryant, for their excellent and very informative presentations. I think we have had a good discussion so far.

I am just going to give a brief summary. Once again I want to remind us about the key issues we are looking at today. We are looking at donor safety issues, talking about the hemoglobin standards and interdonation interval. We are also looking at blood supply issues, and we are concerned about the impacts with any changes in the hemoglobin standards or interdonation interval on the blood supply.

I have mentioned this before, what our current regulatory requirements are for hemoglobin and the interdonation intervals. Currently we require a hemoglobin level of no less than 12.5 grams per deciliter or a hematocrit of 38 percent for both male and female allogeneic donors. We also require an interdonation interval of not more than once every eight weeks for all blood donors.

I have shown you this slide before. This is just a comparison of our standards together with the international standards. So I think the point here is that this is not just a headache within the United States, this is an issue that is being looked at in other countries too, and therefore you can see the variability and numbers or requirements for blood donors, depending on the country.

We have discussed hemoglobin standards today and the possible options. These are possible options. I'm not suggesting any particular option to go with. Basically from what we discussed here, we could stay with our current standard of 12.5 grams per deciliter for male donors or we could go up to 13.0 grams per deciliter or 13.5 grams per deciliter. These are possible options.

Looking at this criterion here, this shows ranges for blood donors or normal hematocrits for males on this side. It nicely shows the ranges that are considered anemic versus normal. Our current standard falls where this green line is. If for example we went up to 13, we would fall right close to the lower limit of normal or close to the lower limits of normal for males.

For females, this is the range for females. Possibly onions could be to stay at the current hemoglobin standard of 12.5 grams per deciliter, or go down to 12.0 grams per deciliter. Once again, this cartoon shows the hematocrit range for females. Anemic is down there. This is considered normal. Currently our standards are set as we want, normal females. If we went further down to closer lower limits of normal, it would fall somewhere down here on this cartoon.

Dr. Eder has shared with us information on the potential impacts of any changes of any standards. Once

again, the study showed that iron deficiency occurs more often among frequent donors, as we have heard today, and iron deficiency may exist despite normal hemoglobin levels. These are levels within acceptable range for blood donation. Anemia related to iron deficiency may lead to donor deferral and loss.

So, repetition again. Perhaps increasing the interdonation interval, keeping in mind that we really don't know the golden number to use, but perhaps decreasing donor donation frequency or increasing the interdonation interval may allow more time for iron recovery. It may also decrease the risk of iron deficiency, and may decrease future donor deferral for low hemoglobins.

So in summary, we have discussed donor safety issues, including raising the hemoglobin standard for men, which may prevent denominators from anemic males, if we look at the physiologic distribution of hemoglobins. Lowering the standard may result however maybe in a modest decrease in iron deficiency. I hear concerns about iron deficiency in females if we lower the standard. Increasing the interdonation interval, while we don't know the exact number to use, may prevent iron deficiency in frequent blood donors.

There are also blood supply issues that have been discussed here. There is a potential gain in female donors if the hemoglobin standard is dropped to 12, for example.

There is a potential loss of male blood donors if the standard is raised for males, and there is a potential loss of both male and female donors if the interdonation interval is adjusted for all donors.

I have five questions for the committee here. I will read them out.

number one is, does the available scientific evidence support changing the donor hemoglobin acceptance standards for males? If yes, what hemoglobin acceptance standard does the committee recommend?

The second question reads, does available scientific evidence support changing the donor hemoglobin acceptance standard for females? If yes, what hemoglobin acceptance standards does the committee recommend?

Third question will be, please comment on the risks and benefits of extending the interdonation intervals as a strategy to prevent iron deficiency in male donors.

Fourth question, please comment on the risks and benefits of extending the interdonation interval as a strategy to prevent iron deficiency in female blood donors.

The final question, if any changes to the hemoglobin standard or interdonation interval were to be made, what mitigations can be considered to lessen possible adverse effects on the blood supply.

I think those are the five questions to the

committee.

DR. HOLLINGER: Thank you, Dr. Illoh. We are going to take a break at this moment until 10:45. There will then be an open public hearing. There has been one person who has asked to speak. If there are some others, try to let us know in the interval, but you will still be allowed to speak.

Then after the open public hearing, then we will have an open committee discussion with the votes on the two questions and other discussion at the time. So thank you.

(Brief recess.)

Agenda Item: Open Public Hearing

DR. HOLLINGER: I think we will move on. For the open public hearing there is something I must read about the open public hearing for the record, and then we will go into that section.

Both the Food and Drug Administration or FDA and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with any company or any group that is likely to be impacted

by the topic of this meeting. For example, the financial information may include the company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So with that out of the way, then we have had two people who have asked to speak. First is Carr-Greer from the AABB, who has asked to speak on their behalf.

MS. CARR-GREER: Thank you, Dr. Hollinger. I am Allene Carr-Greer, Director of Regulatory Affairs for AABB, so the AABB of course pays my expenses. Yesterday you were informed about who the AABB is, so I will not repeat that.

FDA today is seeking advice from this committee on the appropriate hemoglobin or hematocrit standards for blood donors and appropriate interdonation intervals. Current AABB standards are in agreement with the rule finalized by FDA in 1999, establishing a minimum hemoglobin requirement of 12.5 grams per deciliter or a hematocrit of 38 percent for both male and female allogeneic donors. This rule also established the interdonation interval of eight weeks for a single-unit donation for males and females.

As noted in the issue summary prepared for this BPAC meeting, the FDA published a proposed rule in November 2007 and requested among other things comments and supporting data on the issues before the committee today. AABB provided no comments to the issue of changing interdonation intervals. With the knowledge that REDS-II data would begin to be available to inform the discussion on acceptable hemoglobin levels, AABB did provide comments. Dr. Illoh referenced the comments earlier this morning in her opening comments. There is an excerpt in the statement that I will not bother to read to you right now because you can read those yourself.

Some of the REDS data was presented in 2008, and that was also referenced earlier this morning. More data that would be informative to the questions asked here today are expected in the near future from the recently completed REDS-II RISE study. As Dr. Cable informed us this morning, much of this information is still under analysis. We believe it is critical to wait for these data so that all available scientific evidence is evaluated and incorporated into the decision making process.

If the data show that gender specific acceptance standards for hemoglobin and hematocrit and/or interdonation intervals are indicated, blood centers will need to develop procedures to insure that these new standards are fully integrated into the rigorous CGMP environment, and it is

especially for that reason that we think we should wait for all data, evaluate it, and make this move at that time.

Thank you for your time.

DR. HOLLINGER: Thank you. Any questions for Allene? There was another person who has asked to speak, Susan Rossman from Gulf Coast Regional Blood Center in Houston.

DR. ROSSMAN: Thank you, Dr. Hollinger. I just have a very brief comment, which is to remind you that all of the studies are done using a whole blood fingerstick. This is a rather crude method. Dr. Bryant presented some data showing that the correlation with the venous studies, which is of course what most hematology is based upon, is not very good. I would urge the FDA in any way that they can to encourage the development of more accurate devices that we can use for donor screening.

Agenda Item: Open Committee Discussion

DR. HOLLINGER: Thank you. Is there anyone else in the public section that would like to say anything? If not, then I think we will close the public hearing and open it up to committee discussion of the questions for the committee. If you could put up at least question one. Question two has to do with females and it is the same. But if you could put them both up at the same time, that would be good, too.

The question that we need to discuss at this time

is, does available scientific evidence support changing the donor hemoglobin acceptance standards for males or for females, and if yes, what hemoglobin acceptance standards does the committee recommend for males or for females.

So with that, can we have some discussion on this topic, why one should do something or not do something at this juncture.

DR. BIANCO: Just reiterating what has been said. That is, we know in terms of the general population and with the data presented by Dr Cable, but particularly by Dr. Eder that there would be an impact. But we don't really understand the more granular effect of that impact, that is, what are the donors that we are going to use and how the population does.

So I think that we need these studies to continue as fast as they can to be confident that standard change would not create problems.

DR. HOLLINGER: So Celso, in that regard, what would you particular be looking for? What kind of information do you think is essential to arrive at some conclusions of interdonational time or hemoglobin standards, changes and so on?

DR. BIANCO: I think that the study, the REDS study, is the one that is going to give us most of the answers. As I said before, I have the feeling that we are,

yes, maybe collecting blood from some donors that are not -- do not have enough iron stores. Maybe we are deferring donors, and Dr. Epstein appointed us that this is less of a concern because we are not affecting the safety of these donors, that could be bled.

But ultimately we do not know what this population is doing in terms of what we are doing. If we change the hemoglobin standards, then we know we may lose four percent of the donors, if we increase the hemoglobin for males. But what is the effect that that is going to have in apheresis donors? Even if apheresis, platelet apheresis donors, hemoglobin is not a very important issue because it is rare that sufficient blood will be lost when there is a problem with the apheresis to create a hemoglobin or an iron loss. But those donors are judged on the basis of their hemoglobin. So if they don't pass the hemoglobin test, it doesn't matter that we are just collecting platelets. They will not donate the apheresis platelets.

So I would like to know a little bit more about that before I am confident that this is not going to create big alterations in the system.

DR. HOLLINGER: I think that is an issue that we haven't discussed much, is apheresis donors, in which the hemoglobin level might not be so important. Dr. McCullough, you had a question?

DR. MC CULLOUGH: Actually Dr. Bianco said it very well. I wonder whether Dr. Eder or Dr. Cable know very much about the characteristics of the male donors who would be lost if the hemoglobin levels were changed. I assume there isn't an awful lot known about who those donors are, but it would be a package of data that it would be nice to see.

DR. CABLE: We didn't look too much, but Alan Mass published a REDS paper looking at all deferrals, much larger numbers, and found age-dependent older men are deferred even now.

The normal hemoglobin in men goes down with age, from NHANES and so on.

So I am thinking, it is not just iron depletion, it is testosterone depletion that might cause low hemoglobin.

DR. GLYNN: I think this is a very complex problem, because it has ramifications whatever we do, we change the hemoglobin cutoff or the interdonation interval. It will have some pretty strong ramifications on availability issues.

So I would think that it would be good to make specific decisions about exactly what needs to be done in terms of the hemoglobin cutoff for the interdonation interval. I again would like to reiterate my opinion that I think you need to think of both at the same time as a strategy going forward.

There might be different options you may want to

take. As was mentioned earlier, there might be the option of iron supplementation, there might be the option of increasing the interdonation interval, there might be various things that will impact what we do.

So I personally think that something needs to be done, but exactly what is not very clear to me now, because I don't think we have all the data. Of course, I am a little biased, but I think we should try to get as much data as we can before making these important decisions, because again it has a high impact on the availability of the blood.

DR. TROXEL: I have a question. I wasn't here for the 2008 meeting. I get the sense that we are having the same reaction now that we had then 18 months ago, which is that we don't have enough information to make this decision.

But I am a little unclear on how the REDS data is actually going to help us, at least with respect to the hemoglobin levels. I think it certainly already has informed to some extent the interdonation interval aspect of this, and interestingly it seems not to have that strong an effect, at least based on the baseline data that we heard about today.

But I am unclear, given that the REDS data is only considering donors who were accepted at the current levels, how exactly we are going to be able to see directly from that what the effect would be if we were to change those levels. Maybe someone who is more involved with that can help,

respond to that.

DR. CABLE: Well, the enrollment donors were all accepted, but then as they gave blood, some of them got deferred. It showed some 900 hemoglobin deferrals. We have that data. Only half of them have contemporaneous iron studies, and we intend to analyze that for what we see. But it is not a huge database, so I'm not sure that it is going to be uniquely useful.

RISE was never intended to address directly the hemoglobin cutoff issue. It was focused very clearly on interdonation interval to donation intensity. I think we will have a lot of data on that, and we will have a little bit on hemoglobin deferral. But to allow you to inform hemoglobin cutoffs across different racial groups, for instance, I'm sure we are not going to have that kind of data.

REDS-II did have a lot of data on who was deferred, with all kinds of variables built into that model, and that was just being deferred in the course of blood center operations at six blood centers over, I think it was two years. Mast et al., it was about a year ago. It is one of the references in the handouts. But that won't tell you what it should be, that just tells you what is happening at a given deferral.

The relationship between hemoglobin and iron has

always been very indirect. Barbara's data suggests it is very indirect. Other peoples' data suggest it is very indirect. It is absolutely not meant to be an iron measure. It has a very soft relationship to iron status, so it is never going to be the be-all and end-all to solve iron or cause iron, either way.

DR. GLYNN: The interdonation interval is mostly what RISE can help us with. But maybe Dr. Brittenham, you can tell me if I am wrong, but I would think that the hemoglobin cutoff where you set that, and then how you decide your interdonation interval, aren't those two things related? Don't you need to take into account one when you do the other one?

DR. BRITTENHAM: Yes. I think this is a very complicated set of questions that needs to be approached with great care. Changing the hemoglobin cutoffs for males in particular is something I am concerned about, especially because of its impact on individuals of African ancestry. If we lose a lot of those, then the blood that we need for sickle cell patients will really be endangered.

So I think that is something where we have no information presented here that needs to be very carefully considered before we would make a change.

At the same time, it is evident that we are taking blood from anemic men, and that that is not an optimal

practice, perhaps I can say is the best way. We are bleeding men who if they came to my hospital I would work up to see why they are anemic. I think that is not a desirable practice.

So there does need to be a change in the standard that is adopted. I think that is unambiguous and clear. How to achieve that is another question.

If I may, let me separate this in a sense from the issue of iron deficiency. Iron becomes relevant to hemoglobin when the stores are exhausted. So it is a simple relationship, as long as you have stores to supply the iron. It is the rate-limiting factor for being able to make new red cells. You can replenish the blood that you have given at donation. But in the absence of that, you are limited to what you can derive from diet, and that itself is very limited.

But it is primarily -- in spite of Dr. Cable's pointing out that as we practice now, with a very low hemoglobin allowed for men, we make men iron deficient when they give three or four times a year. But for women it is primarily an issue in those who give frequently. Even first-time donors, perhaps ten percent of women who come to first donation are already iron depleted or iron deficient, because their iron status is marginal to begin with. When they become frequent donors, these are committed women who are really

trying to do good. So I am very concerned about trying to alter the hemoglobin level for them.

When you hear that the normal hemoglobin for women is really 12, that is true if you are using the method of looking at the NHANES data after you have excluded the iron deficiency individuals. But the donors that we are seeing include a majority among the women who frequently give blood, include a majority of iron deficient women. That number will increase if you decrease the level.

So my sense is that by decreasing the hemoglobin level in women that you will get a temporary benefit, but then those will become iron depleted, and in the long run you are going to lose more donors, or the benefit will be very, very minimal. Initially you can do it, but then these women will become iron depleted and then subsequently deferred, discouraged, and many of them lost.

Trying to solve the problem of iron deficiency by changing the interdonation interval isn't an optimal solution. As I said, ten percent of women are already iron deficient. That means their diet as they are having it already isn't doing it. So no matter how long you proceed, they will still be iron deficient.

So I don't think that it is practically possible without great restrictions and great impacts on the blood supply to solve the problem of iron deficiency by changing

the interdonation interval.

DR. HOLLINGER: On the same comments, what about iron supplementation?

DR. BRITTENHAM: I think iron supplementation is a solution. It is a solution that I think blood centers have been very reluctant to adopt for some reasons that are understandable and some that are less so.

The concept that is best is to replace -- first of all, I think it is a program that primarily should be limited to women, who are frequent donors. Someone who gives once or twice a year doesn't need additional iron. It is those committed women who are frequent donors that really need attention. I think programs should be targeted to them, and that the intent of the program should be to prevent iron deficiency, not to treat it.

If you have someone who is already anemic and iron deficient, you never *a priori* tell whether it is because they have given blood or some other cause. But if you give each time short term iron replacement that is intended to just replace the iron that has been lost at blood donation, then I think that is a program that could solve these issues and that could increase the blood supply while preventing the iron deficiency.

I think this is something that needs to be demonstrated practically in blood centers. Theory is

wonderful, but you need sound evidence to know just how to proceed.

DR. TROXEL: Those comments are very helpful. I agree with Simone that it is very difficult to disentangle the cutoff from the interval, because obviously they are related and they are trying to get at the same thing, although they may not be doing it all that well, perhaps.

But again, I am just a little concerned that none of this observational data ultimately is going to be able to inform this question in any satisfying way. One option would be to put off making a decision now or making a recommendation now, and to do an experiment in which we in some limited number of settings try out a couple of different cutoffs. Ideally we could do some nice factorial design where we have different cutoffs and different intervals, and we could get a real sense of what the joint effects of those two things are.

Now, I'm not sure that is a realistic suggestion, because then we won't do anything, and be back here in five years trying to make a decision. But then at least we would have presumably the information that would directly inform that. Whether that could be combined with a formal test of the iron replacement concepts starts to get complicated, and maybe too many things going on at once, but that is the kind of information that will give us a solid basis for making a

decision. Whereas, I feel now that we are trying to do the best we can with this limited data, but the observational data just can't address specifically the question that we are being asked.

DR. BRITTENHAM: I think you have really said exactly what the problem is. It is ten years since we had an NIH consensus conference in which Celso was the leader, to bring these issues. In the meantime, maybe not nothing, but little has happened.

Going on with the status quo, I think we are running up against a point now where we have been -- I think one of the reactions to the suggestion about introducing iron supplementation programs by the blood centers is that from their point of view, economically it was easier to recruit a new donor than to take care of the donors they have. Perhaps now we are reaching a point where that is no longer true.

DR. BIANCO: One point that you made, Gary, that may make this a more manageable issue for blood centers, and since I am associated with many, not a single one, I can't answer for them, is that you restricted it today, very focused it, on females that donate frequently.

What would be the cutoffs for that? That is, which group would that be? What is a frequent donor, a female that donates frequently? Because that makes it more manageable in a certain way. If it is half of the females donating or a

third of them, to reduce it to one-sixth of the population or something like that.

DR. BRITTENHAM: I think it is women who donate three or more times a year.

MS. BAKER: A question for the panelists. Are you aware of any economic studies that have looked at the costs of implementing the supplemental program for frequent female donors? And will the REDS study address that?

DR. GLYNN: For the cost, no, we haven't looked at different options. It is not an interventional study which might need to be done next. But no, we are not looking at supplementation for example or cost of the different things.

Rich, do you think we could do that? I don't think so.

DR. CABLE: One of the problems with -- it was a great workshop, but one of the problems with it was that it said that iron supplementation should be conducted in the context of clinical trials, basically, is essentially what it says. Having been involved in a little bit in trying to design some of these clinical trials, you need data safety monitoring boards. You are talking about millions of dollars here, because you can't just go out and give it to a bunch of donors and see what happens. You can go out and give it to a bunch of donors and not see what happens. Then it is not research and no one can stop you, but you can't find out what

happens without IRBs, DSMBs, OSMBs, FDA, yadda yadda. It gets to be extraordinarily complicated.

So I don't think it can be studied without enormous resources. Whether it can be done after it is shown to be effective for limited resources would have to be part of a study. But it needs to be funded by somebody, because blood centers don't feel capable of funding this kind of research themselves.

I think you are right, it is an expensive study to do because you are giving drugs to people, even if it is just little iron pills.

DR. GLYNN: I don't think there is any problem with Rich mentioning that you submitted an application for an intervention study following some of the donors who were involved in RISE.

DR. CABLE: Barbara and I and Alan Mast and Joe Kisse, and three of the centers in REDS proposed to take these well characterized donors, recruit them into a study of supplements, and I think it is five arms, as I remember it, education, placebo education, placebo pill, and two low levels of iron, 18 and 37, 38, no 60. We didn't go with 60, although we got feedback in reviews that we should have gone to 60.

So it is five arms, two observational education arms with a control and three drug arms with a control. The

reason to use the RISE donors is, they have shown themselves to be compliant, they are certainly frequent donors, and they are well characterized before and after the iron. But that has not been funded yet, has it?

DR. GLYNN: No, that is under review.

DR. CABLE: It is okay if I say that, too.

DR. HOLLINGER: One of the questions, just to ask the committee again, does anyone on the committee find a problem with their retaining the standard at the current time for men at 12.5? Do they see a safety problem, a health problem or others for males now? I'm not talking about females, at the current level.

DR. BOWER: I do find it problematic that we are essentially saying that we can take donations from anemic males. That is what the data shows. Granted, I will say that we don't know that we are doing them any harm, but still, I think it would be hard for me to say, sure, go ahead and take blood from an anemic male.

DR. HOLLINGER: Is there any available data that this is harmful in some way from a health standpoint? I understand what you are saying. I'm just trying to say, do we have any evidence, maybe there is no evidence, that it is harmful? Certainly nothing was presented here today on this. We have talked about PICA and we have talked about restless leg syndrome and a few other things, without looking at what

levels we are talking about that are causing this.

MS. BAKER: Perhaps a related question, is there any problem with the blood that the anemic men are donating? Any problem to the donor recipient?

DR. HOLLINGER: Anybody have any -- yes.

DR. RAGNI: I have a question. For any donor, if they are anemic it seems to me that it would be medically appropriate to figure out if they are iron deficient and replace them. I understand there may be studies, but if we are taking blood from individuals, especially if we are taking blood repeatedly, but if we are taking blood and their hemoglobin has fallen, or we start out with a low hemoglobin, as a physician I wonder if they are iron deficient, and it has been proven time and time again that iron supplementation can improve that standard.

Folks who have iron deficiency anemia, many of them do not feel well. There are headaches, irritability, fatigue, the standard stuff. So I guess I would just ask that question as an important question to people who take blood as part of donations.

DR. BIANCO: But the question, Dr. Ragni, is how would you decide that those people are iron deficient? That is what we are having trouble.

DR. RAGNI: I'm not sure. Certainly what we do in practice is measure the iron TIBC or ferritin and make a

decision, and then treat if they are deficient.

But it seems to me that is the piece that is missing here, and needs to be implemented more than changing numbers. I think we need to take care of folks who are giving blood and are becoming or are already anemic.

DR. HOLLINGER: Any other comments on these questions? Because we can certainly put it to a vote for the committee. Dr. Troxel, you were concerned about the fact that the REDS study might not provide the information. Is there something that you would add to it or that you would like to see?

They talked about the fact that it might have some interdonational information, but less so on the standards of the hemoglobin.

DR. TROXEL: Obviously it is going to be informative on many aspects of this. Certainly the longitudinal data will give us some information about people who are deferred at some point during the study and then what happens to them subsequently. But what we really need to know are these counterfactual things, which are what would happen if you would only be deferred if you were at 12 rather than 12.5, or 13, or whatever those different cutoffs might be. Without doing some kind of a randomized study that includes those different scenarios, I don't think there is any way that we can get directly at that from the REDS study.

So I feel unsure myself as to what the right thing to do here is, but I am concerned that quote waiting for the additional analyses on the current studies to provide us with the information will just lead to the same discussion in another year, because we won't have that information. We will have a little bit more information then, but not the kind of information that we feel we need, I think, to make an informed decision.

DR. HOLLINGER: I think we will go ahead and vote on the first question. On your microphones you will see three buttons that are blinking right now. There is a yes, an abstain and a no. These are attached to your name. So we will vote simultaneously and then after that the answers will be put on the screen, so we can see, and it will indicate what everybody voted at that time. Then Celso, I will ask you -- before the votes are put up on the screen I will ask you how you would vote.

DR. BRITTENHAM: I do want to say, my sense of how to answer these questions has to do with the last question about what should be done to mitigate.

For example, I think that it is clear that we should not be bleeding iron deficient men. So the standard should be changed and it should be raised to 13.5. I don't think we can recommend making that the standard at present without looking into how that can be mitigated in question

five. So I just ask for guidance in a way for how to do this.

DR. HOLLINGER: The question says, does the available scientific evidence support changing the donor hemoglobin acceptance standard for males.

DR. BRITTENHAM: So my answer to that would be unambiguously yes. These are anemic men that we are bleeding. But that is different than saying I want this to be implemented without careful consideration of how it would affect the blood supply.

DR. EPSTEIN: I think FDA understands this point. That is why we are trying to parse the issue. In the end, when we make policy, we have to look at everything together.

So we have heard your comment, it is on record, we get the point. But the threshold question is, should we be trying to make a change or not.

DR. HOLLINGER: So you have the question before you. Yes, abstain or no. I am going to ask each of you to vote now. Celso, before it comes up, do you have a comment on how you would vote?

(Whereupon, a vote was taken.)

DR. BIANCO: I thought that you said after it comes up. I agree entirely with what Dr. Brittenham said. Yes, I think that the standard should be changed to address the issue of these men that are iron deficient. But I don't know

how to define those men in the context of the blood donation as we do it. I am sure that there are things that we can discuss on question five that could be done to make it better.

DR. HOLLINGER: I just asked for a yes, abstain or no, Celso.

DR. BIANCO: I said yes.

DR. HOLLINGER: So let's see how the vote went. This is getting scary since yesterday. We are getting complete agreement.

DR. EMERY: The panel has made a decision. They all have voted yes. No abstentions. Dr. Hollinger voted yes. Dr. Manno voted yes. Dr. Ragni voted yes. Dr. Brittenham voted yes. Dr. McCullough voted yes. Dr. Glynn voted yes. Judith Baker voted yes. Dr. Bower voted yes. Dr. Troxel voted yes. And Dr. McComas voted yes.

DR. HOLLINGER: So that was that section. It does say there is a second part to that. If yes, what hemoglobin acceptance standard does the committee recommend? I think they just want comments on this basically, and there has been a fair amount of discussion. Does anyone want to put out a number, or do you want to just say that it should be closer to a normal level for males?

DR. BRITTENHAM: I would advocate 13.5. I think it is the level that is normal, that the evidence suggests is

the normal for males.

DR. GLYNN: I don't know that we can pick a number unless we have looked at other things, like what would be the impact on availability from various race ethnic groups and different things. So again, I don't think we are ready to take that vote yet. At least I'm not. I know it is higher than 12.5.

DR. HOLLINGER: I tend to agree with you, Dr. Glynn. You would have to look at the availability and how much deferrals there would be and how much loss there would be. In many cases male blood may be useful, but I would also say that since I have not heard much problems with males donating at 12.5, then I certainly would not see much problems for me anyway at 13 or something at that level. But we don't have the data, and it would just be an assumption and not from scientific evidence. Anybody else have a comment?

DR. GLYNN: Use from other countries, like U.K. uses 13.5, to get their input in terms of what went into their decision to use a particular cutoff. Some of them have 13.

DR. MC CULLOUGH: We have accepted the data set that we were shown as the gold standard, but we might also want to be sure there aren't other reasonable data sets around there, so there is not some surprise that these

numbers aren't ideal.

DR. HOLLINGER: Those are the comments. Let's go on to the second question. We have had a fair amount of discussion. Does anybody have any specific comments they want to make before we vote on the second question? Does the available scientific evidence support changing the donor hemoglobin acceptance standard for females?

DR. MC CULLOUGH: Use the Chairman's prerogative to skip this if you want, but there are two related questions to iron deficiency, and several brought this one up earlier. We talk about all the known symptoms of iron deficiency, but is there much understanding of what kind of clinical impact there is for not full-blown iron deficiency, but ferritin levels in the range of ten to 50 or 60 or 70?

I am trying to get at, do we know anything about how much of a clinical problem this is and how much people might be harmed by having ferritins in those levels.

Then the other question which is maybe even more off the subject is, and maybe Gary would know this, how is the norma range of ferritin decided? How good is our understanding of what these values in the lower range of ferritins really mean? That is what I am trying to get at.

DR. HOLLINGER: Anyone like to respond to that?

DR. BRITTENHAM: First of all, with respect to the question about, is ferritin useful for determining who is

truly iron deficient and not, I think unequivocally yes. There is now a WHO standard. There is I think general agreement about how to identify individuals.

There are quibbles over a few micrograms per liter of ferritin, but I'm not sure how important that is. So I think we can identify using ferritin in individuals whose iron stores are exhausted.

The measure that actually was used in the RISE study is really superior, because it lets you evaluate iron status over the whole range. You can use this measure to estimate how much depletion, how much tissue iron depletion you have. So that is really a superior way of doing the measurement.

I think there is evidence that there are clinical impacts that vary from person to person, but negative from being iron depleted as well as iron deficient.

Maybe the best convenient reference that is included in our material, the article that Bruce Newman did in 2006, is a summary of this.

DR. HOLLINGER: One of the problems I have with this question myself is the issue not so much of whether hemoglobin levels are changed or not, but it ties in with the interdonation intervals as well. It is not asking this question here, it is asking about the hemoglobin acceptance standards. To me, that would make perhaps a difference. One

might consider lowering the hemoglobin level, but if you do, then increasing the interdonation level. I don't know if anyone else is struggling with that same problem or am I alone with this. Any comments?

DR. GLYNN: I have mentioned the same thing before, but I don't think you can really separate the one from the other. It is very difficult to extricate one from the other.

The other thing that doesn't make sense to me is that right now, 12.5 is the major cause of deferral because of low hemoglobin. So i can't imagine why we would go to 12 from 12.5. It would seem to me you would defer even more eventually, more women. So to me, I don't really understand why we would do that.

DR. HOLLINGER: I will come back to Dr. Brittenham again, since you decided that you would go up to 13.5 for males because that is anemic. Would you go down to 12.2 or 12.0 for females?

DR. BRITTENHAM: No. As I said before, my concern about doing that is that then we will be accepting an increased number of iron deficient women. I think that the longer term impact of this on the blood supply would be negative.

I think it is not something we should do. It means we would be taking blood from iron deficient women. What needs to be considered is what happens to the donor after the

donation. We will take a unit of blood from someone who weighs 110 pounds. If you do that, you can reduce their hemoglobin by something between 1.5 and two grams. So you can take somebody who comes to you at 12 and reduce them to something a little more than ten. I think that is not a good thing to do.

DR. HOLLINGER: Then they would need a transfusion, wouldn't they?

DR. BRITTENHAM: Exactly. It seems not an optimal solution to things, to take donors and reduce them to people who need transfusions.

DR. GLYNN: We do not need the complication of an autologous transfusion.

DR. HOLLINGER: Any other comments from the group before we vote?

DR. MANNO: There is probably no one who knows more about iron than Dr. Brittenham in this room, but there are consequences of iron deficiency that are well documented in children. At long term, cognitive deficiency problems that are associated with iron deficiency anemia. I'm sure there are some data with regard to other abnormalities beside anemia and anemia-related symptoms in adults, particularly adult females.

DR. BRITTENHAM: Yes, there are, and there are cognitive things that come as a result of that. But as I

said, in some of the material for the meeting, that is summarized in Dr. Newman's paper.

DR. HOLLINGER: If no further discussion, then let's vote on this question. You have again yes, abstain and no, base on the question of, does available scientific evidence support changing the donor hemoglobin acceptance standard for females. So I am going to ask you all to vote now. Celso, could you tell us how you would vote?

(Whereupon, a vote was taken.)

DR. BIANCO: I would agree with Dr. Brittenham and would not support a change for females.

DR. HOLLINGER: So could we see the results of the voting?

DR. EMERY: Everyone has voted. The panel has voted, and there are zero yeses, there is one abstention, and there are nine noes. Dr. McComas has voted no. Dr. Troxel has voted no. Dr. Bower has voted no. Dr. Glynn has voted no. Dr. Manno has voted no. Dr. Hollinger has voted abstain. Dr. Ragni has voted no. Dr. Brittenham has voted no. Dr. McComas has voted no. Dr. Bower has voted no. Dr. Baker has voted no, I'm sorry.

DR. HOLLINGER: Any comments on the second part of the question? We didn't vote yes, so there are no comments on that section.

Let me go on. There are a couple of other

questions. We have had a fair amount of discussion. But the third question is, please comment on the risks and benefits of extending interdonation intervals as a strategy to prevent iron deficiency in male donors. Anyone want to make any comments about that? Nobody, okay.

Then please comment on the risks and benefits of extending interdonation intervals as a strategy to prevent iron deficiency in female donors. Comments?

DR. BIANCO: Not really a comment, but just to reiterate that from the data we saw, even if Dr. Glynn is absolutely correct, that we have to link both hemoglobin levels and interdonation intervals, the influence of interdonation intervals was much less clear than what we saw with hemoglobin. That is, as a strategy it didn't really work.

The second thing that is a major concern that some of us have expressed is that this could affect the rare donor, the donor that is very important for the sickle cell patient, for the sensitized patient, and others, and the O negatives and the male plasma.

DR. MC CULLOUGH: Also, the way the question is phrased, it provides only one option of dealing with this situation. I think it is important to allow some flexibility to sort out potential other strategies to deal with the situation, other than just changing the interval.

DR. HOLLINGER: Would you allow those strategies to be regulated by the blood organizations rather than mandated by the FDA?

DR. MC CULLOUGH: I could imagine an AABB standard that might say that the blood establishment has to put in place a mechanism to mitigate problems of iron deficiency or something along those lines, that might begin to address this issue, but provide some flexibility.

DR. MC COMAS: This is just to second a point that Dr. Glynn made earlier. It would be very helpful if there were a comparison with some of these other countries, in looking at the minimum hemoglobin rates and the interdonation intervals in other countries. You have got the United Kingdom, which has 112 days as the interval donation period, in Australia 84 days. They have some different rates, or rates that they were considering.

It seems to me, as we have done in the past, borrowing some of that expertise would be very helpful to understand how they chose their rates versus their hemoglobin levels.

DR. EPSTEIN: I think the way FDA is trying to look at the question about interdonation interval in asking what its pros and cons are, we are thinking, if we can't get to monitoring the iron store and if we can't get to giving iron, is there or isn't there an independent value to changing the

interdonation interval.

I will admit that the data are somewhat discouraging, although if we look at the preliminary RISE analysis, it seems to suggest that a 16-week interval starts to have a statistically meaningful effect in reducing the likelihood of hemoglobin based deferral. You are way out to the end point. Once you are dropping hemoglobin, it is because you can't mobilize enough iron or replace enough iron from diet. So a little unhappy because you are looking at the extreme end point.

But nevertheless, and maybe we should put the graph back up, 16 weeks looked like a break point to me. You start to have benefit. That may not be compatible with maintaining the blood supply, which is a dilemma. But what we are trying to do with this question is dissociate the issue of monitoring and managing iron, because we are not sure we are going to get there.

So if we can't monitor and measure iron, should we or shouldn't we be looking at a positive risk to benefit of changing interdonation interval. That is really the thing about which we want feedback.

DR. GLYNN: I think that is going to be a very important variable to look at, but I think what we haven't seen yet, because we have not done the analysis, is maybe some subgroup analysis. It might be that in some specific

younger woman -- you may define some subgroups where you see a particular pattern that we don't know yet. Do you want to comment on that, Rich?

DR. CABLE: I think although the RISE study was not designed to look at hemoglobin relationships, it was clearly designed to look at this subject. So I would urge you to wait to see that data before getting anywhere down the decision making tree.

The other thing I would like to say is, I don't know that I agree with Jay that looking at that data makes me think of a break point. But that is why we need more analysis. But when you look at the effect of one donation a year on a man, that is just about the amount that an actively menstruating woman loses in a year in menses. So you are not going to be able to get to a point with managing frequency where blood donors look like non-blood donors with respect to their ferritin levels. They are going to be lower, and they are going to be therefore quote abnormal, unquote, or different from normal, outside the reference range.

Until you get to some understanding of what that means, and I don't think we know anything about that, I think it is really hard to say what ferritin levels you are aiming for. Even if you were trying to manage iron, you would have to answer that question. I don't think anybody knows what the ferritin should be in blood donors. It is going to be

lower than regular people. If a bunch of doctors look at it, they are going to say these people are sick.

For instance, Boydler's cutoff values in his editorial used a one-tailed five percent test. What he said is that five percent of normal men are anemic. That is what he said. So I think that guy that goes in to see his doctor, a diagnosis, ICD-48 code, for anemia, which I think we all know is ridiculous.

So anemia needs a cutoff, but I think it is really fast and loose with the language to talk about 13.7, which is his number for Caucasians, diagnosing anemia or sickness in a healthy donor population. I think it is very damaging. I would like to de-medicalize this discussion to some extent by pointing out these apparent paradoxes.

DR. BRITTENHAM: He is really talking about how you try to identify somebody in a population. Normally we each have our own optimal hemoglobin level. When you give a unit of blood, as long as you have iron stores you can restore that.

So it is having sufficient stores to replace the blood that you have given that I think becomes the critical point with respect to ferritin.

DR. CABLE: One way to use hemoglobin more creatively would be, every first-time donor get a venous hemoglobin level. We certainly can do that. Put it in the

record, and that becomes that donor's normal, developed from ranges around that for John Smith; the women, too.

In other words, I don't see why we need to be talking about population norms when we have got different races, different ages. A first-time donor comes to you, you didn't cause any of their problems if they have problems. If you diagnose them as having problems, send them to their doctor. If they are healthy, just keep them that way.

It seems to me like rather than measuring ferritin, which is expensive and difficult, we can all measure hemoglobin, and that is probably a reasonable way to manage a donor for a long time, anyway.

So I just put that forth. Looking at populations is difficult. There are normal men who will have hemoglobins at 13.3. What you are telling them is, you are not going to be able to donate blood. It doesn't make sense to me.

DR. BRITTENHAM: This would certainly be a radical restructuring of the blood donation system.

DR. HOLLINGER: It is interesting, in the study with the iron supplementation, how rapidly erythropoiesis is increased. The hemoglobin goes up very quickly, within a month or less, but it takes awhile for the iron stores to be repleted. They take a lot longer. So I think obviously if you are just looking at hemoglobin, it doesn't take much to make them back up to a normal quote level in that regard.

The other question is, if any changes to the hemoglobin standard or interdonation interval were to be made, what mitigations can be considered to lessen possible adverse effects on the blood supply. I think we have probably gone through that quite a bit.

Anybody else have any comments that will be helpful to the FDA in regard to this question, what you think maybe needs to be done or could be done, should be done, to arrive at a conclusion? This has come up now before this committee on several occasions with basically no action.

Jay, is there any specific --

DR. EPSTEIN: Just a technical question, both for Barbara Bryant and for Richard or Simone. One test that would be expeditious is the CBC with indices. Most blood centers can have a hemocytometer or already do.

So if you followed donors serially for their MCV, MCHC, RDW, are those indices sufficient to tell you when a donor is getting into trouble with their iron. So my question really is, from the NIH study, do you already know the answer? And from the RISE study, will we know an answer?

DR. BRYANT: In the NIH study we did follow the MCVs. We followed those even in the control donors, and the MCVs do drop. As your ferritin level drops, your iron stores drop and you don't make red blood cells that are the same

size and have as much hemoglobin in them. So we do know that the MCV drops. Also, when we iron replace, the MCV went back up into normal range.

DR. EPSTEIN: Really what I am asking is is it good enough? Is it a poor man's ferritin? Or in managing donors is it sufficiently predictive that we could deem it adequate?

DR. BRYANT: I do believe it is probably a poor man's ferritin. What is normal MCV? Maybe your normal MCV is 98, so by the time I get you down to about an 83, you are really in trouble. Whereas, some people may start at 87 and then going down to 83 is not that big of a difference.

So once again, it is a relative thing. We looked at that even with hemoglobins. How many donors did I have in my control arm that I had to call men with hemoglobins with 16.2 and tell them, by the way, your ferritin is low. Or maybe they were 16.2 and now they were down to 13.5 and their ferritin was two.

So there is a long way to drop down, but it is what comes first. The ferritin seems to drop, then the MCV follows, the RDW increases and the hemoglobin is next.

DR. BRITTENHAM: All the measures that you do on red cells are telling you about iron restricted in erythropoiesis. When you can no longer have enough iron to put into the hemoglobin to make an adequate volume, the MCV falls. That precedes the fall in the hemoglobin below the

population level. So these are late indicators.

There is one measure that hasn't been discussed that is a feasible way of identifying those with lower iron stores. That is the erythrocyte zinc protoporphyrin. That was widely used in the era when there was lead poisoning, as a way of detecting it, but isn't now. If you want a cheap easy immediate way of measuring that can be done just on a fingerstick as well, erythrocyte zinc protoporphyrin tells you that.

It again is only telling you when iron stores have been exhausted, and then if there is not enough iron to be incorporated into hemoglobin, the red cell takes up zinc, and then you can measure the zinc protoporphyrin by its fluorescence. So that is another measure that might be considered.

DR. GLYNN: In answer to Jay's question about RISE, one of the slides that Rich presented at the end showed that we are going to look at all the lab measures that we have, including CBC indices, et cetera and then see which ones predict development of iron depletion or hemoglobin deferral.

DR. MC COMAS: This is just one additional comment in relation to item five. If iron supplements are considered a way to lessen the adverse effects at some point in the future, I think that the FDA ought to proceed, after looking carefully at some data that would demonstrate that donors

would take the supplements. It is one thing to alleviate the conscience of the blood centers to hand it out or the FDA, but it is quite another to determine whether or not people will actually follow through with that. I think there would be a lot of people who wouldn't ever take it. But that is an empirical question.

DR. BIANCO: Whatever we do to mitigate, I think that what we need at the present time and with the current state of knowledge to current science is flexibility. I think that Dr. Benjamin said it very well early during the discussion.

I don't think that we have a prescription, a recipe, at this point of what we can exactly do. The zinc protoporphyrin may be a solution. I don't look at those issues like you do. But I don't know how simple it is to measure it, what would it be in the general population and all that. I think all that we have to understand in the donor population, and other measurements that could be useful. But that should be the focus of some specific studies. I don't know how easy and what kind of repositories were created with those studies, or if any of them would be suitable for these type of measurements.

DR. HOLLINGER: Are there any other comments from the committee? If not, I want to thank the committee for the last two days. I think there has been some good information

put forward. I hope the FDA appreciates that.

So we stand adjourned until December 14-15 for our next meeting. Thank you all.

(Whereupon, the meeting was adjourned at 11:55 a.m.)